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The synthesis and biological activity of novel anthracenone-pyranones and anthracenone-furans

James E. Rixson [a], James R. Abraham [a], Yuki Egoshi [a,b], Brian W. Skelton [c], Kelly Young [d], Jayne Gilbert [d], Jennette A. Sakoff [d], Kersten M. Gericke [e], Adam McCluskey [f,*], Scott G. Stewart [a,*]

[a] The School of Chemistry and Biochemistry, The University of Western Australia, Crawley, WA 6009, Australia
[b] Department of Materials and Life Sciences, Faculty of Science and Technology, Sophia University, 7-1 Kioicho, Chiyoda-ku, Tokyo 102-8554, Japan
[c] Centre for Microscopy, Characterisation and Analysis, The University of Western Australia, Crawley, WA 6009, Australia
[d] Department of Medical Oncology, Calvary Mater Newcastle Hospital, Edith Street, Waratah, 2298 NSW, Australia
[e] Bayer Pharma AG, Medicinal Chemistry, 42096 Wuppertal, Germany
[f] Chemistry Building, The University of Newcastle, University Drive, Callaghan, NSW 2308, Australia

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ABSTRACT

An efficient and divergent methodology for the synthesis of new anthracenone-pyranones and anthracenone-furans is described. Key reactions discussed in these syntheses include an aldehyde promoted annulation with a β-keto-sulfoxide, a domino alkyne insertion/carbonylation/Nu-acylation and a DMEDA promoted Castro–Stephens reaction. We also report the in vitro growth inhibition of these compounds in a range of human cancer cells. The natural product BE-26554A displayed good cell growth activity on BE2-C neuroblastoma and SMA glioblastoma cell lines at 0.17 and 0.16 μM (GI_{50}), respectively. Of note, were a CF_3 functionalised anthracenone 4-pyranone (chromone) derivative **22**, and an anthracenone-furan derivative **54** which displayed 0.20 μM and 0.38 μM growth inhibition, respectively, in the BE2-C neuroblastoma cell line.

1. Introduction

The structural class of anthrapyranones have a remarkable range of biological activity mainly as anti-bacterial agents, anti-tumour and anti-fungal compounds. Some examples in this family of compounds include pluramycin A (**1**), kidamycin, altromycin B, hedamycin topopyronone C (**2**), λ-indomycinone[1] and the antibiotic saptomycin E (**3**) (Fig. 1). Generally, the molecular mode of action of this class compounds is thought to go through an intercalation with the major groove of DNA along with covalent bonding with N7 of guanine. The effectiveness of this mode of action, is reliant on substituents at the C5, C8 and C10 positions (mostly carbohydrates) and the C2 epoxide moiety for the guanine alkylation process.[2–4] In one early study an altromycin B-DNA adduct was investigated using two-dimensional ^{1}H–^{15}N HMBC experiments to identify the epoxide alkylation position in DNA. Interestingly, neopluramycin, which differs from pluramycin (**1**) in that it has a single olefin in place of the epoxide, also has anti-tumour activity (leukemia L-1210),[5] however this compound shows little, if any, DNA sequence selectivity compared to pluramycin (**1**).[6]

Simple epoxide-anthrapyranones have also been isolated, for example, in 1994, the Banyu Pharma group isolated the natural product BE-26554A (**4**) from *Streptomyces* A26554 cultures.[7] In this early report and brief study, the natural product epoxide (**4**) was described to have an IC_{50} value of 0.001 μM (or 10 nM) against P338 Leukaemia cells. Unfortunately, any indication of the epoxide stereochemistry was not identified in this isolation study. Aside from the anthrapyranones, the 4-pyranone ring system alone has also been reported to effect murine leukaemia cell (L1210) growth.[8]

Several groups have developed syntheses of anthrapyranones, most commonly through various approaches to the 4-pyranone ring system D ring. These key reactions include; the Baker–Venkataraman rearrangement with cyclisation,[9,10] a 6-*endo-dig* cyclisation of alkyne ketones,[11–15] a Friedel–Crafts acylation[16] and cyclisation of β-diketones[17,18] among others.[19,20] In 2013, we described a racemic synthesis of anthrapyranones through the annulation of a β-keto-sulfoxide and an aldehyde.[21] Interestingly, a recent report on a non-metal mediated synthetic ring forming processes on simple chromones has come to light[22] along with the oxidative alkylation of these ring systems.[23]

* Corresponding authors.
E-mail addresses: Adam.McCluskey@newcastle.edu.au (A. McCluskey), scott.stewart@uwa.edu.au (S.G. Stewart).

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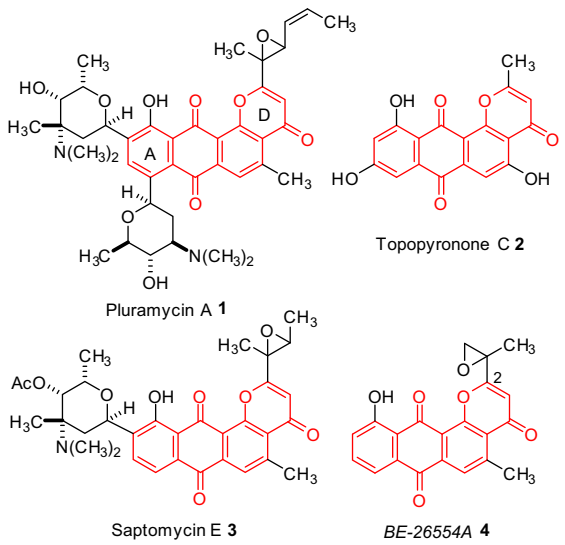


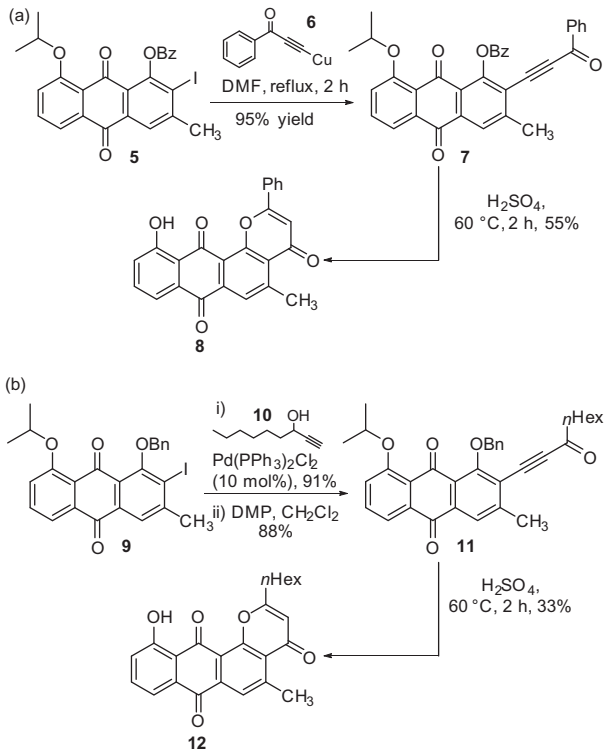
Figure 1. Chemical structures of selected natural product anthrapyranones.

The varying biological activity of the pluramycin class of compounds, with different substitution at C2, reflects the importance of this region of the molecule. As part of furthering our investigations into this class of compounds we were interested in developing efficient syntheses of the anthracenone ring system with varying D-rings, as well as investigating the role which this ring system plays in the biological activity. In our synthetic studies several approaches to the 4-pyranone core of the anthrapyranones were developed. Initially, an approach using an acid induced ring closure of anthraquinone-yne-ones was conceived (Scheme 1a). This tactic has been pursued by several groups including that of Shvartsberg.[24,25] The anthraquinone-yne-one could be prepared either using a Castro–Stevens reaction or the related Sonogashira palladium catalysed process. Thus treatment of benzoyl protected phenol **5** with phenyl copper acetylene **6** provided the yne-one **7** in excellent yield (95%).[24] Subjection of compound **7** to sulphuric acid provided the phenyl 4-pyranone **8** in 55% yield through hydration of the alkyne and cyclisation through a phenoxide. Alternatively, hydration using *p*-TsOH provided a crude mixture of the isopropyl-ether 4-pyranone and phenol-4-pyranone **8** (1:3.7 by NMR analysis of the crude product).[26]

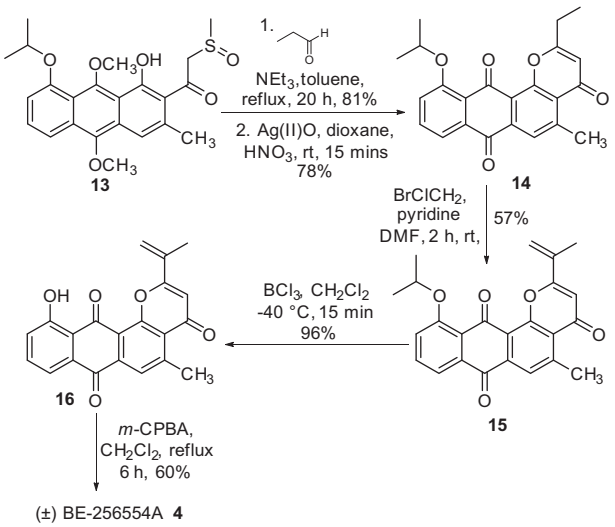
As we required an alkyl, or alkenyl, substituent at the C2 position to begin SAR studies, an alkyl substituted alkyne was incorporated into the initial C–C bond forming process. Following several unsuccessful reaction trails with the benzoyl protected derivative **5** the corresponding benzyl protected phenol **9** was used (Scheme 1b). Treating compound **9** with the alkyne alcohol **10** gave the desired alkyne in excellent yield (91%). Oxidation of this product with Dess–Martin periodinane furnished yne-one **11**, in 88% yield. Unfortunately, treatment with *p*-TsOH did not provide any pyranone compound **26**, however revisiting the previously used sulfuric acid conditions only resulted in 33% of the desired alkyl anthrapyranone **12**. As this annulation process was low yielding we decided to pursue a more efficient synthetic route. Unfortunately, following the piperidine and aminovinyl ketone method devised by the Shvartsberg group,[24] only afforded a complex mixture of products.

A synthetic route through key β-keto sulfoxide **13** was ultimately successful in the efficient preparation of the 4-pyranone ring system bearing an alkyl side chain.[21,27–29] Eventually this intermediate **13** was also used *en route* to the natural product (±)-BE-26554A (**4**) (Scheme 2).[21] The β-keto-sulfoxide-annulation procedure with propionaldehyde was especially high yielding (81%) which provided the impetus to expand this reaction to other aldehydes. Coupled with the Augustine olefination procedure by Krohn et al., this sequence could provide a range of substituted 4-pyranone derivatives.[10,30]

We next examined this first group of compounds (**4**, **8** and **12**, **14** and **16**) for in vitro cell growth inhibition against a panel of nine human cancer cell lines including: HT29 (colorectal carcinoma); MCF-7 (breast adenocarcinoma); A2780 (ovarian carcinoma); H460 (lung carcinoma); A431 (epidermoid carcinoma); DU145 (prostate carcinoma); BE2-C (neuroblastoma); SJG2 (glioblastoma); MIA (pancreatic carcinoma) and SMA (glioblastoma). As in previous investigations,[31–33] an initial screen was carried out



Scheme 1. Synthesis of (a) phenyl and (b) alkyl anthrapyranones.



Scheme 2. Summary of the final stages of the synthesis of (±)-BE-26554A (4).[21]

treating each of the cell lines at a compound concentration of 25 μM. If, in this preliminary assay, the compound was considered potent with a high percentage inhibition (>90% across all cell lines evaluated or >100% against more than two cell lines) and suitably soluble (in the DMSO/water solution), then a more detailed dose response evaluation was conducted. This allowed determination of the compound GI_{50} and these values are presented in Table 1.

Unfortunately, the C2 hexyl and phenyl substituted anthrapyranone compounds (**8** and **12**, respectively) were not potent as cell growth inhibitors in any of the cancer cell lines tested. The racemic mixture of the natural product (±)-**4** however was highly growth inhibitory across the range of the cancer cell lines. Of particular note was the effect against BE2-C, SMA and A2780 cell lines, at 0.17, 0.16 and 0.29 μM, respectively. Compound **14** disclosed moderate cytotoxicity with the exception of only having weak potency on the SJ-G2 cell line. The alkene precursor **16** was mainly three times more potent across the range of cell lines tested. It is clear that in most of the cell lines the epoxide (±)-**4** is more active than the precursor alkene **16**, however at this stage it is impossible to gauge if the epoxide moiety is directly playing a role in the mode of action of (±)-BE-26554A (**4**).

A slight modification of the original synthetic pathway (Scheme 2) facilitated access to additional anthrapyranone derivatives (Fig. 2). Condensation of alternate aldehydes with the β-keto-sulfoxide **13**, were also successful in producing alternatively C2-alkyl substituted 4-pyranones (65–83% yield). As in the original synthetic scheme these products could be subjected to a silver oxide Ag(II)O oxidation with or without subsequent isopropyl deprotection (BCl_3) to prepare compounds **18**, **21** and **22** (ESI†). The methyl ethers **19** and **20** were accessed through treatment of the parent phenols with CH_3I. These modifications allowed exploration of the A ring alkyl ether and the length of the C2 side chain as well as the effect of a metabolically stable CF_3 group with **21** and **22** on the observed cytotoxicity.[34,35]

Phenol **18** with GI_{50} values of 1.4–3.2 μM was nearly equipotent with **16**, and the methyl ethers **19** and **20** showed a slight drop in activity relative to **4** with GI_{50} values ranging from 4.1 to 14 and 5.3 to 7.1 μM, respectively.

These data suggest that the phenol-OH moiety is not pivotal to activity. The combination of O-methylation and introduction of a $-CF_3$ moiety rendered **21** insoluble in the assay medium, however the phenol **22** demonstrated enhanced cytotoxicity across the panel of cell lines examined with GI_{50} values of 0.2–2.9 μM, with the highest level of activity noted with the BE2-C cell line.

Following the promising results of the anthrapyranone compounds (4-pyranone D-ring, Table 1) we investigated a series of D-ring 2-pyranones to determine if this isomer had an effect on the biological activity. This series of compounds were prepared through a domino alkyne insertion/carbonylation/Nu-acylation reaction, described in our earlier publication (Scheme 3).[21] We have found in previous investigations approached using palladium mediated domino reactions to be effective for rapid ring formation and sub-structural diversity.[36–40]

In most cases under our reaction conditions the regioisomer **24** predominated in favour of compound **25**. Moreover, in many of our reactions involving various alkynes, the regioisomer **25** was not observed. For example, the specific formation of regioisomer **41**, confirmed by X-ray crystallographic studies (Fig. 3), is the sole product of the reaction with TMS–acetylene.

