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Synthesis of caged 2,3,3a,7a-tetrahydro-3,6-methanobenzofuran-7(6*H*)-ones: Evaluating the minimum structure for apoptosis induction by gambogic acid

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Abstract—We have reported the discovery of gambogic acid (GA) as a potent apoptosis inducer and the identification of transferrin receptor as its molecular target. In order to understand the basic pharmacophore of GA for inducing apoptosis and to discover novel and simplified derivatives as potential anti-cancer agents, we explored the synthesis of caged 2,3,3a,7a-tetrahydro-3,6-methanobenzofuran-7(6*H*)-ones (4-oxatricyclo[4.3.1.0]decan-2-ones). Three types of 2,3,3a,7a-tetrahydro-3,6-methanobenzofuran-7(6*H*)-ones based on xanthone, 2-phenylchromene-4-one and benzophenone, were synthesized using a Claisen/Diels–Alder reaction cascade. All the reactions produced the targeted caged compound as well as its neo-isomer. The caged compounds based on xanthone and 2-phenylchromene-4-one were found to maintain the apoptosis inducing and cell growth inhibiting activity of GA, although with less potency. The caged compounds based on benzophenone were found to be inactive. Our study determined the minimum structure of GA for its apoptosis inducing activity, which could lead to the development of simple derivatives as potential anti-cancer drugs.

1. Introduction

Apoptosis, also called programmed cell death, plays critical roles in normal cell development as well as elimination of excessive or dysfunctional cells.[1] Caspases are known to be crucial for the execution of apoptosis.[2] Among the caspases, caspase-3 has been called an executioner caspase and it cleaves multi-protein substrates in cells, leading to irreversible cell death.[3] Inadequate apoptosis, such as due to defects in the molecular machinery to activate the caspase cascade, is one of the hallmarks of many cancer cells.[4]

It is known that many clinically used anti-cancer drugs kill tumor cells through the induction of apoptosis. Therefore, promoting apoptosis is a promising strategy that could lead to the discovery and development of new anti-cancer agents.[5] Several novel approaches to promote apoptosis via targeting key proteins in the apoptosis pathway, including Bcl-2 inhibitors,[6] inhibitors of MDM2-p53 interaction,[7] inhibitors of XIAP,[8] and Smac mimetics,[9] are currently being explored.

Toward our goal of discovering and developing novel apoptosis inducers as potential anti-cancer drugs, we have developed a cell-based high-throughput screening (HTS) assay for the identification of apoptosis inducers using a proprietary fluorescent caspase-3 substrate.[10,11] Using this technology, we have discovered several series of potent apoptosis inducers, including 4-aryl-chromenes[12] and 3,5-diaryl-oxadiazoles,[13] as well as identified their molecular targets.[14,15]

We have reported the discovery and SAR studies of gambogic acid (**1**, GA) (Chart 1) as a novel apoptosis inducer.[16] The 9,10 carbon–carbon double bond of the α,β-unsaturated ketone in **1** was found to be critical for its apoptosis inducing activity, and the 9,10 saturated derivative **2** was found to be devoid of apoptosis inducing and anti-proliferative activity. The 6-hydroxy and 30-carboxy groups were found to tolerate a variety of modifications.[16] Applying the SAR data, the

Keywords: Gambogic acid; Apoptosis inducer; Cell growth inhibition; 2,3,3a,7a-Tetrahydro-3,6-methanobenzofuran-7(6*H*)-ones; Claisen/Diels–Alder reaction cascade; Potential anti-cancer drugs.
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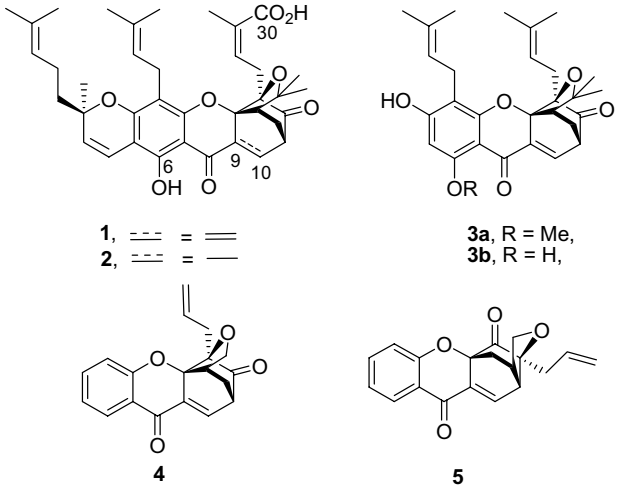


Chart 1.