The simple *n*-hexyl derivatives **26** and **27** displayed poor growth inhibition, neither of these analogues progressing to a full dose response evaluation. The nitrile derivative **29** displayed only moderate cytotoxicity (GI_{50} 3.2–22 μM), however the isopropyl derivative **28** was relatively inactive (Table 2).

In most of the remaining 2-pyranone cases (Table 2) the activity was weak to moderate at ca. 10–40 μM. These systems also seemed not to indicate a clear difference in activity depending on the position of the R group (i.e., if the isomer **24** or **25** was tested) as shown in derivatives **34**–**37**. The exception to the observed moderate activity in these 2-pyranone examples was found in the slight improvement in potency of the A ring benzylated derivative **33**. We believe this may simply be driven by the higher lipophilicity of the OBn derivative compared to the O^iPr potentially leading to greater cell permeability.

Given the D ring 2-pyranone system overall resulted in no potency enhancements, we sought an alternative ring system to confirm if the earlier evaluated 4-pyranone ring system was essential for potent biological activity. In this regard our attention turned to the installation of a furan moiety to an anthracenone core. From a synthetic standpoint, these analogues were also of interest as they

Table 1
Growth inhibition (GI_{50}, μM) of several anthrapyran-4-one derivatives against a panel of cancer cell lines[a]

Compd[b]	HT29[c]	U87[d]	MCF-7[e]	A2780[f]	H460[g]	A431[h]	Du145[i]	BE2-C[j]	SJ-G2[d]	MIA[k]	SMA[l]
4	2.0 ± 0.38	0.99 ± 0.13	1.3 ± 0.20	0.29 ± 0.01	2.1 ± 0.31	0.95 ± 0.12	0.84 ± 0.17	0.17 ± 0.04	0.8 ± 0.25	0.9 ± 0.16	0.16 ± 0.05
8	—	—	—	—	—	—	—	—	—	—	—
12	—	—	—	—	—	—	—	—	—	—	—
14	4.8 ± 0.62	8.7 ± 3.7	4.3 ± 0.88	5.8 ± 1.5	6.9 ± 2.5	5.7 ± 0.77	1.9 ± 0.000	2.2 ± 0.15	16 ± 7.3	3.4 ± 0.36	3.9 ± 1.9
16	1.6 ± 0.12	3.4 ± 0.12	1.4 ± 0.07	1.6 ± 0.23	3.9 ± 0.20	1.8 ± 0.07	1.5 ± 0.06	5.9 ± 0.21	4.7 ± 0.99	2.0 ± 0.34	1.7 ± 0.20
17	Insoluble										
18	3.2 ± 0.94	2.8 ± 0.72	1.8 ± 0.06	2.4 ± 0.22	1.4 ± 0.27	1.6 ± 0.10	1.2 ± 0.15	1.8 ± 0.26	1.7 ± 0.13	1.7 ± 0.15	1.5 ± 0.19
19	4.5 ± 0.25	14 ± 4.7	4.1 ± 0.20	5.3 ± 0.23	4.8 ± 0.18	5.7 ± 0.35	4.8 ± 0.34	4.1 ± 0.033	4.3 ± 0.15	5.4 ± 0.32	6.5 ± 1.3
20	5.5 ± 0.058	6.4 ± 0.42	6.4 ± 0.33	6.4 ± 0.20	5.3 ± 0.31	6.6 ± 0.15	5.3 ± 0.56	6.1 ± 0.000	5.3 ± 0.17	7.1 ± 0.32	6.0 ± 0.36
21	Insoluble										
22	0.94 ± 0.18	2.9 ± 0.85	0.28 ± 0.035	0.34 ± 0.027	0.87 ± 0.46	0.51 ± 0.20	0.29 ± 0.012	0.20 ± 0.018	0.49 ± 0.007	0.28 ± 0.000	0.48 ± 0.17

[a] All compounds were initially assayed at 25 μM in each cell line for growth inhibition and if potent a full dose response analysis was conducted from which the GI_{50}, μM value was calculated. This value is the concentration of compound that induces 50% growth inhibition after 72 h exposure. (—) indicates the compound had low growth inhibition level in the initial assay.
[b] All assays were completed in triplicate with the standard error indicated.
[c] Colon carcinoma.
[d] Glioblastoma.
[e] Breast carcinoma.
[f] Ovarian carcinoma.
[g] Lung carcinoma.
[h] Skin carcinoma.
[i] Prostate carcinoma.
[j] Neuroblastoma.
[k] Pancreatic carcinoma.
[l] Spontaneous murine astrocytoma.

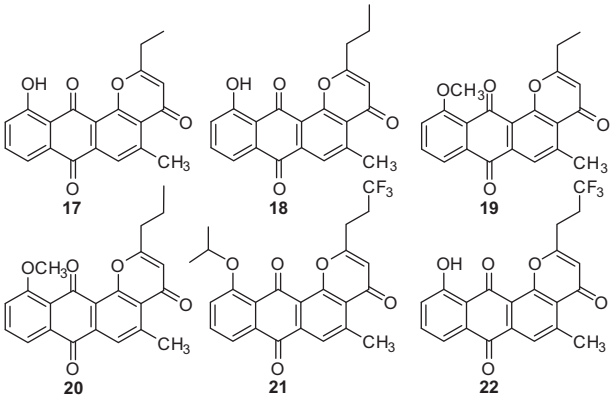


Figure 2. Newly prepared anthrapyranone analogues.

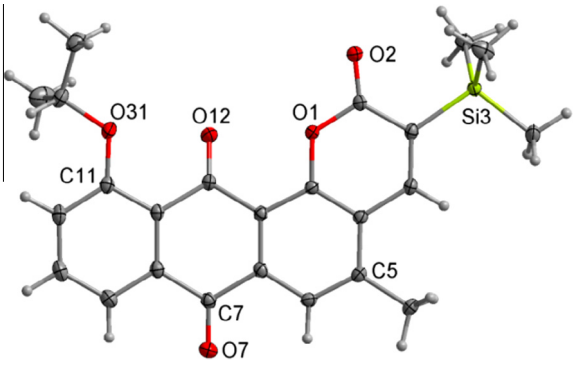
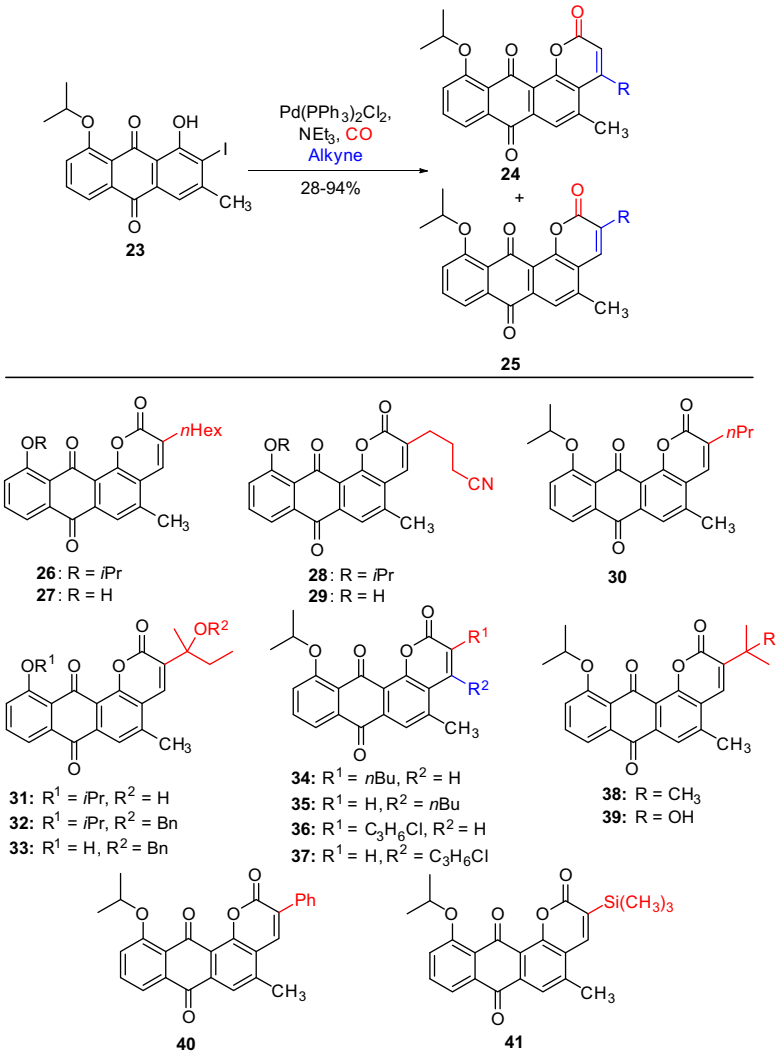


Figure 3. Structure of the compound **41**. Ellipsoids have been drawn at the 50% probability level (CCDC No. 931990).

are poorly represented in the literature.[41,42] Additionally, the furan oxygen atom would be in a similar position to the previous analogues and it was believed that C2 group on the furan would occupy a similar region of space as the C2 position of the 4-pyranone. We envisaged these compounds could be prepared through a Castro–Stephens protocol.[43–46] In several examples *ortho*-substituted halides had previously been used in heterocycle synthesis including both furans and isocoumarins, while in situ quenching of these reactions have been reported to produce pyrazoles.[24,47–50] Initially, a range of copper acetylides were prepared simply by treating an alcoholic solution of the terminal alkynes with a mixture of excess CuCl in NH_4OH (28%) in EtOH. Given the inherent



Scheme 3. Products from the domino alkyne insertion/carbonylation/Nu-acylation reaction.

Table 2
Growth inhibition (GI_{50}, μM) of the various anthrapyran-2-ones in a panel of human cancer cell lines[a]

Compd[b]	HT29[c]	U87[d]	MCF-7[e]	A2780[f]	H460[g]	A431[h]	Du145[i]	BE2-C[j]	SJ-G2[d]	MIA[k]	SMA[l]
26	—	—	—	—	—	—	—	—	—	—	—
27	—	—	—	—	—	—	—	—	—	—	—
28	—	—	—	—	—	—	—	—	—	—	—
29	14 ± 2.7	11 ± 3.5	12 ± 3.4	10 ± 1.7	9.0 ± 1.6	12 ± 0.33	3.2 ± 0.52	11 ± 4.3	22 ± 9.5	15 ± 6.7	9.8 ± 6.2
30	—	—	—	—	—	—	—	—	—	—	—
31	11 ± 0.29	25 ± 2.2	16 ± 0.67	19 ± 0.33	16 ± 0.33	15 ± 0.00	26 ± 1.3	22 ± 2.1	9.0 ± 1.8	14 ± 1.2	23 ± 1.2
32	—	—	—	—	—	—	—	—	—	—	—
33	5.6 ± 0.10	14 ± 1.9	5.3 ± 0.70	7.0 ± 0.13	5.1 ± 0.13	4.0 ± 0.29	8.8 ± 0.31	6.7 ± 0.40	3.9 ± 0.57	3.9 ± 0.41	6.1 ± 0.07
34	—	—	—	—	—	—	—	—	—	—	—
35	18 ± 1.3	14 ± 3.8	15 ± 1.7	9.5 ± 1.5	19 ± 1.5	20 ± 1.0	11 ± 1.5	13 ± 3.3	13 ± 2.9	13 ± 2.0	12 ± 3.6
36	15 ± 2.0	16 ± 0.88	19 ± 4.3	21 ± 1.8	19 ± 1.5	17 ± 2.0	20 ± 1.2	33 ± 6.6	15 ± 3.4	20 ± 4.3	19 ± 1.3
37	24 ± 2.6	12 ± 2.7	8.8 ± 1.6	12 ± 3.2	25 ± 2.6	12 ± 3.8	24 ± 2.7	27 ± 2.7	27 ± 4.7	17 ± 4.0	16 ± 3.6
38	13 ± 0.88	17 ± 0.88	14 ± 1.3	12 ± 0.33	20 ± 1.5	17 ± 0.58	29 ± 6.1	33 ± 2.4	12 ± 2.0	12 ± 0.33	12 ± 0.33
39	30 ± 0.58	30 ± 0.58	20 ± 1.2	28 ± 1.7	22 ± 2.3	19 ± 1.2	40 ± 3.8	27 ± 3.9	14 ± 1.2	23 ± 3.2	30 ± 0.58
40	—	—	—	—	—	—	—	—	—	—	—
41	11 ± 0.44	19 ± 1.7	13 ± 1.3	13 ± 1.2	21 ± 1.2	19 ± 0.67	27 ± 1.7	28 ± 5.8	14 ± 3.4	11 ± 0.44	11 ± 0.00

[a] All compounds were initially assayed at 25 μM in each cell line for growth inhibition and if potent a full dose response analysis was conducted from which the GI_{50}, μM value was calculated. This value is the concentration of compound that induces 50% growth inhibition after 72 h exposure. (—) indicates the compound had a low growth inhibition level in the initial assay.
[b] All assays were completed in triplicate with the standard error indicated.
[c] Colon carcinoma.
[d] Glioblastoma.
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[f] Ovarian carcinoma.
[g] Lung carcinoma.
[h] Skin carcinoma.
[i] Prostate carcinoma.
[j] Neuroblastoma.
[k] Pancreatic carcinoma.
[l] Spontaneous murine astrocytoma.

poor solubility of cuprous acetylides these species were analysed by elemental analysis and used without further purification (ESI†).

Following the original Castro–Stevens protocol we trailed reactions in pyridine at high temperatures in order to solubilise the copper acetylide. Unfortunately, in each of these examples a large amount of decomposition was also observed. Given this concern we attempted to carry out these reactions at a lower temperature by first improving the solubility of the copper acetylide through the addition of dimethylethylenediamine (DMEDA), a ligand commonly used in the copper catalysed Ullmann–Goldberg condensation.[51]

The result from this reaction modification led to a collection of furans containing electron withdrawing and donating groups being formed in a range of yields (Table 3 and Fig. 4). The aliphatic, ketone and nitrile copper acetylides performed most optimally in the reaction (85–54% yield).

As expected using the alkyl alcohol and the alkyl chloride as coupling partners resulted in a lower yield of the furan. Following the preparation of compound **56** a simple oxidation with Dess–Martin periodinane allowed for the synthesis of the corresponding ketone **58**. As previously described both of these compounds could be deprotected using either BCl_3 or *p*-TsOH to the phenols **57** and **59** (ESI†).

Through the coupling partner diversity of the previously described reaction (Table 3) we prepared the anthracenefurans containing a C2 position hydrogen bond donor or acceptor groups, as well as aliphatic tethers. Anthracenefurans **43**, **45**, **47** (C2 phenyl substitution confirmed by X-ray crystallographic studies, Fig. 5) and **48** displayed low levels of cytotoxicity (Table 4).