30-carboxy group was used to prepare a series of reagents, including biotin labeled and fluorescent labeled molecules, leading to the identification of transferrin receptor as the molecular target of GA.[17] More recently, GA has been reported to inhibit NF-kappaB signaling pathway and potentiating apoptosis through its interaction with the transferrin receptor.[18] GA also has been reported to selectively induce apoptosis of human hepatoma SMMC-7721 cells, while having relatively less effect on human normal embryonic hepatic L02 cells, suggesting that GA might be a highly effective anti-cancer drug candidate with low toxicity to normal tissue.[19]

In addition, GA has been reported recently to inhibit the catalytic activity of human topoisomerase II-α by binding to its ATPase domain,[20] as well as to inhibit angiogenesis through suppressing vascular endothelial growth factor-induced tyrosine phosphorylation of KDR/Flk-1.[21] A derivative of GA, acetyl isogambogic acid, has been reported to efficiently elicit cell death in melanoma cells and to inhibit ATF2 transcriptional activities, activate JNK, and increase c-Jun transcriptional activities.[22] *N*-(2-Ethoxyethyl)gambogamide (NG-18), a derivative of GA, also has been reported to efficiently induce apoptosis in cultured human cancer cells associated with up-regulation of the pro-apoptotic Bcl-2 family member Bax, and down-regulation of anti-apoptotic protein Bcl-2.[23] Interestingly, gambogic amide, the amide derivative of GA, has been reported recently to selectively bind to TrkA and robustly induce its tyrosine phosphorylation and downstream signaling activation, including Akt and MAPKs, and to strongly prevent glutamate-induced neuronal cell death and provoke prominent neurite outgrowth in PC12 cells, suggesting that gambogic amide might provide an effective treatment for neurodegenerative diseases and stroke.[24]

GA is a natural product isolated from the gamboge resin of *Garcinia hanburyi* tree in Southeast Asia. The structure of GA was confirmed by X-ray crystallographic analysis.[25] It contains a unique caged 2,3,3a,7a-tetrahydro-3,6-methanobenzofuran-7(6*H*)-one (4-oxatricyclo [4.3.1.0]decan-2-one) ring system which is found in the natural products in the genus *Garcinia*.[26] Several natural products containing this caged system, including 1-*O*-methylforbesione (**3a**)[27] and forbesione (**3b**)[28] (Chart 1) have been prepared recently via total synthesis. More recently, the synthesis and biological evaluation of simple caged *Garcinia* xanthones **4** and its neo-isomer **5** have been reported.[29] All these compounds were prepared using a Claisen/Diels–Alder reaction cascade.[30] The reaction in general produced the regular scaffold that is presented in the natural products from *Garcinia* (**1**–**4**), as well as a neo-scaffold as in **5**.[31]

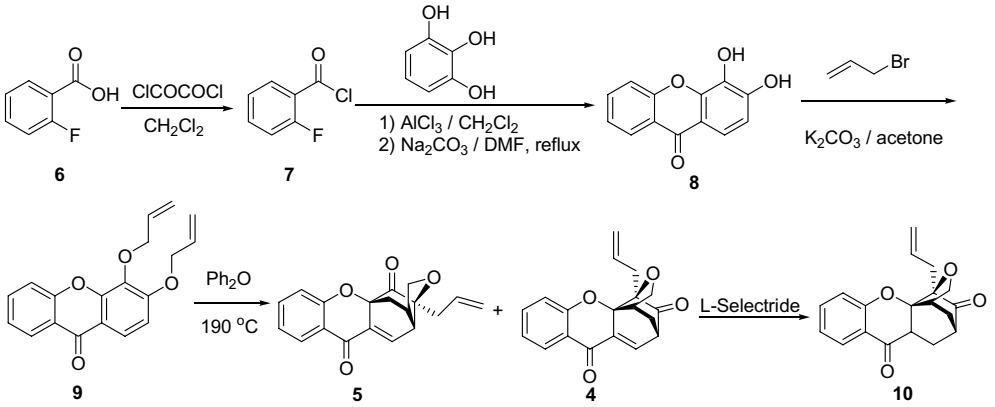
Since our SAR studies showed that the C=C of the α,β-unsaturated ketone in **1** is critical for its apoptosis inducing activity, while the 6-hydroxy and 30-carboxy group could tolerate a variety of modifications, we have been interested in the synthesis of simple derivatives of GA such as **4**.[32] These molecules would be useful to determine the role of the side groups and the tetracyclic pyran–xanthone structure for the apoptosis inducing activity of GA. In addition, they also could lead to the development of simple and novel derivatives of GA as potential anti-cancer drugs. Herein we report the synthesis of three groups of simple derivatives of GA based on xanthone, 2-phenylchromene-4-one and benzophenone, and the characterization of these compounds as apoptosis inducers.

2. Results and discussion

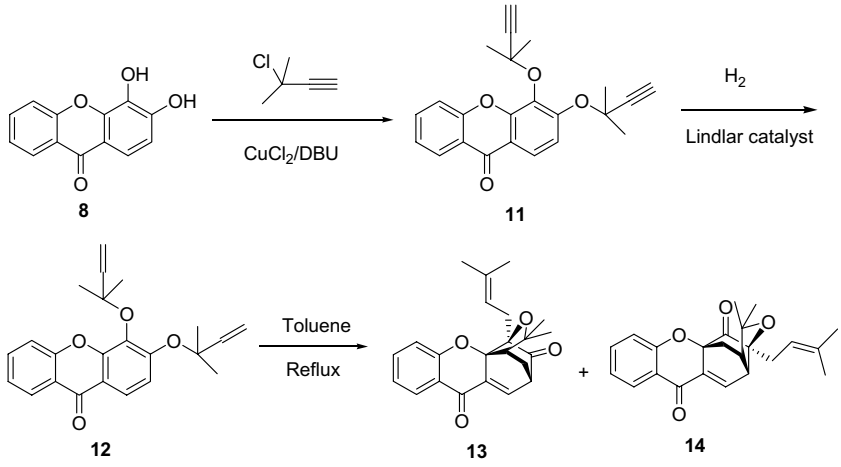
2.1. Chemistry

The xanthone-based caged compounds **4** and **5** were synthesized using procedures similar to Nicolaou and Li[27] and Batova et al.[29] as shown in Scheme 1. 3,4-Dihydroxy-9*H*-xanthen-9-one (**8**) was prepared from reaction of 2-fluorobenzoyl chloride (**7**) with pyrogallol and aluminum chloride, followed by cyclization of the intermediate benzophenone in the presence of sodium carbonate. Reaction of **8** with allyl bromide in the presence of potassium carbonate produced 3,4-bis-allyloxy-9*H*-xanthen-9-one (**9**). Compound **9** was heated in diphenyl ether at 190 °C to produce targeted compound **4** as well as its neo-isomer **5**. The ^{1}H NMR spectra of **4** and **5** have distinct patterns both in the aromatic region and non-aromatic region, in agreement with what has been reported by Batova et al.[29] Treatment of compound **4** with L-Selectride selectively reduced the C=C double bond in the α,β-unsaturated ketone to give compound **10**, similar to what has been observed for GA.[16]

The xanthone-based caged compounds **13** and **14** were prepared using procedures similar to Batova et al.[29] as shown in Scheme 2. Reaction of xanthone **8** with 3-chloro-3-methyl-1-butyne in the presence of cupric chloride and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) produced 3,4-bis-(1,1-dimethyl-prop-2-ynyloxy)-9*H*-xanthen-9-one (**11**). Reduction of **11** by hydrogen using Lindlar catalyst produced 3,4-bis-(1,1-dimethyl-allyloxy)-9*H*-xanthen-9-one (**12**). When compound **12** was refluxed in toluene, it produced the targeted compound **13** as well as its neo-isomer **14**. This is different from



Scheme 1.