The other analogues were effective as cell growth inhibition agents throughout the various cell lines with a few exceptions. The simple 2-alkyl substituted furans, as the free phenols, had moderate (**44**, GI_{50} values of 9.3–32 μM) and good (**46**, GI_{50} values of 0.86–6.6 μM) cell growth inhibition, but were essentially inactive as the corresponding isopropyl ethers **43** and **45**. Shortening of the alkyl chain improved the activity given the *n*-propyl **45** displayed good sub-micromolar activity against BE2-C (0.88 μM) and Du145 (0.86 μM) cell lines. Surprisingly, the benzoyl derivative **49** (Fig. 5), also containing an isopropoxy group on the A-ring, was potent and the phenol **50** was not. Possibly the increase in lipophilicity of derivative **49** has an influence on the activity of this compound. This substrate is particularly interesting given its potency in the BE2-C and Du145 cell lines at 0.95 and 0.83 μM respectively.

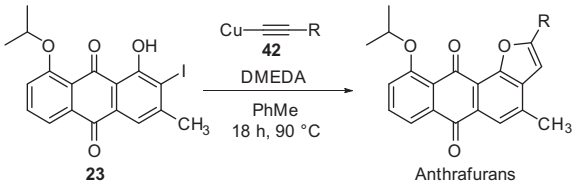
The butanyl-nitrile and the *n*-propyl chloride derivatives, **52** and **54**, both bearing an A-ring phenol had modest to high activity across the cell lines evaluated with GI_{50} values of 0.46–32 and 0.59–23 μM, respectively. The cyano-substituted compound **52** showed strong growth inhibition against Du145 cells of 0.46 μM. The C2 alkyl chloride moiety (in **53** and **54**) was chosen as a mimic similar to the electrophilic ability of epoxide moiety contained within pluramycin A (**1**).

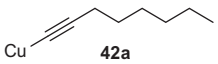
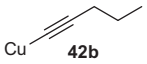
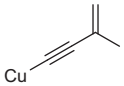
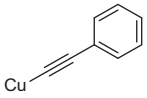
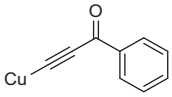
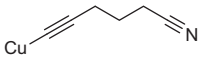
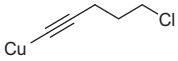
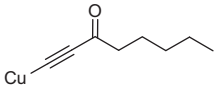
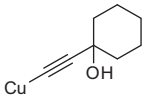
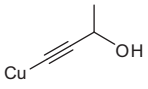
Thus, this was expected to undergo a similar alkylation reaction with the base guanine. In most of the cell lines, **54** had an improved activity (GI_{50} values of 0.38–1.9 μM, on exclusion of SJ-G2 cell line with GI_{50} = 37 μM) compared to the simple alkyl derivative **46** (GI_{50} values of 0.86–6.6 μM). Again the growth inhibition activity of anthracenefuran **54** in BE2-C was excellent at 0.38 μM. Of the ketone containing compounds (**55**, **58** and **59**) the derivative **55** was the most effective at inhibiting cell growth with GI_{50} values of 0.75–6.8 μM. Compounds **56** and **57**, having a hydrogen-bond donor in the side-chain, exhibited moderate GI_{50} values of 14–35 and 7.3–28 μM, respectively.

2. Conclusions

In this study we have designed new synthetic pathways to three anthracenone-pyranones and anthracenone-furans from related

Table 3
Synthesis of anthracene-furans through a Castro–Stephens reaction



Entry	Copper acetylide	Furan yield[a] (%)	Product
1	 42a	85	**43**
2	 42b	70	**45**
3	 42c	0	–
4	 42d	64	**47**
5	 6	54	**49**
6	 42e	80	**51**
7	 42f	49	**53**
8	 42g	65	**55**
9	 42i	13	–
10	 42j	27	**56**

[a] Aryl iodide **23**, copper acetylide (1.1–1.5 equiv) and DMEDA, (3.5 equiv), toluene (5 mL), 90 °C, 18 h.

aryl iodide precursors. These procedures provided a series of anthracenone containing compounds exhibiting good to modest growth inhibition in a range of cancer cell lines. Given these results, it is evident that the type of D-ring *O*-heterocycle influences the cytotoxic effects of these normally DNA-interchelating class of compounds. Among the forty four compounds tested, those which displayed potent activity against a variety of tumour cells, were the natural product BE-26554A (**4**) and its alkene precursor **16**. Other derivatives of note were the potent CF_3-alkyl anthracenone-pyranone **22**, and the anthracenone-furan derivative **54** showing 0.20 μM and 0.38 μM growth inhibition respectively in the BE2-C neuroblastoma cell line.

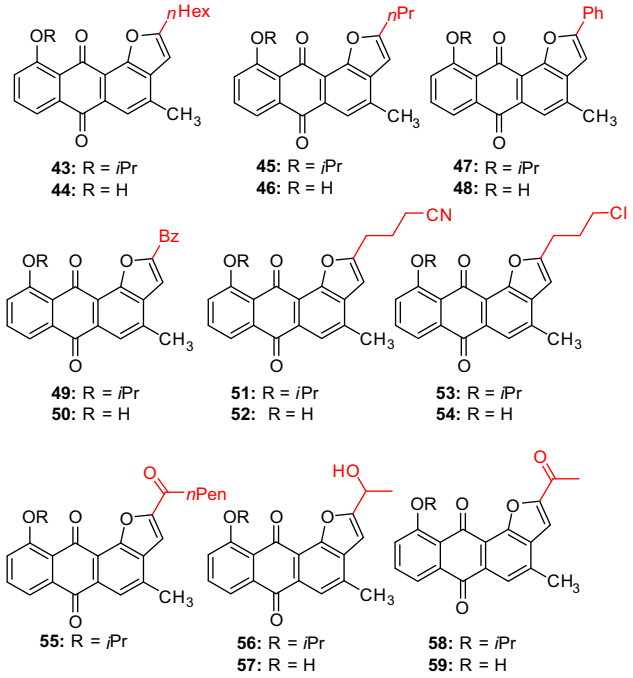


Figure 4. Prepared novel anthracenone-furan derivatives.

3. Experimental

3.1. General protocol

Starting materials and reagents were available from Sigma–Aldrich or Merck chemical companies. All reactions were performed under argon and at ambient temperature unless stated otherwise. All solvents used in reactions were anhydrous unless noted otherwise. Anhydrous solvents were distilled over the appropriate drying agent or acquired from a Pure Solv 5-Mid Solvent Purification System (Innovative Technology Inc.). ^{1}H and ^{13}C Nuclear Magnetic Resonance (NMR) spectra were acquired on a Varian 300, Varian 400 or a Bruker AV500 Bruker AV600 spectrometer and all signals δ are reported in parts per million (ppm). ^{1}H and ^{13}C assignments were made with the aid of DEPT, COSY, HSQC and HMBC sequences where appropriate. Chemical shifts were referenced to the residual (partially) undeuterated solvents and reported in parts per million (ppm). Infrared spectra samples were prepared using the KBr disc method or measured directly with an ATR adapter and acquired on a Perkin Elmer Spectrum One spectrometer at 2 cm^{-1} resolution. Melting points were recorded on a Reichart heated-stage microscope. The reported retention factors (R_f) were acquired via Thin Layer Chromatography (TLC) performed on Merck silica gel 60 F254 pre-coated aluminium sheets. Column chromatography was performed using silica gel 60 (0.04–0.063) supplied by Merck. Chromatography solvents were distilled prior to use. High pressure reactions were carried out in a high-pressure laboratory autoclave Model I from Carl Roth. DMEDA is *N*,*N*′-dimethylethylenediamine. Compounds **4**, **9**, **13**–**16**, **23**, **26**–**41** have been prepared and characterised previously.[21] Non-1-yn-3-one (**10**) was prepared according to the procedure by Braddock et al.[52]

3.1.1. General procedure for the deprotection of the isopropyl group; Method A

$TsOH{\cdot}H_2O$ (1.5 equiv) was added to a magnetically stirred solution or suspension of isopropylether–anthrapyranone in xylene (0.01–0.04 mM) and heated to reflux for 5–20 min monitoring

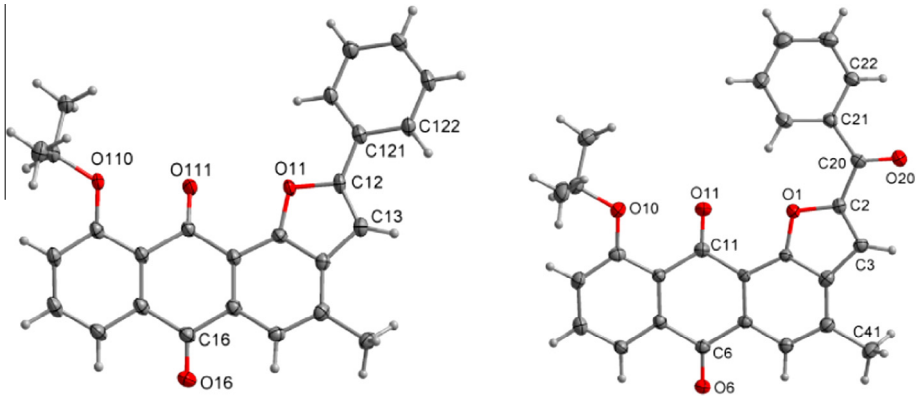


Figure 5. Structures of the compounds **47** (molecule 1 only) (CCDC No. 1032509) and **49** (CCDC No. 1032511).

Table 4
Growth inhibition (GI_{50}, μM) of the various anthrafuranones in a panel of human cancer cell lines

Compd[b]	HT29[c]	U87[d]	MCF-7[e]	A2780[f]	H460[g]	A431[h]	Du145[i]	BE2-C[j]	SJ-G2[d]	MIA[k]	SMA[l]
43	—	—	—	—	—	—	—	—	—	—	—
44	17 ± 1.5	25 ± 2.6	15 ± 2.5	12 ± 2.2	17 ± 1.2	18 ± 0.58	25 ± 2.0	21 ± 1.9	32 ± 3.4	13 ± 2.4	9.3 ± 1.8
45	—	—	—	—	—	—	—	—	—	—	—
46	1.2 ± 0.62	6.6 ± 1.7	2.2 ± 0.21	1.5 ± 0.15	3.1 ± 0.63	2.3 ± 0.09	0.86 ± 0.032	0.88 ± 0.035	1.0 ± 0.065	1.7 ± 0.49	1.3 ± 0.17
47	—	—	—	—	—	—	—	—	—	—	—
48	—	—	—	—	—	—	—	—	—	—	—
49	1.4 ± 0.13	2.3 ± 0.49	1.1 ± 0.26	2.1 ± 0.44	2.9 ± 0.57	1.77 ± 0.09	0.95 ± 0.13	0.83 ± 0.14	36 ± 1.7	1.7 ± 0.31	2.2 ± 0.12
50	—	—	—	—	—	—	—	—	—	—	—
51	11 ± 3.5	6.1 ± 0.10	5.9 ± 2.3	6.4 ± 0.83	9.4 ± 0.83	9.8 ± 1.1	7.7 ± 1.0	23 ± 4.7	8.4 ± 1.3	10 ± 1.4	10 ± 1.7
52	1.9 ± 0.09	11 ± 3.55	4.7 ± 0.82	6.5 ± 2.40	15 ± 3.2	13 ± 0.67	0.46 ± 0.10	0.99 ± 0.11	32 ± 6.6	2.6 ± 1.1	5.4 ± 3.0
53	18 ± 0.88	18 ± 1.0	13 ± 1.9	11 ± 0.33	27 ± 2.2	23 ± 3.8	25 ± 5.0	43 ± 5.1	25 ± 3.8	34 ± 2.7	22 ± 2.5
54	1.9 ± 0.05	0.97 ± 0.24	0.66 ± 0.02	0.45 ± 0.009	1.9 ± 0.82	0.59 ± 0.03	0.44 ± 0.02	0.38 ± 0.02	37 ± 2.6	0.55 ± 0.003	0.69 ± 0.08
55	0.88 ± 0.003	4.2 ± 1.2	2.0 ± 0.07	2.3 ± 1.4	6.8 ± 2.5	1.4 ± 0.09	0.85 ± 0.03	0.75 ± 0.13	4.2 ± 0.89	1.1 ± 0.16	1.8 ± 0.48
56	24 ± 3.5	35 ± 2.8	24 ± 2.7	16 ± 1.0	17 ± 1.7	19 ± 1.0	28 ± 3.2	20 ± 1.0	14 ± 0.67	19 ± 0.58	29 ± 2.8
57	13 ± 1.7	20 ± 2.3	21 ± 1.5	7.3 ± 0.33	17 ± 3.4	9.0 ± 2.1	28 ± 5.7	19 ± 4.6	17 ± 2.4	15 ± 2.3	12 ± 2.3
58	9.7 ± 0.67	8.4 ± 1.3	3.5 ± 0.27	5.0 ± 0.50	17 ± 0.67	5.8 ± 1.1	1.9 ± 0.13	4.6 ± 0.78	2.2 ± 0.058	9.7 ± 0.88	2.3 ± 0.29
59	4.7 ± 0.95	5.5 ± 1.8	2.1 ± 0.13	2.0 ± 0.067	9.6 ± 1.2	4.8 ± 1.5	2.0 ± 0.17	2.9 ± 0.43	1.8 ± 0.033	9.5 ± 0.29	1.5 ± 0.21

[a] All compounds were initially assayed at 25 μM in each cell line for growth inhibition and if potent a full dose response analysis was conducted from which the GI_{50}, μM value was calculated. This value is the concentration of compound that induces 50% growth inhibition after 72 h exposure. (—) indicates the compound had a low cytotoxicity level in the initial assay.
[b] All assays were completed in triplicate with the standard error indicated.
[c] Colon carcinoma.
[d] Glioblastoma.
[e] Breast carcinoma.
[f] Ovarian carcinoma.
[g] Lung carcinoma.
[h] Skin carcinoma.
[i] Prostate carcinoma.
[j] Neuroblastoma.
[k] Pancreatic carcinoma.
[l] Spontaneous murine astrocytoma.

every 5 min by tlc (10% EtOAc/PhMe). The reaction mixture was cooled to room temperature, diluted with $NaHCO_3$ (satd aq) and extracted with CH_2Cl_2 (20 mL × 3), dried over $MgSO_4$ and concentrated under reduced pressure. The residue was then purified by column chromatography (silica, 100% PhMe → 20% EtOAc/PhMe) to give the highly coloured phenol as orange to yellow crystalline solids.