Scheme 2.

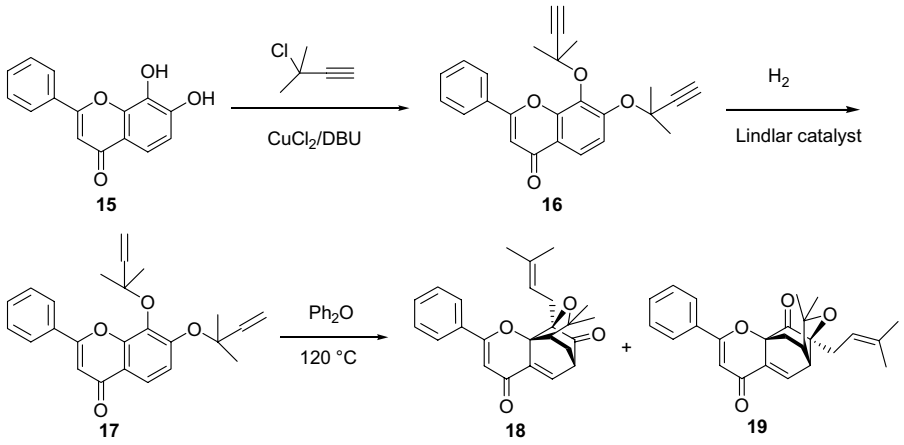
Batova et al.[29] which reported that heating of **12** in DMF at 120 °C or MeOH/H_2O at 100 °C produced only compound **13**. This is probably due to the different solvents and conditions used in the reaction. The ^{1}H NMR signals of the aromatic region of **14** give a distinct pattern that is similar to that of the corresponding neo-isomer **5**. Correspondingly, the pattern of ^{1}H NMR signals of the aromatic region of isomer **13** have a distinct pattern that is similar to that of the corresponding isomer **4**.

The 2-phenylchromene-4-one-based caged compounds **18** and **19** were prepared by the method similar to **13** and **14** as shown in Scheme 3. Reaction of 7,8-dihydroxy-2-phenyl-4*H*-chromen-4-one (**15**) with 3-chloro-3-methyl-1-butyne in the presence of cupric chloride and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) produced 7,8-bis-(1,1-dimethyl-prop-2-ynyloxy)-2-phenyl-4*H*-chromen-4-one (**16**), which was reduced by hydrogenation using Lindlar catalyst to produce 7,8-bis-(1,1-dimethyl-allyloxy)-2-phenyl-4*H*-chromen-4-one (**17**). Compound **17** was heated in diphenyl ether at 120 °C to produce the target compound **18** as well as its neo-isomer **19**. It was observed that the ^{1}H NMR signals of isomer **18** from 2.7 to 2.3 ppm have a pattern that is similar to those of the corresponding isomer **13** in the same region, while the ^{1}H NMR signals of the neo-isomer **19** from 2.7 to 1.9 ppm are similar to those of the corresponding neo-isomer **14** from 2.6 to 1.8 ppm.

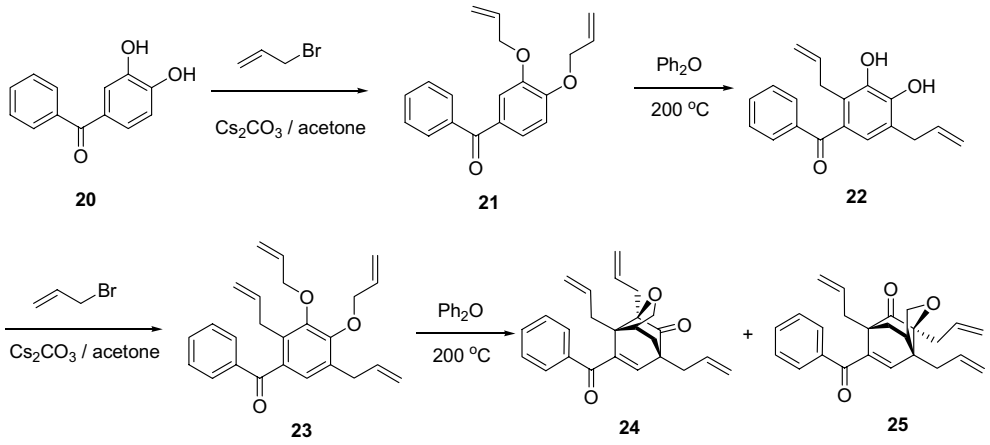
The benzophenone-based caged compounds **24** and **25** were prepared similar to **4** and **5** as shown in Scheme 4. Reaction of 3,4-dihydroxybenzophenone (**20**) with allylbromide in the presence of cesium carbonate produced 3,4-bis-allyloxy-benzophenone (**21**), which was heated in diphenyl ether at 200 °C to produce (2,5-diallyl-3,4-dihydroxy)-benzophenone (**22**). Reaction of **22** with allylbromide in the presence of cesium carbonate produced (2,5-diallyl-3,4-bis-allyloxy)-benzophenone (**23**). Compound **23** was heated in diphenyl ether at 200 °C to produce the target compound **24** as well as its neo-isomer **25**.