3.1.2. General procedure for the deprotection of the isopropyl group, Method B

BCl_3 (1 M in heptane, 2 equiv) was added dropwise to a magnetically stirred solution of the isopropyl ether (1 equiv) in CH_2Cl_2 at −40 °C. The ensuing mixture was stirred for 15 min before quenching with $NaHCO_3$ (sats 20 mL) and warming to room temperature. The mixture was treated with water and the solution was extracted with CH_2Cl_2, dried over $MgSO_4$, concentrated and the residue purified by column chromatography.

3.1.3. General procedure for the methylation of phenols

MeI (2.0 equiv) was added to a magnetically stirred solution of phenol–anthraquinone and K_2CO_3 (3 equiv) in DMF (0.01–0.04 mM) and heated to 40 °C for 16 h. The reaction mixture was cooled to room temperature, diluted with H_2O and extracted with CH_2Cl_2 (20 mL × 3), dried over $MgSO_4$ and concentrated under reduced pressure. The resulting residue was then purified by column chromatography (silica, 100% PhMe → 30% EtOAc/PhMe) to give the methylated phenol.

3.1.3.1. 8-Isopropoxy-3-methyl-9,10-dioxo-2-(3-oxo-3-phenylprop-1-yn-1-yl)-9,10-dihydroanthracen-1-yl benzoate (7). A mixture of anthraquinone iodide **5** (277 mg, 0.526 mmol) and (3-oxo-3-phenylprop-1-yn-1-yl)copper (**6**) (152 mg, 0.786 mmol) in DMF (20 mL) was heated to reflux for 1 h. The reaction mixture was concentrated and purified by column chromatography (silica, 0–5% EtOAc in PhMe) to give the

anthraquinone **7** (207 mg, 0.392 mmol, 75%) as an orange oil. R_f = 0.49 (5% EtOAc in PhMe). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.42–8.33 (m, 2H), 8.10 (d, J = 0.7 Hz, 1H), 8.06–7.99 (m, 2H), 7.87 ('dd', J = 7.7, 1.1 Hz, 1H), 7.70 ('ddd', J = 7.1, 2.6, 1.3 Hz, 1H), 7.62 ('dd', J = 8.3, 7.7 Hz, 1H), 7.60–7.53 (m, 2H), 7.46 ('tt', J = 7.5, 1.3 Hz, 1H), 7.31–7.28 (m, 1H), 7.12 (dd, J = 8.3, 7.5 Hz, 2H), 4.49 (hept, J = 6.1 Hz, 1H), 2.74 (d, J = 0.6 Hz, 3H), 1.28 (b'dd', J = 13.5, 6.4 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 182.8 (C=O), 180.5 (C=O), 177.3 (C=O), 164.9 (C-Ar), 158.7 (C-Ar), 152.4 (C-Ar), 149.0 (C-Ar), 136.4 (C-Ar), 135.1 (C-Ar), 134.5 (CH-Ar), 134.3 (C-Ar), 134.3 (CH-Ar), 133.9 (CH-Ar), 130.9 (2 × CH-Ar), 129.6 (2 × CH-Ar), 129.5 (C-Ar), 128.7 (2 × CH-Ar), 128.5 (2 × CH-Ar), 125.5 (CH-Ar), 125.3 (C-Ar), 124.7 (C-Ar), 123.9 (CH-Ar), 122.7 (C-Ar), 120.1 (CH-Ar), 97.2 (C≡C), 84.5 (C≡C), 73.9 (CH), 22.0 (2 × CH_3), 21.6 (CH_3). IR (Neat, cm^{-1}): 2979 (C-H), 2930 (C-H), 2201 (C≡C), 1742 (C=O), 1674 (C=O), 1638, 1583, 1450. HRMS APCI: (m/z) calculated for $C_{34}H_{25}O_6$ [M+H]$^+$: 529.1651; found: 529.1663.

3.1.3.2. 11-Hydroxy-5-methyl-2-phenyl-4*H*-naphtho[2,3-*h*]chromene-4,7,12-trione (8). H_2SO_4 (98%, 5 mL) was added to anthraquinone **7** (122 mg, 0.231 mmol) and slowly heated to 60 °C for 1 h. The mixture was poured carefully into H_2O (50 mL) and extracted with CH_2Cl_2 (3 × 30 mL), dried ($MgSO_4$), concentrated and purified by column chromatography (silica, 0–2% EtOAc in PhMe) to give the anthrapyranone **8** (49 mg, 0.127 mmol, 55%) as a yellow solid. R_f = 0.33 (2% EtOAc in PhMe). Mp ⩾260 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.99 (s, 1H), 8.32 (dd, J = 6.4, 2.4 Hz, 2H), 8.11 (s, 1H), 7.84 (dt, J = 7.4, 1.0 Hz, 1H), 7.70 (t, J = 7.7 Hz, 1H), 7.65–7.58 (m, 3H), 7.41–7.37 (m, 1H), 6.94 (s, 1H), 3.06 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 187.6 (C=O), 182.1 (C=O), 179.4 (C=O), 163.4 (C-Ar), 162.8 (CH-Ar), 156.6 (C-Ar), 150.0 (C-Ar), 136.6 (CH-Ar), 136.3 (C-Ar), 132.5 (C-Ar), 132.3 (CH-Ar), 130.8 (C-Ar), 129.4 (2 × CH-Ar), 127.1 (2 × CH-Ar), 126.9 (C-Ar), 126.1 (CH-Ar), 125.6 (CH-Ar), 120.1 (C-Ar), 119.6 (CH-Ar), 117.0 (C-Ar), 109.1 (CH-Ar), 24.4 (Ar-CH_3). IR (KBr pellet, cm^{-1}): 3463 (O-H), 3065 (C-H), 2924 (C-H), 2852 (C-H), 2651 (C=O), 1636 (C=O), 1462. HRMS EI$^+$: (m/z) calculated for $C_{24}H_{14}O_5$ [M+H]$^+$: 382.0841; found: 382.0844.

3.1.3.3. 1-(Benzyloxy)-8-isopropoxy-3-methyl-2-(3-oxooct-1-yn-1-yl)anthracene-9,10-dione (11) through 1-(benzyloxy)-2-(3-hydroxynon-1-yn-1-yl)-8-isopropoxy-3-methylanthracene-9,10-dione. A warmed (60 °C) degassed solution of Na_2CO_3 (310 mg, 2.92 mmol) in H_2O (4 mL) was added to a preheated well stirred mixture of aryl iodide **9** (500 mg, 0.976 mmol), $Pd(PPh_3)_2Cl_2$ (68 mg, 0.098 mmol) and propargyl alcohol **10** (272 mg, 1.95 mmol) in dioxane (15 mL). The ensuing solution was then heated to 80 °C for 3 h. The reaction mixture was concentrated and purified by column chromatography (silica, 0 → 10% EtOAc in PhMe) to give the title anthraquinone alcohol (207 mg, 0.392 mmol, 75%) as an orange oil. R_f = 0.36 (10% EtOAc in PhMe). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (s, 1H), 7.76 (d, J = 7.6 Hz, 1H), 7.65 (d, J = 7.1 Hz, 2H), 7.54 (t, J = 8.0 Hz, 1H), 7.35 ('t', J = 7.3 Hz, 2H), 7.30 (m, J = 7.2 Hz, 1H), 7.23 (m, J = 10.1 Hz, 1H), 5.20 (s, 2H), 4.61 (hept, J = 6.1 Hz, 1H), 4.53 (bt, J = 6.7 Hz, 1H), 2.45 (s, 3H), 1.99 (s, 1H), 1.74–1.59 (m, 3H), 1.40 (m, 6H), 1.24 (d, J = 10.8 Hz, 8H), 0.83 (t, J = 6.7 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 183.6 (C=O), 182.2 (C=O), 159.7 (C-Ar), 158.0 (C-Ar), 146.9 (C-Ar), 137.6 (CH-Ar), 135.2 (C-Ar), 133.8 (CH-Ar), 133.0 (C-Ar), 128.6 (2 × CH-Ar), 128.4 (2 × CH-Ar), 128.1 (CH-Ar), 127.0 (C-Ar), 125.7 (C-Ar), 125.6 (C-Ar), 123.3 (CH-Ar), 122.5 (CH-Ar), 119.5 (CH-Ar), 103.5 (C-Ar), 79.3 (C≡C), 76.3 (C≡C), 73.1 (O-CH(CH_3)$_2$), 63.2 (Ph-CH_2), 62.9 (CH-OH), 37.8 (HO-CH_2), 37.6 (HO-CH_2), 31.8 (CH_2), 29.1 (CH_2), 29.0 (CH_2), 25.3 (CH_2), 25.1 (CH_2), 22.7 (CH_2), 22.2 (2 × CH_3), 21.5 (Ar-CH_3), 14.2 (CH_3); IR (Neat, cm^{-1}): 3324 (O-H), 2925 (C-H), 2857 (C-H), 1672 (C=O), 1581 (C=O), 1322, 1281. HRMS APCI: (m/z) calculated for $C_{34}H_{37}O_5$ [M+H]$^+$: 525.2641; found: 525.2651.

Dess–Martine Periodinane (455 mg, 1.13 mmol) was added portion-wise to a solution of anthraquinone alcohol (478 mg, 0.867 mmol) in CH_2Cl_2 (15 mL) and the mixture stirred at room temperature for 2 h. The resulting mixture was quenched by the simultaneous addition of $Na_2S_2O_3$ (1 M, 10 mL) and $NaHCO_3$ (satd 10 mL) and stirred for 30 min. The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (2 × 30 mL). The combined organic layers were dried over $MgSO_4$, concentrated and purified by column chromatography (silica, 0 → 5% EtOAc in PhMe) to give the anthraquinone **11** (400 mg, 0.786 mmol, 88%) as an orange oil. R_f = 0.26 (5% EtOAc in PhMe). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.88 (d, J = 0.7 Hz, 1H), 7.81 (dd, J = 7.7, 1.1 Hz, 1H), 7.71–7.66 (m, 2H), 7.61 (dd, J = 8.3, 7.7 Hz, 1H), 7.42–7.36 (m, 2H), 7.36–7.30 (m, 2H), 5.25 (s, 2H), 4.67 (hept, J = 6.1 Hz, 1H), 2.58 (s, 3H), 2.56 (t, J = 7.3 Hz, 2H), 1.63–1.69 (m, 2H), 1.46 (d, J = 6.0 Hz, 6H), 1.22–1.33 (m, 6H), 0.88 (t, J = 7.0 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 187.8 (C=O), 183.4 (C=O), 181.8 (C=O), 161.2 (C-Ar), 158.1 (C-Ar), 148.4 (C-Ar), 136.9 (C-Ar), 135.1 (C-Ar), 134.7 (C-Ar), 134.0 (CH-Ar), 129.0 (2 × CH-Ar), 128.5 (2 × CH-Ar), 128.4 (CH-Ar), 126.9 (C-Ar), 125.4 (C-Ar), 123.4 (C-Ar), 123.0 (C-Ar), 122.5 (CH-Ar), 119.5 (CH-Ar), 98.2 (C≡C), 84.1 (C≡C), 73.0 (Ph-CH_2), 45.8 (COH), 31.6 (CH_2), 28.8 (CH_2), 24.1 (CH_2), 22.6 (CH_2), 22.2 (2 × CH_3), 21.5 (Ar-CH_3), 14.13 (CH_3). IR (Neat, cm^{-1}): 2957 (C-H); 2929 (C-H), 2858 (C-H), 2195 (C≡C), 1670 (C=O), 1582, 1262. HRMS APCI: (m/z) calculated for $C_{34}H_{37}O_5$ [M+H]$^+$: 525.2641; found: 525.2665.

3.1.3.4. 11-Hydroxy-5-methyl-2-hexyl-4*H*-naphtho[2,3-*h*]chromene-4,7,12-trione (12). H_2SO_4 (98%, 5 mL) was added to anthraquinone **7** (100 mg, 0.236 mmol) and slowly stirred at room temperature for 4 h. The mixture was poured carefully into H_2O (50 mL) and extracted with CH_2Cl_2 (3 × 30 mL), dried ($MgSO_4$), concentrated and purified by column chromatography (silica, 0 → 2% EtOAc in PhMe) to give the anthrapyranone **12** (30 mg, 0.078 mmol, 33%) as a yellow solid. R_f = 0.33 (2% EtOAc in PhMe). Mp = 175–178 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.87 (s, 1H), 8.04 (s, 1H), 7.80 (dd, J = 7.5, 1.1 Hz, 1H), 7.68–7.64 (m, 1H), 7.35 (dd, J = 8.4, 1.2 Hz, 1H), 6.25 (s, 1H), 3.01 (s, 3H), 2.74 (t, J = 7.6 Hz, 2H), 1.93–1.86 (m, 2H), 1.46 (d, J = 7.2 Hz, 2H), 1.39–1.33 (m, 4H), 0.91 (t, J = 7.0 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 187.4 (C=O), 182.1 (C=O), 179.3 (C=O), 169.7 (C-Ar), 162.7 (C-Ar), 156.9 (C-Ar), 149.8 (C-Ar), 136.4 (Ar-CH), 136.0 (C-Ar), 132.4 (C-Ar), 126.6 (C-Ar), 125.7 (Ar-CH), 125.4 (Ar-CH), 119.9 (C-Ar), 119.4 (Ar-CH), 117.0 (C-Ar), 112.2 (Ar-CH), 34.0 (CH_2), 31.6 (CH_2), 28.8 (CH_2), 26.5 (CH_2), 24.4 (CH_2), 22.6 (Ar-CH_3), 14.2 (CH_3). HRMS APCI: m/z calculated for $C_{24}H_{23}O_5$ [M+H]$^+$: 391.1545; found: 391.1596. IR (Neat, cm^{-1}) 3062 (C-H), 2954 (C-H), 2919 (C-H), 2852 (C-H), 1669 (C=O), 1651 (C=O), 1625 (C=O), 1583 (C=C), 1456, 1269, 776.

3.1.3.5. 2-Ethyl-11-hydroxy-5-methyl-4*H*-naphtho[2,3-*h*]chromene-4,7,12-trione (17). Anthra-4-pyranone **17** was prepared according to the general procedure for the deprotection of the isopropyl group, Method A, using the anthra-4-pyranone **14** (67 mg, 0.151 mmol) in xylene (5 mL). The anthrafuran **17** was obtained as orange crystals (53 mg, 0.131 mmol, 87%). R_f = 0.27 (10% EtOAc in PhMe); mp = 248–251 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.86 (s, 1H), 8.05 (s, 1H), 7.80 (dd, J = 7.5, 1.2 Hz, 1H), 7.69–7.63 (m, 1H), 7.35 (dd, J = 8.4, 1.2 Hz, 1H), 6.26 (s, 1H), 3.05–2.95 (m, 2H), 3.00 (s, 3H) 2.80 (q, J = 5.0 Hz, 2H), 1.44 (t, J = 5.0 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 187.4 (C=O), 182.1 (C=O), 179.4 (C=O), 170.6 (C-Ar), 162.7 (C-Ar), 156.8 (C-Ar), 149.9 (C-Ar), 136.4 (Ar-CH), 136.1 (C-Ar), 132.4 (C-Ar), 126.6 (C-

Ar), 125.7 (Ar-CH), 125.4 (Ar-CH), 119.9 (C-Ar), 119.4 (Ar-CH), 117.0 (C-Ar), 111.4 (Ar-CH), 27.4 (CH_2), 24.4 (Ar-CH_3), 11.0 (CH_3). HRMS APCI: calculated for $C_{20}H_{15}O_5$ $[M+H]^+$: 335.0919; found: 335.0906. IR (Neat, cm^{-1}) 2976 (C-H), 1646 (C=O), 1621 (C=O), 1262, 907.

3.1.4. General method for the synthesis of anthra-4-pyranones via β-ketosulfoxides

Piperidine (catalytic) was added to a solution of β-keto-sulfoxide (1 equiv) and aldehyde (2.0 equiv) in toluene (5 mL). The ensuing mixture was slowly heated to reflux for 2–3 h, cooled to room temperature and purified by column chromatography (silica, PhMe → ca. 10–20% EtOAc/PhMe) to give the product pyran-4-one generally as an orange-yellow solid.[21]

3.1.4.1. 11-Hydroxy-5-methyl-2-propyl-4*H*-naphtho[2,3-*h*]chromene-4,7,12-trione (18): Three steps through 11-isopropoxy-7,12-dimethoxy-5-methyl-2-propyl-4*H*-naphtho[2,3-*h*]chromen-4-one. Anthra-4-pyranone **18** was prepared according to the general procedure for the synthesis of anthra-4-pyranones via β-ketosulfoxides. β-Keto-sulfoxide **13** (189 mg, 0.513 mmol) and butyraldehyde (93 μL, 1.03 mmol) in toluene (5 mL) were added to the reaction flask. The anthra-4-pyranone dimethoxy anthracene was obtained as orange-yellow crystals (153 mg, 4.26 mmol, 83%). R_f = 0.25 (10% EtOAc in PhMe). Mp = 112–117 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86 (dd, J = 8.6, 0.9 Hz, 1H), 7.79 (d, J = 1.2 Hz, 1H), 7.45 (dd, J = 8.6, 7.6 Hz, 1H), 6.86 (d, J = 7.5 Hz, 1H), 6.33 (s, 1H), 4.83–4.72 (m, 1H), 4.03 (s, 3H), 3.96 (s, 3H), 2.96 (d, J = 1.1 Hz, 3H), 2.77 (t, J = 7.5 Hz, 2H), 1.95–1.86 (m, 2H), 1.52 (d, J = 6.0 Hz, 6H), 1.09 (t, J = 7.4 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 180.1 (C=O), 167.2 (C-Ar), 157.5 (C-Ar), 155.3 (C-Ar), 152.1 (C-Ar), 146.8 (C-Ar), 134.7 (C-Ar), 130.2 (C-Ar), 127.4 (CH-Ar), 126.2 (C-Ar), 120.4 (C-Ar), 120.0 (C-Ar), 119.7 (CH-Ar), 115.8 (C-Ar), 114.6 (CH-Ar), 113.1 (CH-Ar), 108.0 (CH-Ar), 71.0 ($OCH(CH_3)_2$), 63.6 (OCH_3), 62.8 (OCH_3), 35.8 (CH_2), 24.1 (2 × CH_3), 22.0 (Ar-CH_3), 20.1 (CH_2), 13.75 (CH_3). HRMS APCI: calculated for $C_{26}H_{28}O_5$, $[M+H]^+$; 421.2015; found: 421.2025. IR (Neat, cm^{-1}) 3092 (C-H), 2967 (C-H), 2935 (C-H), 1659 (C=O), 1630, 1363, 656.

3.1.4.2. 11-Isopropoxy-5-methyl-2-propyl-4*H*-naphtho[2,3-*h*]chromene-4,7,12-trione. HNO_3 (4 M, ca. 3.5 mL) was added gradually as a steady stream into stirred mixture of anthra-4-pyranone dimethoxy anthracene (197 mg, 0.485 mmol) and Ag(II)O (300 mg, 2.42 mmol) in 1,4-dioxane (7 mL) until all of the suspended Ag(II)O dissolved. The mixture was stirred for 15 min before H_2O (20 mL) was added. The mixture was extracted with CH_2Cl_2 (3 × 30 mL), washed with H_2O (100 mL), dried over $MgSO_4$, and the combined organic extracts concentrated and the residue purified by column chromatography (silica, 100% PhMe → 15% EtOAc/PhMe) to give the anthraquinone (157 mg, 0.403 mmol, 83%) as a yellow solid. R_f = 0.35 (10% EtOAc in PhMe). Mp = 204–206 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.83 (d, J = 0.5 Hz, 1H), 7.79 (dd, J = 7.6, 0.9 Hz, 1H), 7.59 (t, J = 8.1 Hz 1H), 7.31 (d, J = 8.1 Hz, 1H), 6.17 (s, 1H), 4.64 (hept, J = 6.1 Hz, 1H), 2.91 (s, 3H), 2.69 (t, J = 7.5 Hz, 2H), 1.93–1.85 (m, 2H), 1.45 (d, J = 6.1 Hz, 6H), 1.05 (t, J = 7.4 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 183.2 (C=O), 180.4 (C=O), 179.5 (C=O), 169.3 (C-Ar), 158.22 (C-Ar), 155.8 (C-Ar), 146.9 (C-Ar), 135.0 (C-Ar), 134.6 (C-Ar), 134.0 (C-Ar), 126.4 (C-Ar), 125.2 (C-Ar), 124.4 (CH-Ar), 122.9 (C-Ar), 122.8 (CH-Ar), 119.6 (CH-Ar), 111.9 (CH-Ar), 73.2 ($OCH(CH_3)_2$), 35.8 (CH_2), 23.9 (CH_2), 22.1 (2 × CH_3), 19.7 (CH_2), 13.7 (CH_3). HRMS APCI: calculated for $C_{24}H_{23}O_5$ $[M+H]^+$: 391.1545; found: 391.1522. IR (Neat, cm^{-1}): 2970 (C-H), 2926 (C-H), 2873 (C-H), 1673 (C=O), 1656 (C=O), 1581 (C=C), 1463, 1285, 750.

3.1.4.3. 11-Hydroxy-5-methyl-2-propyl-4*H*-naphtho[2,3-*h*]chromene-4,7,12-trione (18). Anthra-4-pyranone **18** was prepared according to the general procedure for the deprotection of the isopropyl group, Method A. Isopropyl anthra-4-pyranone (32 mg, 0.082 mmol) in xylene (3 mL) were added to the reaction flask. The anthrapyranone **18** was obtained as yellow crystals (26 mg, 0.074 mmol, 90%). R_f = 0.35 (10% EtOAc in PhMe). Mp = 185–187 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.81 (s, 1H), 7.97 (s, 1H), 7.75 (d, J = 7.3 Hz, 1H), 7.63 (t, J = 7.9 Hz, 1H), 7.31 (d, J = 8.3 Hz, 1H), 6.22 (s, 1H), 2.97 (s, 3H), 2.70 (t, J = 7.5 Hz, 2H), 1.92 (d, J = 7.4 Hz, 2H), 1.08 (t, J = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 187.2 (C=O), 181.9 (C=O), 179.1 (C-Ar), 169.3 (C-Ar), 162.6 (C-Ar), 156.7 (C-Ar), 149.8 (C-Ar), 136.4 (Ar-CH), 135.9 (C-Ar), 132.3 (C-Ar), 126.5 (C-Ar), 125.6 (Ar-CH), 125.4 (Ar-CH), 119.7 (C-Ar), 119.3 (Ar-CH), 116.8 (C-Ar), 112.3 (Ar-CH), 35.9 (CH_2), 24.3 (CH_2), 20.0 (Ar-CH_3), 13.7 (CH_3). HRMS APCI: *m*/*z* calculated for $C_{21}H_{17}O_5$ $[M+H]^+$: 349.1076; found: 349.1070. IR (Neat, cm^{-1}) 3073 (C-H), 2962 (C-H), 2927 (C-H), 1663 (C=O), 1637 (C=O), 1582 (C=C), 1456, 1280, 671.

3.1.4.4. 2-Ethyl-11-methoxy-5-methyl-4*H*-naphtho[2,3-*h*]chromene-4,7,12-trione (19). Anthra-4-pyranone **19** was prepared according to the general procedure for the methylation of the phenol group using anthra-4-pyranone **17** (68 mg, 0.20 mmol). The anthrapyranone **19** was obtained as a yellow-orange solid (61 mg, 0.18 mmol, 86%). R_f = 0.38 (30% EtOAc in PhMe). Mp = 220–222 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, J = 0.7 Hz, 1H), 7.86 (dd, J = 7.7 Hz, 1.1 Hz), 7.68 ('t', J = 8.0 Hz, 1H), 7.35 (dd, J = 8.5 Hz, 0.9 Hz, 1H), 6.21 (s, 1H), 4.04 (s, 3H), 2.96 (d, J = 0.7 Hz, 3H), 2.78 (dq, J = 7.5 Hz, 0.6 Hz, 2H), 1.41 (t, J = 7.5 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 183.3 (C=O), 180.8 (C=O), 179.7 (C=O), 170.8 (C-Ar), 159.8 (C-Ar), 156.1 (C-Ar), 147.4 (C-Ar), 135.0 (C-Ar), 134.6 (Ar-CH), 126.6 (C-Ar), 124.6 (Ar-CH), 123.5 (C-Ar), 122.6 (C-Ar), 119.4 (Ar-CH), 118.6 (Ar-CH), 111.1 (Ar-CH), 56.8 (OCH_3), 27.4, 24.1 (Ar-CH_3), 11.1. HRMS APCI: *m*/*z* calculated for $C_{21}H_{17}O_5$ $[M+H]^+$: 349.1076; found: 349.1066. IR (KBr Pellet, cm^{-1}) 2967 (C-H), 2931 (C-H), 2942 (C-H), 1669 (C=O), 1647 (C=O), 1584 (C=C), 1274, 1226, 952.

3.1.4.5. 11-Methoxy-5-methyl-2-propyl-4*H*-naphtho[2,3-*h*]chromene-4,7,12-trione (20). Anthra-4-pyranone **20** was prepared according to the general procedure for the methylation of the phenol group using anthra-4-pyranone **18** (30 mg, 0.086 mmol). The anthrapyranone **20** was obtained as a yellow solid (20 mg, 0.055 mmol, 64%). R_f = 0.26 (20% EtOAc in PhMe); mp = 214–217 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, J = 0.8 Hz, 1H), 7.88 (dd, J = 7.8, 1.1 Hz, 1H), 7.68–7.72 (m, 1H) 7.37 (dd, J = 8.5, 1.0 Hz, 1H), 6.22 (s, 1H), 4.05 (s, 3H), 2.97 (d, J = 0.7 Hz, 3H), 2.72 (t, J = 7.4 Hz, 2H), 1.92 (dq, 7.4 Hz, 7.4 Hz, 2H), 1.07 (t, J = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 183.3 (C=O), 180.9 (C=O), 179.6 (C=O), 169.6 (C-Ar), 159.8 (C-Ar), 156.1 (C-Ar), 147.4 (C-Ar), 135.1 (C-Ar), 134.6 (Ar-CH), 134.6 (Ar-CH), 126.6 (C-Ar), 124.6 (Ar-CH), 123.6 (C-Ar), 122.6 (C-Ar), 119.4 (Ar-CH), 118.6 (Ar-CH), 112.0 (Ar-CH), 56.9 (O-CH_3), 36.0 (Ar-CH_2), 24.1 (CH_2), 20.1 (Ar-CH_3), 13.7 (CH_3). HRMS APCI: *m*/*z* calculated for $C_{22}H_{19}O_5$ $[M+H]^+$: 363.1232; found: 363.1245. IR (KBr Pellet, cm^{-1}) 2927 (C-H), 2842 (C-H), 1671 (C=O), 1648 (C=O), 1585 (C=C), 1301, 1264, 944, 754.

3.1.4.6. 11-Isopropoxy-5-methyl-2-(3,3,3-trifluoropropyl)-4*H*-naphtho[2,3-*h*]chromene-4,7,12-trione (21). HNO_3 (4 M, ca. 3 mL) was added gradually as a steady stream into stirred mixture of dimethoxy anthracene (140 mg, 0.295 mmol) and Ag(II)O (183 mg, 1.47 mmol) in 1,4-dioxane (7 mL) until all of the suspended Ag(II)O dissolved. The mixture was stirred for 15 min before H_2O (20 mL) was added. The mixture was extracted with

CH_2Cl_2 (3 × 30 mL), washed with H_2O (100 mL), dried ($MgSO_4$), and the combined organic extracts concentrated. The resulting residue was purified by column chromatography (silica, PhMe → 15% EtOAc/PhMe) to give anthraquinone **21** (113 mg, 0.254 mmol, 86%) as a yellow-orange solid. R_f = 0.18 (10% EtOAc in PhMe). Mp = 262–263 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.94 (d, J = 0.8 Hz, 1H), 7.86 (dd, J = 7.7, 1.1 Hz, 1H), 7.65 (dd, J = 8.3, 7.8 Hz, 1H), 7.36 (d, J = 7.8 Hz, 1H), 6.27 (s, 1H), 4.68 (hept, J = 6.2 Hz, 1H), 3.01 (dd, J = 9.2, 6.4 Hz, 2H), 2.97 (d, J = 0.6 Hz, 3H), 2.87 (ddt, J = 18.2, 10.6, 9.0 Hz, 2H), 1.48 (d, J = 6.1 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 183.3 (C═O), 180.6 (C═O), 179.3 (C═O), 165.0 (C-Ar), 158.4 (C-Ar), 155.7 (C-Ar), 147.3 (C-Ar), 135.3 (C-Ar), 134.8 (C-Ar), 134.3 (CH-Ar), 126.4 (C-Ar), 125.1 (C-Ar), 124.9 (CH-Ar), 122.9 (CH-Ar), 122.9, 119.8 (CH-Ar), 112.5 (CH-Ar), 73.3 ($OC(CH_3)_2$), 30.4 (q, J = 29.8 Hz, CF_3), 27.0 (q, J = 3.5 Hz, CH_2CF_3), 23.9 (Ar-CH_3), 22.1 (2 × CH_3). HRMS APCI: calculated for $C_{24}H_{20}O_5F_3$: 445.1263; found: 445.1286. IR (Neat, cm^{-1}): 3058 (C-H), 2985 (C-H), 2932 (C-H), 1674 (C═O), 1655 (C═O), 1582 (C═C).