2.2. Induction of apoptosis

The apoptosis inducing activity of the caged molecules was measured by our cell- and caspase-based HTS assay[33] in human breast cancer cells T47D, human colon cancer cells HCT116 and hepatocellular carcinoma cancer cells SNU398, and the results are summarized in Table 1. The xanthone-based compound **4** is about 10 times less active than GA (**1**) as an apoptosis inducer in HCT116 and SNU398 cells, two of three cell lines



Scheme 3.



Scheme 4.

Table 1. Caspase activation activity of caged 2,3,3a,7a-tetrahydro-3,6-methanobenzofuran-7(6*H*)-ones

Compound	EC_{50} (μM)[a]		
	T47D	HCT116	SNU398
1	0.70 ± 0.08	0.70 ± 0.02	0.70 ± 0.07
2	>20	>20	>20
4	>20	7.1 ± 0.4	5.7 ± 0.1
5	5.9 ± 0.4	>20	5.1 ± 0.2
10	>20	>20	>20
13	3.0 ± 0.07	2.3 ± 0.2	0.90 ± 0.06
14	2.7 ± 0.05	1.9 ± 0.1	1.5 ± 0.04
18	5.1 ± 0.04	5.4 ± 0.05	2.6 ± 0.04
19	4.8 ± 0.1	3.6 ± 0.4	2.5 ± 0.01
24	>20	>20	>20
25	>20	>20	>20

[a] Data are means of three or more experiments and are reported as means ± standard error of the mean (SEM).

tested, indicating that the simple structure of **4** still maintains some of the apoptosis inducing activity of GA, and that the side groups contribute to the apoptosis activity of GA. The neo-isomer **5** is about as active as **4** in inducing apoptosis and also is active in two of three cell lines tested, suggesting that the caged structure is important for apoptosis inducing activity, and the positions of the caged structure fused with the bicyclic chroman-4-one are not critical for activity.

When the carbon–carbon double bond in the α,β-unsaturated ketone of **4** was reduced, compound **10** was found to be inactive up to 20 μM in all three cell lines. This is similar to the reported SAR of GA (**10** vs. **2**),[16] showing that the carbon–carbon double bond is essential for apoptosis inducing activity of GA and its simple caged derivatives.

The xanthone-based tetramethyl compound **13** was found to be about 3- to 7-fold more active than **4**, confirming that the side group of GA contributes to its activity. Compound **13** was about three to four times less active than GA (**1**) in T47D and HCT116 cells, and about as active as GA in SNU cells, indicating that compound **13** has good apoptosis inducing activity. The neo-isomer **14** was found to be about as active as **13**, confirming that how the caged structure fused with the bicyclic chroman-4-one is not critical for its activity. Interestingly, the 4-phenylchromene-2-one-based compound **18** was found to be only about 2-fold less active than **13**, indicating that the 6-phenylpyran-4-one ring in **18** can be used to replace the chroman-4-

one ring in **13**. Thus the tetracyclic pyran–xanthone structure of GA can be reduced to a bicyclic chromen-4-one structure and still maintain some of its apoptosis inducing activity. Similarly as observed above, the neo-isomer **19** was found to be about as active as that of **18**.