3.1.4.7. 11-Hydroxy-5-methyl-2-(3,3,3-trifluoropropyl)-4*H*-naphtho[2,3-*h*]chromene-4,7,12-trione (22). Anthra-4-pyranone **22** was prepared according to the general procedure for the deprotection of the isopropyl group, Method A, using anthra-4-pyranone **21** (67 mg, 0.151 mmol). The anthrapyranone **22** was obtained as orange crystals (53 mg, 0.131 mmol, 87%). R_f = 0.27 (10% EtOAc in PhMe). Mp = 248–251 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.79 (s, 1H), 8.05 (s, 1H), 7.80 (dd, J = 7.5, 1.2 Hz, 1H), 7.69–7.63 (m, 1H), 7.36 (dd, J = 8.4, 1.2 Hz, 1H), 6.31 (s, 1H), 3.05–2.95 (m, 2H), 3.00 (s, 3H) 2.91–2.78 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 187.3 (C═O), 181.9 (C═O), 178.8 (C-Ar), 165.2 (C-Ar), 162.8 (C-Ar), 156.6 (C-Ar), 150.0 (C-Ar), 136.6 (Ar-CH), 136.2 (C-Ar), 132.3 (C-Ar), 127.6 (C-Ar), 126.4 (C-Ar), 126.0 (Ar-CH), 125.6 (Ar-CH), 125.4 (C-Ar), 119.8 (C-Ar), 119.6 (Ar-CH), 116.9 (C-Ar), 112.9 (Ar-CH), 30.6 (q, JC-F = 29.9 Hz, CF_3), 27.1 (q, J = 3.5 Hz, CH_2CF_3), 24.3 (Ar-CH_3). HRMS APCI: m/z calculated for $C_{21}H_{13}F_3O_5$: 402.0715; found: 402.0716. IR (Neat, cm^{-1}) 3067 (C-H), 2925 (C-H), 2853 (C-H), 1659 (C═O), 1636 (C═O), 1584 (C═C), 1456, 1373, 1088, 654.

3.1.5. General method for the synthesis of cuprous acetylide (Table 3)

A solution of alkyne (1 equiv) in EtOH (0.3 M) was added slowly over 1 min to a magnetically stirred solution of CuCl (1.2 equiv) in NH_4OH (28%, 1.6 M). The mixture was stirred for 15 min upon which time the cuprous acetylide precipitated. H_2O (100 mL per 1 mL of alkyne) is added and the precipitate collected by vacuum filtration, washed with NH_4OH (5%, 25 mL per 100 mL of alkyne × 2) plus H_2O (25 mL per 1 mL of alkyne × 2) and dried in a vacuum desiccator overnight to give the cuprous acetylide as a coloured powder and which was used without need for further purification.

3.1.5.1. Oct-1-ynylcopper 42a. Prepared using the general procedure for the synthesis of cuprous acetylides using *n*-octyne (1.00 mL, 6.78 mmol). The resulting cuprous acetylide **42a** (725 mg, 4.20 mmol, 62%) was isolated as a yellow powder and used without need for further purification. Mp ⩾180 °C decomposes. IR (Neat, cm^{-1}) 2959 (C-H), 2933 (C-H), 2891 (C-H), 2858 (C-H), 2874 (C-H), 1928 (C≡C), 1473, 1460, 717. Anal. Calcd for $C_8H_{13}Cu$: C, 55.63; H, 7.59; N, 0.00. Found: C, 55.65; H, 7.68; N, 0.00.

3.1.5.2. Pent-1-ynylcopper 42b. Prepared using the general procedure for the synthesis of cuprous acetylides using *n*-pentyne (1.00 mL, 10.14 mmol). The resulting cuprous acetylide **42b** (781 mg, 5.98 mmol, 59%) was isolated as a yellow powder and used without need for further purification. Mp ⩾180 °C decomposes. IR (Neat, cm^{-1}) 2955 (C-H), 2937 (C-H), 1930 (C≡C), 715.

3.1.5.3. (Phenylethynyl)copper 42d. Prepared using the general procedure for the synthesis of cuprous acetylides using phenylacetylene (1.0 mL, 9.10 mmol). Phenylethynyl-copper **42d** (824 mg, 5.05 mmol, 55%) was obtained as a bright yellow powder and used without further purification. Mp ⩾180 °C decomposes; IR (KBr, cm^{-1}) 3048 (C-H), 1930 (C≡C), 1906 (C≡C), 1595, 1482, 1441, 744, 682. Anal. Calcd for C_8H_5Cu: C, 58.35; H, 3.06; N, 0.00. Found: C, 58.60; H, 2.97; N, 0.00.

3.1.5.4. (3-Oxo-3-phenylprop-1-ynyl)copper 6. Prepared using the general procedure for the synthesis of cuprous acetylides using 1-phenyl-2-propyn-1-one (264 mg, 2.03 mmol). 3-Oxo-3-phenylprop-1-ynyl-copper **6** (216 mg, 1.12 mmol, 55%) was obtained as a red powder and used without further purification. Mp ⩾180 °C decomposes; IR (KBr, cm^{-1}) 3057 (C-H), 2923 (C-H), 1932 (C≡C), 1906 (C≡C), 1611 (C═O), 1575, 1243, 688. Anal. Calcd for C_9H_5CuO: C, 56.10; H, 2.62; N, 0.00. Found: C, 56.17; H, 2.64; N, 0.00.

3.1.5.5. (5-Cyanopent-1-ynyl)copper 42e. Prepared using the general procedure for the synthesis of cuprous acetylides using 5-hexynenitrile (0.2 mL, 1.91 mmol). 5-Cyanopent-1-ynyl-copper **42e** (102 mg, 1.09 mmol, 57%) was obtained as a yellow powder and used without further purification. Mp ⩾180 °C decomposes. IR (Neat, cm^{-1}) 3343 (OH), 2941 (C-H), 2247 (C≡N), 1570, 1424, 901. Anal. Calcd for C_6H_6NCu: C, 46.29; H, 3.89; N, 9.00. Found: C, 46.34; H, 3.77; N, 9.01.

3.1.5.6. (5-Chloropent-1-ynyl)copper 42f. Prepared using the general procedure for the synthesis of cuprous acetylides using 5-chloro-1-pentyne (0.5 mL, 5.04 mmol). 5-Chloropent-1-ynyl-copper **42f** (498 mg, 3.02 mmol, 60%) was obtained as a yellow powder and used without further purification. Mp ⩾180 °C decomposes. IR (neat, cm^{-1}) 3576, 2954, (C-H), 1930 (C≡C), 1425, 1264, 770, 651; Anal. Calcd for C_5H_6ClCu: C, 36.37; H, 3.66; N, 0.00. Found: C, 36.31; H, 3.59; N, 0.00.

3.1.5.7. (3-Oxooct-1-ynyl)copper 42g. Prepared using the general procedure for the synthesis of cuprous acetylides using 1-octyne-3-one (233 mg, 1.88 mmol). The 3-oxooct-1-ynyl-copper **42g** (221 mg, 1.18 mmol, 63%) was obtained as an orange powder and used without further purification. Mp ⩾180 °C decomposes; IR (Neat, cm^{-1}) 3676, 2960 (C-H), 2935 (C-H), 2901 (C-H), 1909 (C≡C), 1639 (C═O), 1409, 1080, 1066, 1057, 720; Anal. Calcd for $C_8H_{11}OCu$: C, 51.46; H, 5.94; N, 0.00. Found: C, 51.33; H, 5.87; N, 0.00.

3.1.5.8. ((1-Hydroxycyclohexyl)ethynyl)copper 42i. Prepared using the general procedure for the synthesis of cuprous acetylides using 1-ethynylcyclohexanol (1.0 g, 8.05 mmol). ((1-Hydroxycyclohexyl)ethynyl)copper **42i** (497 mg, 2.66 mmol, 33%) was obtained as a yellow powder. Mp = >180 °C decomposes. IR (Neat, cm^{-1}) 3371 (OH), 2931 (C-H), 2856, 1703 (C≡C), 1447, 1067, 964. This copper acetylide was extremely sensitive to the atmosphere and used without further purification.

3.1.6. General method for the synthesis of anthrafuranones

A mixture of aryl iodide **5** (200–300 mg, 1 equiv), cuprous acetylide (1.1–1.5 equiv) and DMEDA, (3.5 equiv) in toluene (5 mL) was heated to 90 °C for 18 h. The reaction mixture was cooled to room temperature and purified directly by column chromatography (silica, ca. 100% PhMe → 20% EtOAc/PhMe) to give the anthrafurans usually as yellow to orange solids.

3.1.6.1. 2-Hexyl-10-isopropoxy-4-methylanthra[1,2-*b*]furan-6,11-dione (43). Anthrafuranone **43** was prepared according to the general method for the synthesis of anthrafuranones using aryl iodide **5** (200 mg, 0.474 mmol), oct-1-ynylcopper **42a** (123 mg, 0.710 mmol) and *N*,*N*′-dimethylethylenediamine, (179 μL, 1.66 mmol). The reaction mixture was cooled to room temperature and purified directly by column chromatography (silica, 100% PhMe → 5% EtOAc/PhMe) to give the anthrafuran **43** (163 mg, 0.403 mmol, 85%) as a yellow solid. R_f = 0.35 (5% EtOAc in PhMe). Mp = 88–92 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.92–7.86 (m, 2H), 7.61 (t, *J* = 8.0 Hz, 1H), 7.30 (d, *J* = 8.4 Hz, 1H), 6.48 (d, *J* = 0.7 Hz, 1H), 4.73 (hept, *J* = 6.0 Hz, 1H), 2.92 (t, *J* = 7.7 Hz, 2H), 2.56 (s, 3H), 1.85–1.78 (m, 2H), 1.50 (d, *J* = 6.1 Hz, 6H), 1.40–1.47 (m, *J* = 14.7, 6.9 Hz, 3H), 1.30–1.37 (m, *J* = 8.9, 5.4 Hz, 5H), 0.90 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (126 MHz, CDCl3) δ 184.0 (C═O), 181.8 (C═O), 165.7 (CH-Ar), 158.9 (CH-Ar), 151.5 (C-Ar), 136.6 (C-Ar), 135.9 (C-Ar), 135.8 (C-Ar), 134.2 (CH-Ar), 128.4 (C-Ar), 123.0 (C-Ar), 121.6 (CH-Ar), 121.3 (CH-Ar), 119.6 (CH-Ar), 118.3 (C-Ar), 100.7 (CH-Ar), 72.3 ($OCH(CH_3)_2$), 31.6 (CH_2), 29.1, 28.9, 27.5, 22.7, 22.2 (2 × CH_3), 19.2, 14.2 (CH_3). HRMS APCI: *m*/*z* calculated for $C_{26}H_{29}O_4$: 405.2066; found: 405.2080. IR (Neat, cm^{-1}) 2979 (C-H), 2920 (C-H), 2850 (C-H), 1663 (C═O), 1579 (C═C), 1238, 950, 749.

3.1.6.2. 2-Hexyl-10-hydroxy-4-methylanthra[1,2-*b*]furan-6,11-dione (44). Anthrafuran **44** was prepared according to the general procedure for the deprotection of the isopropyl group, Method A, using anthrafuran **43** (34 mg, 0.084 mmol). The anthrafuran **44** was obtained as an orange solid (18 mg, 0.050 mmol, 59%). R_f = 0.50 (2% EtOAc in PhMe). Mp = 126–131 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.75 (s, 1H), 7.94 (d, *J* = 0.8 Hz, 1H), 7.78 (dd, *J* = 7.5, 1.1 Hz, 1H), 7.62 (dd, *J* = 8.3, 7.6 Hz, 1H), 7.28–7.25 (m, 1H), 6.51 (t, *J* = 0.9 Hz, 1H), 2.93 (t, *J* = 7.7 Hz, 2H), 2.59 (d, *J* = 0.7 Hz, 3H), 1.83 (dt, *J* = 15.4, 7.6 Hz, 2H), 1.46 (dt, *J* = 9.5, 7.1 Hz, 2H), 1.42–1.30 (m, 4H), 0.97–0.88 (m, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 188.5 (C═O), 182.8 (C═O), 166.0 (C-Ar), 162.4 (C-Ar), 151.6 (C-Ar), 138.0 (C-Ar), 136.5 (C-Ar), 136.4 (Ar-CH), 133.5 (C-Ar), 129.4, 124.4 (Ar-CH), 122.8 (Ar-CH), 119.4 (Ar-CH), 116.5 (C-Ar), 116.1 (C-Ar), 100.9 (Ar-CH), 31.6 (CH_2), 29.1 (CH_2), 28.9 (CH_2), 27.6 (CH_2), 22.7 (CH_2), 19.5 (Ar-CH_3), 14.2 (CH_3). HRMS APCI: *m*/*z* calculated for $C_{23}H_{23}O_4$ $[M+H]^+$: 363.1596; found: 363.1605. IR (KBr Pellet, cm^{-1}) 2954 (C-H), 2928 (C-H), 2849 (C-H), 1666 (C═O), 1629 (C═O), 1583 (C═C), 1449, 1256, 750.

3.1.6.3. 10-Isopropoxy-4-methyl-2-propylanthra[1,2-*b*]furan-6,11-dione (45). The anthrafuran **45** was prepared applying the general procedure for the synthesis of anthrafurans using aryl iodide **5** (300 mg, 0.710 mmol) and cuprous acetylide **42b** (111 mg, 0.853 mmol). The anthrafuran **45** (179 mg, 0.494 mmol, 70%) was obtained as a yellow solid. R_f = 0.27 (2.5% EtOAc in PhMe). Mp = 159–162 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93–7.84 (m, 2H), 7.60 (dd, *J* = 8.3, 7.7 Hz, 1H), 7.29 (d, *J* = 8.0 Hz, 1H), 6.47 (t, *J* = 0.9 Hz, 1H), 4.72 (hept, *J* = 6.0 Hz, 1H), 2.89 (t, *J* = 7.6 Hz, 2H), 2.55 (d, *J* = 0.6 Hz, 3H), 1.90–1.80 (m, *J* = 15.0, 7.5 Hz, 2H), 1.49 (d, *J* = 6.1 Hz, 6H), 1.04 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 183.9 (C═O), 181.7 (C═O), 165.4 (C-Ar), 158.8 (C-Ar), 151.4 (C-Ar), 136.5 (C-Ar), 135.9 (C-Ar), 135.8 (C-Ar), 134.1 (CH-Ar), 128.4 (C-Ar), 123.0 (C-Ar), 121.6 (CH-Ar), 121.3 (CH-Ar), 119.6 (CH-Ar), 118.3 (C-Ar), 100.9 (CH-Ar), 72.3 ($OCH(CH_3)_2$), 30.8 ($CH_2CH_2CH_3$), 22.2 (2 × CH_3), 21.0 ($CH_2CH_2CH_3$), 19.2 (Ar-CH_3), 13.9 (CH_3). HRMS EI: calculated for $C_{23}H_{22}O_4$: 362.1518; found 362.1520. IR (Neat, cm^{-1}) 2930 (C-H), 2932 (C-H), 1668 (C═O), 1577 (C═C), 1243, 950, 753.

3.1.6.4. 10-Hydroxy-4-methyl-2-propylanthra[1,2-*b*]furan-6,11-dione (46). Anthrafuran **46** was prepared according to the general procedure for the deprotection of the isopropyl group, Method A, using anthrafuran **45** (43 mg, 0.119 mmol). The anthrafuran **46** was obtained as an orange solid (29 mg, 0.091 mmol, 77%). R_f = 0.35 (1% EtOAc in PhMe). Mp = 155–162 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.72 (s, 1H), 7.89 (s, 1H), 7.76 (d, *J* = 7.5 Hz, 1H), 7.60 (t, *J* = 7.6 Hz, 1H), 7.24 (d, *J* = 8.3 Hz, 1H), 6.48 (s, 1H), 2.89 (t, *J* = 7.5 Hz, 2H), 2.56 (s, 3H), 1.91–1.81 (m, 2H), 1.08 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 188.4 (C═O), 182.7 (C═O), 165.6 (C-Ar), 162.4 (C-Ar), 151.5 (C-Ar), 138.0 (C-Ar), 136.4 (C-Ar), 136.3 (Ar-CH), 133.5 (C-Ar), 129.4 (C-Ar), 124.3 (Ar-CH), 122.7 (Ar-CH), 119.3 (Ar-CH), 116.4 (C-Ar), 116.0 (C-Ar), 101.0 (Ar-CH), 30.8 ($CH_2CH_2CH_3$), 21.1 ($CH_2CH_2CH_3$), 19.4 ($ArCH_3$), 13.9 (CH_3). HRMS EI: *m*/*z* calculated for $C_{20}H_{16}O_4$: 320.1049; found: 320.1051. IR (KBr Pellet, cm^{-1}) 2960 (C-H), 2872 (C-H), 1664 (C═O), 1634 (C═O), 1581 (C═C), 1468, 790, 694.

3.1.6.5. 10-Isopropoxy-4-methyl-2-phenylanthra[1,2-*b*]furan-6,11-dione (47). The anthrafuran **47** was prepared applying the general procedure for the synthesis of anthrafurans using aryl iodide **5** (200 mg, 0.474 mmol) and cuprous phenylacetylide **42d** (117 mg, 0.710 mmol). The anthrafuran **47** (120 mg, 0.303 mmol, 64%) was obtained as a yellow solid. R_f = 0.19 (5% EtOAc in PhMe). Mp = 215–218 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.06–8.00 (m, 2H), 7.90 (dd, *J* = 7.6, 1.1 Hz, 1H), 7.89 (d, *J* = 0.9 Hz, 1H), 7.61 (dd, *J* = 8.3, 7.6 Hz, 1H), 7.50–7.45 (m, 2H), 7.42–7.38 (m, 1H), 7.33–7.29 (m, 1H), 7.05 (s, 1H), 4.74 (hept, *J* = 6.1 Hz, 1H), 2.61 (d, *J* = 0.8 Hz, 3H), 1.54 (d, *J* = 6.1 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 183.7 (C═O), 181.3 (C═O), 160.9 (C-Ar), 158.9 (C-Ar), 151.7 (C-Ar), 136.6 (C-Ar), 136.4 (C-Ar), 135.9 (C-Ar), 134.2 (CH-Ar), 129.6 (CH-Ar), 129.5 (C-Ar), 129.1 (C-Ar), 128.9 (2 × Ph-H), 125.9 (2 × Ph-H), 123.1 (C-Ar), 121.9 (C-Ar), 121.6 (CH-Ar), 119.8 (CH-Ar), 118.6 (CH-Ar), 99.7 (CH-Ar), 72.6 ($OCH(CH_3)_2$), 22.2 (2 × CH_3), 19.2 (Ar-CH_3). HRMS APCI: *m*/*z* calculated for $C_{26}H_{21}O_4$: 397.1440; found: 397.1454. IR (Neat, cm^{-1}) 2968 (C-H), 2920 (C-H), 2850 (C-H), 1664 (C═O), 1578 (C═C), 1187, 965, 742.

3.1.6.6. 10-Hydroxy-4-methyl-2-phenylanthra[1,2-*b*]furan-6,11-dione (48). Anthrafuran **48** was prepared according to the general procedure for the deprotection of the isopropyl group Method A using anthrafuran **47** (45 mg, 0.113 mmol). The anthrafuran **48** was obtained as orange-red crystals (35 mg, 0.098 mmol, 87%). R_f = 0.50 (5% EtOAc in PhMe). Mp = 246–250 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.83 (s, 1H), 8.04–8.00 (m, 2H), 7.82 (dd, *J* = 7.5, 1.1 Hz, 1H), 7.64 (dd, *J* = 8.4, 7.5 Hz, 1H), 7.57–7.49 (m, 2H), 7.46 (d, *J* = 7.4 Hz, 1H), 7.30 (dd, *J* = 8.4, 1.2 Hz, 1H), 7.13 (s, 1H), 2.69 (d, *J* = 0.7 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 188.3 (C═O), 182.8 (C═O), 162.5 (Ar), 161.2 (Ar), 151.8 (Ar), 138.5 (Ar), 136.7 (Ar), 136.4, 133.5 (Ar), 130.1 (Ar), 130.1 (Ar), 129.3 (Ar), 129.2 (PhCH), 129.0 (Ar), 125.8 (PhCH), 124.4 (Ar), 123.1 (Ar), 119.5 (Ar), 116.6 (Ar), 116.5 (Ar), 99.8 (Ar), 19.6 (Ar-CH_3). HRMS APCI: *m*/*z* calculated for $C_{23}H_{15}O_4$: 355.0970; found: 355.0970. IR (Neat, cm^{-1}) 3112 (C-H), 2920 (C-H), 1659 (C═O), 1639 (C═O), 1594, 1574, 744.

3.1.6.7. 2-Benzoyl-10-isopropoxy-4-methylanthra[1,2-*b*]furan-6,11-dione (49). The anthrafuran **49** was prepared applying the general procedure for the synthesis of anthrafurans using aryl iodide **5** (200 mg, 0.474 mmol) and (3-oxo-3-phenylprop-1-ynyl)-copper **6** (137 mg, 0.710 mmol). The anthrafuran **49** (109 mg, 0.256 mmol, 54%) was obtained as a red solid. R_f = 0.34 (10% EtOAc in PhMe). Mp = 195–198 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ

8.48–8.42 (m, 2H), 7.94 (d, J = 0.8 Hz, 1H), 7.89 (dd, J = 7.6, 1.1 Hz, 1H), 7.69–7.65 (m, 2H), 7.57–7.65 (m, 3H), 7.33 (d, J = 7.8 Hz, 1H), 4.70 (hept, J = 6.1 Hz, 1H), 2.66 (d, J = 0.7 Hz, 3H), 1.51 (d, J = 6.1 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 183.5 (C=O), 182.8 (C=O), 180.4 (C=O), 158.9 (C-Ar), 156.8 (C-Ar), 152.4 (C-Ar), 139.3 (C-Ar), 136.3 (C-Ar), 135.5 (C-Ar), 134.4 (CH-Ar), 133.7 (C-Ar), 133.6 (CH-Ar), 132.0 (C-Ar), 130.5 (2 × Ar-H), 128.8 (2 × Ar-H), 123.0 (C-Ar), 122.6 (CH-Ar), 122.1 (CH-Ar), 120.1 (CH-Ar), 119.4 (C-Ar), 112.9 (CH-Ar), 73.0 ($OCH(CH_3)_2$), 22.2 (2 × CH_3), 19.3 (Ar-CH_3). HRMS APCI: calculated for $C_{27}H_{21}O_5$: 425.1389; found: 425.1391; IR (Neat, cm^{-1}) 3097 (C-H), 2928 (C-H), 2870 (C-H), 1687 (C=O), 1668 (C=O), 1583 (C=C), 1260, 966, 746.

3.1.6.8. 2-Benzoyl-10-hydroxy-4-methylanthra[1,2-*b*]furan-6,11-dione (50). Anthrafuran **50** was prepared according to the general procedure for the deprotection of the isopropyl group Method A using anthrafuran **49** (20 mg, 0.047 mmol). The anthrafuran **50** was obtained as yellow solid (15 mg, 0.039 mmol, 83%). R_f = 0.29 (5% EtOAc in PhMe). Mp = 246–256 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.73 (s, 1H), 8.41–8.36 (m, 2H), 8.11 (d, J = 0.8 Hz, 1H), 7.84 (dd, J = 7.5, 1.1 Hz, 1H), 7.73 (s, 1H), 7.72–7.70 (m, 1H), 7.68 (dd, J = 8.3, 7.5 Hz, 1H), 7.63 ('t', J = 7.6 Hz, 2H), 7.34 (dd, J = 8.4, 1.1 Hz, 1H), 2.75 (d, J = 0.8 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 187.5 (C=O), 183.0 (C=O), 182.5 (C=O), 162.6 (Ar), 156.9 (Ar), 152.6 (Ar), 141.6 (Ar), 136.7 (Ar), 136.3 (Ar), 133.9 (Ar), 133.9 (Ar), 133.2 (Ar), 130.3 (ArCH), 129.0 (ArCH), 124.9 (Ar), 123.3 (Ar), 119.8 (Ar), 117.6 (Ar), 116.4 (Ar), 113.0 (Ar), 19.7 (Ar-CH_3). HRMS APCI: m/z calculated for $C_{24}H_{15}O_5$: 383.0919; found: 383.0923. IR (Neat, cm^{-1}) 3111 (C-H), 3079 (C-H), 1667 (C=O), 1643 (C=O), 1633 (C=O), 1591 (C=C), 1541, 749.

3.1.6.9. 4-(10-Isopropoxy-4-methyl-6,11-dioxo-6,11-dihydroanthra[1,2-*b*]furan-2-yl)butanenitrile (51). The anthrafuran **51** was prepared using the general procedure for the synthesis of anthrafurans using aryl iodide **5** (200 mg, 0474 mmol) and 5-cyanopent-1-ynyl-copper **42e** (111 mg, 0.710 mmol). The anthrafuran **51** (147 mg, 0.379 mmol, 80%) was obtained as an orange solid. R_f = 0.15 (10% EtOAc in PhMe). Mp = 118–128 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93–7.82 (m, 2H), 7.61 (t, J = 8.0 Hz, 1H), 7.30 (d, J = 8.3 Hz, 1H), 6.56 (s, 1H), 4.73 (hept, J = 6.0 Hz, 1H), 3.09 (t, J = 7.3 Hz, 2H), 2.54 (s, 3H), 2.50 (t, J = 7.1 Hz, 2H), 2.22 (tt, J = 7.2 Hz, 2H), 1.49 (d, J = 6.0 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 183.7 (C=O), 181.5 (C=O), 161.8 (CH-Ar), 158.9 (CH-Ar), 151.6 (C-Ar), 136.3 (C-Ar), 135.9 (C-Ar), 135.7 (C-Ar), 134.3 (CH-Ar), 128.9 (C-Ar), 122.8 (C-Ar), 121.8 (CH-Ar), 121.4 (CH-Ar), 119.6 (CH-Ar), 119.1 (C≡N), 118.4 (C-Ar), 102.3 (CH-Ar), 72.4 ($OCH(CH_3)_2$), 27.6 (Furan-CH_2), 23.6 ($CH_2CH_2CH_2$), 22.2 (2 × CH_3), 19.2 (Ar-CH_3), 16.7 (N≡CCH_2). HRMS APCI: m/z calculated for $C_{24}H_{22}NO_4$: 388.1549; found: 388.1555. IR (Neat, cm^{-1}) 2977 (C-H), 2945 (C-H), 2247 (C≡N), 1663 (C=O), 1581 (C=C), 1278, 1241, 969, 746.

3.1.6.10. 4-(10-Hydroxy-4-methyl-6,11-dioxo-6,11-dihydroanthra[1,2-*b*]furan-2-yl)butanenitrile (52). Anthrafuran **52** was prepared according to the general procedure for the deprotection of the isopropyl group Method A using anthrafuran **51** (33 mg, 0.047 mmol). The anthrafuran **52** was obtained as an orange solid (22 mg, 0.064 mmol, 75%). R_f = 0.20 (5% EtOAc in PhMe). Mp = 241–243 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.71 (s, 1H), 8.01 (d, J = 0.8 Hz, 1H), 7.82 (dd, J = 7.5, 1.1 Hz, 1H), 7.65 (dd, J = 8.3, 7.5 Hz, 1H), 7.29 (dd, J = 8.4, 1.1 Hz, 1H), 6.66 (s, 1H), 3.14 (t, J = 7.3 Hz, 2H), 2.63 (s, 3H), 2.54 (t, J = 7.0 Hz, 2H), 2.25 (t, J = 7.2 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 188.4 (C=O), 182.8 (C=O), 162.5 (C-Ar), 162.2 (C-Ar), 151.8 (C-Ar), 138.6 (C-Ar), 136.6 (Ar-CH), 135.9 (C-Ar), 133.5 (C-Ar), 130.1 (C-Ar), 124.5 (Ar-CH), 123.1 (Ar-CH), 119.6 (Ar-CH), 119.0 (C-Ar), 116.5 (C-Ar), 116.4 (C-Ar), 102.6 (Ar-CH), 27.6 (CH_2), 23.7 (CH_2), 19.5 (Ar-CH_3), 16.8 (CH_3). HRMS APCI: m/z calculated for $C_{21}H_{16}NO_4$ $[M+H]^+$: 346.1079; found: 346.1070. IR (KBr Pellet, cm^{-1}) 3136 (C-H), 3075 (C-H), 2915 (C-H), 2245 (C≡N), 1655 (C=O), 1636 (C=O), 1574 (C=O), 1456, 1311, 776.