The benzophenone-based compound **24** was found to be inactive up to 20 μM in all the three cell lines, suggesting that a bicyclic structure such as that in **18** might be the minimum to maintain the apoptosis inducing activity of GA. Similarly, the neo-isomer **25** also was found to be inactive up to 20 μM in all the three cell lines. It is also possible that the two extra 2-propenyl groups in the bridge heads of **24** and **25** might have negative effects on their biological activity. Another possible explanation is that because the carbonyl in the benzoyl group is not part of a ring structure fused into the caged structure, the carbonyl group is not in the same plane as the C=C bond in the caged structure due to some unfavorable steric interaction. Therefore the α,β-unsaturated ketone in **24** and **25** might not be able to function similarly as the one in GA as well as compounds **4** and **14**.

2.3. Growth inhibition

The caged compounds were also tested by the traditional growth inhibition assay to confirm that the active compounds can inhibit cancer cell growth. The growth inhibition assays in T47D, HCT116 and SNU398 cells were run in a 96-well microtiter plate as described previously.[34] The 50% growth inhibition (GI_{50}) is defined as the concentration of drug causing 50% inhibition in absorbance compared with control untreated cells. GI_{50} values are summarized in Table 2.

Compounds **4** and **5** were found to have GI_{50} values of 1–2 μM in the three cell lines tested and to be about 10- to 15-fold less active than GA (**1**). Interestingly, compounds **4** and **5** were reported to be inactive in an inhibition of cell proliferation assay.[29] This is probably due to the difference in the concentration of compounds used in the assays as well as sensitivity of the assays. Similarly to compound **2**, compound **10** was found to be inactive up to 20 μM in all the three cell lines, confirming the importance of the carbon–carbon double bond in the α,β-unsaturated ketone for the apoptosis inducing and growth inhibiting activities of GA and its derivatives. Interestingly, compounds **13** and **14** were found to have GI_{50} values of around 0.2 μM in the three cell lines, and were about as active as GA (**1**), indicating these simple GA derivatives have good cell growth inhibiting activity but less apoptosis inducing activity. Compounds **18** and **19** were found to be about 5-fold less active than **13** and **14**. Compound **24**, which was not active in the apoptosis induction assay, also was found to be inactive in the growth inhibition assay up to 20 μM in all the three cell lines.

Table 2. Inhibition of cell proliferation activity of caged 2,3,3a,7a-tetrahydro-3,6-methanobenzofuran-7(6*H*)-ones

Compound	GI_{50} (μM)[a]		
	T47D	HCT116	SNU398
1	0.20 ± 0.01	0.10 ± 0.01	0.20 ± 0.01
2	>20	>20	>20
4	1.6 ± 0.06	1.6 ± 0.03	1.9 ± 0.2
5	1.4 ± 0.07	1.5 ± 0.08	1.5 ± 0.08
10	>20	>20	>20
13	0.20 ± 0.01	0.20 ± 0.01	0.20 ± 0.02
14	0.30 ± 0.08	0.20 ± 0.02	0.30 ± 0.03
18	1.4 ± 0.03	1.1 ± 0.03	1.2 ± 0.02
19	1.0 ± 0.03	0.9 ± 0.01	1.2 ± 0.06
24	>20	>20	>20

[a] Data are means of three experiments and are reported as means ± standard error of the mean (SEM).

3. Conclusion

In conclusion, we have synthesized three groups of caged 2,3,3a,7a-tetrahydro-3,6-methanobenzofuran-7(6*H*)-ones based on tricyclic xanthone, bicyclic 2-phenylchromene-4-one and mono-cyclic benzophenone as simple derivatives of GA. The xanthone and 2-phenylchromene-4-one-based caged molecules **4**, **13** and **18**, as well as the corresponding neo-isomers **5**, **14** and **19**, were found to induce apoptosis in our cell-based assay. These molecules are 5–10 times less potent than GA. The benzophenone-based caged molecule **24** and its neo-isomer **25** were found to be inactive in the apoptosis induction assay. Similar to GA, the carbon–carbon double bond in the α,β-unsaturated ketone of compound **4** was found to be essential for its apoptosis inducing activity and reduction of the carbon–carbon double bond in **4** produced compound **10** which was found to be inactive in the apoptosis assay. The compounds that are active in the caspase activation assay also were found to be active in the growth inhibition assay. Our synthesis and biological studies determined the minimum structure of GA for its apoptosis inducing and cell growth inhibiting activities, which could lead to the design and synthesis of simple derivatives of GA as potential anti-cancer drugs.