3.1.6.11. 2-(3-Chloropropyl)-10-isopropoxy-4-methylanthra[1,2-*b*]furan-6,11-dione (53). The anthrafuran **53** was prepared using the general procedure for the synthesis of anthrafurans. Aryl iodide **5** (200 mg, 0.474 mmol) and (5-chloropent-1-ynyl)copper **42f** (117 mg, 0.710 mmol) were used. The anthrafuran **53** (92 mg, 0.232 mmol, 49%) was obtained as an orange solid. R_f = 0.29 (5% EtOAc in PhMe). Mp = 120–125 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86–7.90 (m, 2H), 7.60 (dd, J = 8.4, 7.7 Hz, 1H), 7.32–7.27 (m, 1H), 4.73 (hept, J = 6.1 Hz, 1H), 3.64 (t, J = 6.3 Hz, 2H), 3.10 (t, J = 7.4 Hz, 2H), 2.55 (d, J = 0.7 Hz, 3H), 2.35–2.27 (m, 2H), 1.49 (d, J = 6.1 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 183.8 (C=O), 181.6 (C=O), 163.1 (C-Ar), 158.9 (C-Ar), 151.6 (C-Ar), 136.1 (C-Ar), 136.1 (C-Ar), 135.8 (C-Ar), 134.2 (CH-Ar), 128.7 (C-Ar), 122.9 (C-Ar), 121.7 (CH-Ar), 121.3 (CH-Ar), 119.6 (CH-Ar), 118.3 (C-Ar), 101.8 (CH-Ar), 72.3 ($OCH(CH_3)_2$), 44.1 (CH_2Cl), 30.3 (Furan-CH_2), 26.1 (CH_2), 22.2 (2 × CH_3), 19.2 (Ar-CH_3). IR (Neat, cm^{-1}) 2974 (C-H), 2924 (C-H), 1667 (C=O), 1578 (C=C), 1257, 964, 809, 639. HRMS APCI: m/z calculated for $C_{23}H_{22}O_4Cl$: 397.1207; found: 397.1194.

3.1.6.12. 2-(3-Chloropropyl)-10-hydroxy-4-methylanthra[1,2-*b*]furan-6,11-dione (54). Anthrafuran **54** was prepared according to the general procedure for the deprotection of the isopropyl group Method A using anthrafuran **53** (200 mg, 0.504 mmol). The anthrafuran **54** was obtained as orange-red crystals (175 mg, 0.494 mmol, 98%). R_f = 0.39 (5% EtOAc in PhMe). Mp = 181–190 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.72 (s, 1H), 7.98 (d, J = 0.6 Hz, 1H), 7.81 (dd, J = 7.5, 1.1 Hz, 1H), 7.64 (dd, J = 8.3, 7.6 Hz, 1H), 7.28 (dd, J = 8.4, 1.1 Hz, 1H), 6.61 (s, 1H), 3.68 (t, J = 6.3 Hz, 2H), 3.15 (t, J = 7.4 Hz, 2H), 2.62 (s, 3H), 2.37–2.28 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 188.4 (C=O), 182.8 (C=O), 163.5 (C-Ar), 162.5 (C-Ar), 151.8 (C-Ar), 138.4 (C-Ar), 136.5 (CH-Ar), 136.2 (C-Ar), 133.5 (C-Ar), 129.8 (C-Ar), 124.5 (CH-Ar), 122.9 (CH-Ar), 119.5 (CH-Ar), 116.5 (C-Ar), 116.2 (C-Ar), 102.0 (C-Ar), 44.0 (CH_2Cl), 30.4 (CH_2), 26.1 (CH_2), 19.5 (Ar-CH_3). HRMS APCI: m/z calculated for $C_{20}H_{16}O_4Cl$: 355.0737; found: 355.0736. IR (Neat, cm^{-1}) 2956 (C-H), 1662 (C=O), 1641 (C=O), 1584 (C=C), 1308, 1078, 1006, 794, 751, 564.

3.1.6.13. 2-Hexanoyl-10-isopropoxy-4-methylanthra[1,2-*b*]furan-6,11-dione (55). The anthrafuran **55** was prepared using the general procedure for the synthesis of anthrafurans using aryl iodide **5** (200 mg, 0.474 mmol) and 3-oxooct-1-ynyl-copper **42g** (133 mg, 0.710 mmol). The anthrafuran **55** (129 mg, 0.308 mmol, 65%) was obtained as a yellow solid. R_f = 0.20 (5% EtOAc in PhMe). Mp = 201–202 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.99 (d, J = 0.7 Hz, 1H), 7.92 (dd, J = 7.6, 1.0 Hz, 1H), 7.66 (t, J = 8.0 Hz, 1H), 7.56 (s, 1H), 7.36 (d, J = 8.2 Hz, 1H), 4.76 (hept, J = 6.0 Hz, 1H), 3.18 (t, J = 7.4 Hz, 2H), 2.67 (s, 3H), 1.86–1.81 (m, 2H), 1.53 (d, J = 6.1 Hz, 6H), 1.46–1.40 (m, 4H), 0.94 (t, J = 7.1 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 192.5 (Furan-C=O), 183.7 (C=O), 180.8 (C=O), 159.1 (C-Ar), 156.8 (C-Ar), 152.3 (C-Ar), 139.4 (C-Ar), 135.6 (C-Ar), 134.5 (CH-Ar), 134.2 (C-Ar), 132.0 (C-Ar), 122.8 (C-Ar), 122.1 (CH-Ar), 122.0 (CH-Ar), 119.9 (CH-Ar), 119.6 (C-Ar), 109.2 (CH-Ar), 72.7 ($OCH(CH_3)_2$), 39.5 (C=OCH_2), 31.5 (C=OCH_2CH_2), 23.6 (CH_2), 22.7 (CH_2), 22.2 (2 × CH_3), 19.3 (Ar-CH_3), 14.1 (CH_3). HRMS APCI: calculated for $C_{26}H_{27}O_5$: 419.1858; found: 419.1855. IR (Neat, cm^{-1}) 2927 (C-H), 2870 (C-H), 1687 (C=O), 1668 (C=O), 1582, 1260, 746.

3.1.6.14. 2-(1-Hydroxyethyl)-10-isopropoxy-4-methylanthra[1,2-*b*]furan-6,11-dione (56). The anthrafuran **56** was prepared using the general procedure for the synthesis of anthrafurans using aryl iodide **5** (200 mg, 0.474 mmol) and (3-hydroxy-3-methylbut-1-ynyl)copper **42h** (94 mg, 0.71 mmol). The anthrafuran **56** (47 mg, 0.128 mmol, 27%) was obtained as a dark orange oil that formed an amorphous solid mass upon standing for 2 days under nitrogen. R_f = 0.30 (30% EtOAc in PhMe). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (dd, J = 7.6, 1.1 Hz, 1H), 7.86 (d, J = 0.8 Hz, 1H), 7.63 (dd, J = 8.4, 7.7 Hz, 1H), 7.32 (d, J = 8.0 Hz, 1H), 6.65 (d, J = 0.8 Hz, 1H), 5.19 (q, J = 6.5 Hz, 1H), 4.74 (hept, J = 6.1 Hz, 1H), 2.52 (d, J = 0.6 Hz, 3H), 1.71 (d, J = 6.6 Hz, 3H), 1.50 (dd, J = 6.0, 0.7 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 183.8 (C═O), 181.8 (C═O), 166.4 (C-Ar), 158.9 (C-Ar), 151.5 (C-Ar), 137.0 (C-Ar), 135.8 (C-Ar), 135.7 (C-Ar), 134.5 (CH-Ar), 129.1 (C-Ar), 122.8 (C-Ar), 121.8 (CH-Ar), 121.5 (CH-Ar), 119.8 (CH-Ar), 118.5 (C-Ar), 100.2 (CH-Ar), 72.5 ($OCH(CH_3)_2$), 64.0 (C-OH), 22.2 ($2 \times CH_3$), 22.2 ($2 \times CH_3$), 21.3 ($CH(OH)CH_3$), 19.2 (Ar-CH_3). HRMS EI: m/z calculated for $C_{22}H_{20}O_5$: 364.1311; found: 364.1316; IR (Neat, cm^{-1}) 3430 (OH), 2976 (C-H), 2930 (C-H), 1667 (C═O), 1589 (C═C), 1239, 969.

3.1.6.15. 10-Hydroxy-2-(1-hydroxyethyl)-4-methylanthra[1,2-*b*]furan-6,11-dione (57). Anthrafuran **57** was prepared according to the general procedure for the deprotection of the isopropyl group, Method B, using anthrafuran **56** (50 mg, 0.138 mmol). The anthrafuran **57** was obtained as yellow crystals (22 mg, 0.067 mmol, 49%). R_f = 0.32 (PhMe). Mp = 178–183 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.71 (s, 1H), 8.02 (s, 1H), 7.82 (d, J = 7.5 Hz, 1H), 7.65 (t, J = 7.9 Hz, 1H), 7.30 (d, J = 8.4 Hz, 1H), 6.88 (s, 1H), 5.35 (q, J = 6.9 Hz, 1H), 2.66 (s, 3H), 2.05 (d, J = 6.9 Hz, 3H), 1.56 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 188.0 (C═O), 182.6 (C═O), 162.6 (C-Ar), 162.4 (C-Ar), 151.8 (C-Ar), 139.4 (C-Ar), 136.5 (CH-Ar), 135.1 (C-Ar), 133.3 (C-Ar), 130.8 (C-Ar), 124.6 (CH-Ar), 123.0 (CH-Ar), 119.5 (CH-Ar), 116.7 (C-Ar), 116.4 (C-Ar), 102.4 (CH-Ar), 49.7 (HCOH), 23.3 (CH_3), 19.5 (Ar-CH_3). IR (Neat, cm^{-1}) 2924 (C-H), 1667 (C═O), 1634 (C═O), 1587 (C═C), 1454, 749.

3.1.6.16. 2-Acetyl-10-isopropoxy-4-methylanthra[1,2-*b*]furan-6,11-dione (58). Dess–Martin periodinane (70 mg, 0.165 mmol) was added portionwise to a magnetically stirred solution of anthrafuran alcohol **56** (50 mg, 0.137 mmol) in CH_2Cl_2 (2 mL). Stirring continued for 1 h before the solution was treated with $NaHCO_3$ (satd 2 mL) $Na_2S_2O_3$ (2 M, 2 mL), H_2O (20 mL) and stirred for a further 1 h. The resulting mixture was extracted with CH_2Cl_2 (20 mL × 3), the combine organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was then purified by column chromatography (silica, 100% PhMe → 20% EtOAc/PhMe) to give the anthrafuran ketone **58** a yellow crystalline solid. R_f = 0.26 (15% EtOAc in PhMe); mp ⩾250 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 ('d', J = 0.8 Hz, 1H), 7.93 ('dd', J = 7.6, 1.1 Hz, 1H), 7.65–7.69 (m, 1H), 7.58 (s, 1H), 7.36 ('d', J = 7.4 Hz, 1H), 4.76 (sept, J = 6.0 Hz, 1H), 2.80 (s, 3H), 2.67 (d, J = 0.8 Hz, 3H), 1.53 (d, J = 6.0 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 189.7 (C═O), 183.7 (C═O), 180.8 (C═O), 159.1 (C-Ar), 156.7 (C-Ar), 152.4 (C-Ar), 139.5 (C-Ar), 134.6 (Ar-CH), 132.2 (C-Ar), 122.7 (C-Ar), 122.2 (Ar-CH), 121.8 (Ar-CH), 119.9 (Ar-CH), 119.7 (C-Ar), 109.4 (Ar-CH), 72.7 ($CH(CH_3)_2$), 27.2 (C═O(CH_3)), 22.2 ((CH_3)$_2$), 19.3 (Ar-CH_3). $C_{22}H_{18}O_5$ $[M+H]^+$: 362.1154; found: 362.1155. IR (Neat, cm^{-1}) 3096 (C-H), 2974 (C-H), 2922 (C-H), 1686 (C═O), 1669 (C═O), 1581 (C═C), 1557 (C═C), 1324, 748.

3.1.6.17. 2-Acetyl-10-hydroxy-4-methylanthra[1,2-*b*]furan-6,11-dione (59). Anthrafuran **59** was prepared according to the general procedure for the deprotection of the isopropyl group Method B using anthrafuran **58** (50 mg, 0.0138 mmol). The anthrafuran **59** was obtained as yellow crystals (21 mg, 0.066 mmol, 48%). R_f = 0.29 (5% EtOAc in PhMe); mp ⩾250 °C, ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.68 (s, 1H), 8.09 (d, J = 0.8 Hz, 1H), 7.84 (dd, J = 7.5, 1.1 Hz, 1H), 7.70–7.65 (m, 1H), 7.61 (s, 1H), 7.33 (dd, J = 8.4, 1.1 Hz, 1H), 2.78 (s, 3H), 2.73 (d, J = 0.8 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 188.9 (C═O), 187.5 (C═O), 182.5 (C═O), 162.6 (C-Ar), 156.6 (C-Ar), 152.4 (C-Ar), 141.7 (C-Ar), 136.7 (CH-Ar), 134.2 (C-Ar), 133.3 (C-Ar), 133.1 (C-Ar), 129.2 (C-Ar), 128.4 (C-Ar), 124.9 (CH-Ar), 123.2 (CH-Ar), 119.8 (CH-Ar), 117.6 (C-Ar), 116.3 (C-Ar), 109.7 (CH-Ar), 27.0 (CH_3), 19.6 (Ar-CH_3). HRMS APCI: m/z calculated for $C_{19}H_{13}O_5$: 321.0755; found: 321.0764. IR (Neat, cm^{-1}) 3362 (C-H), 3100 (C-H), 1689 (C═O), 1668 (C═O), 1591 (C═C), 1558, 1467, 784, 661.

3.2. Cell culture and stock solutions

Stock solutions were prepared as follows and stored at 20 °C: analogues were prepared as 20 mM solutions in DMSO. All cell lines were cultured at 37 °C, under 5% CO_2 in air, and were maintained in Dulbecco's modified Eagle's medium (Trace Biosciences, Australia) supplemented with 10% foetal bovine serum, 10 mM sodium bicarbonate penicillin (100 IU/mL), streptomycin (100 μg/ml) and glutamine (4 mM).

3.3. MTT in vitro growth inhibition assay

Cells in logarithmic growth were transferred to 96-well plates. Growth inhibition was determined by plating cells in duplicate in 100 μl medium at a density of 2500–4000 cells/well. On day 0 (24 h after plating) when the cells were in logarithmic growth, 100 μl medium with or without the test agent was added to each well. After 72-h drug exposure growth inhibitory effects were evaluated using the MTT (3-[4,5-dimethyltriazol-2-yl]-2,5-diphenyltetrazolium bromide) assay and absorbance read at 540 nm. Percentage growth inhibition was determined at a fixed drug concentration of 25 μM. A value of 100% is indicative of total cell growth inhibition. If the percentage inhibition was >90% across all cell lines evaluated or >100% against more than two cell lines and suitably soluble (in the DMSO/water solution), then a more detailed dose–response evaluation was conducted, allowing for the calculation of a GI_{50} value. This value is the drug concentration at which cell growth is inhibited by 50% based on the difference between the optical density values on day 0 and those at the end of drug exposure.

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Supplementary data

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