4. Experimental

4.1. General methods and materials

The ^{1}H NMR spectra were recorded at Varian 300 MHz. Chemical shifts are reported in ppm (δ) and J coupling constants are reported in Hz. The ^{13}C NMR spectra were recorded at Varian 75 MHz and chemical shifts are reported in ppm (δ). MS spectra analysis was performed by HT Laboratory, Inc. (San Diego, CA). Elemental analyses were performed by Numega Resonance Labs, Inc. (San Diego, CA). Reagent grade solvents were used without further purification unless otherwise specified. Flash chromatography was performed on Merck silica gel 60 (230–400 mesh) using reagent grade solvents. Human breast cancer cells T47D, human colon cancer cells HCT116 and hepatocellular carcinoma cancer cells SNU398 were obtained from the American Type Culture Collection (Manasas, VA).

4.1.1. 3,4-Dihydroxy-9*H*-xanthen-9-one (8). To a stirring solution of 2-fluorobenzoic acid (5.09 g, 36.3 mmol) and dichloromethane (110 mL) in an ice bath under argon was added dropwise a solution of oxalyl chloride (2.0 M in dichloromethane, 21 mL, 42 mmol), followed by dimethylformamide (6 drops). The ice bath was removed and the solution was stirred at room temperature for 1.5 h. The solution was then concentrated by rotary evaporation. The product was dissolved in hexane (3× 50 mL) and the mixture was filtered. The filtrate was rotary evaporated to yield 5.42 g of colorless oil. The oil was added dropwise to a mixture of pyrogallol (6.48 g, 51.3 mmol), aluminum chloride (14.6 g, 110 mmol), chloroform (250 mL) and dichloromethane (700 mL), and the solution was stirred for 17 h at room temperature. The solution was then refluxed for 3 h and cooled to room temperature. The solution was washed with 1 N HCl (3× 500 mL). The organic layer was filtered, dried over sodium sulfate, and evaporated to yield an oil. The oil was added to dimethylformamide (120 mL) with sodium carbonate (8.11 g, 76.5 mmol) and it was refluxed for 3.5 h. The solution was concentrated by rotary evaporation with heating, and the residue was purified by column chromatography (95:5 chloroform/methanol) to give a solid. The solid was washed with hexane (2× 35 mL), filtered and dried to yield compound **8** (2.10 g, 25%) as off-white solids. ^{1}H NMR (DMSO-d_6): 8.16 (d, J = 7.4, 1H), 7.84 (t, J = 7.6, 1H), 7.64 (d, J = 8.5, 1H), 7.57 (d, J = 8.8, 1H), 7.44 (t, J = 7.4, 1H), 6.94 (d, J = 8.5, 1H).

4.1.2. 3,4-Bis-allyloxy-9*H*-xanthen-9-one (9). A stirred solution of compound **8** (290 mg, 1.27 mmol), allyl bromide (800 μL, 9.20 mmol) and potassium carbonate hydrate (1.28 g, 7.77 mmol) in acetone (15.0 mL) was refluxed for 2.5 h. The solution was cooled to room temperature and dichloromethane was added. The mixture was filtered and the filtrate was rotary evaporated to yield compound **9** (372 mg, 95%) as white solids. ^{1}H NMR (DMSO-d_6): 8.33 (dd, J = 7.8, 1.8, 1H), 8.07 (d, J = 8.8, 1H), 7.72 (ddd, J = 8.1, 7.0, 1.7, 1H), 7.56 (dd, J = 8.5, 0.6, 1H), 7.38 (ddd, J = 7.8, 7.1, 1.0, 1H), 7.00 (d, J = 9.1, 1H), 6.15 (m, 2H), 5.48 (m, 1H), 5.38 (m, 2H), 5.25 (m, 1H), 4.74 (m, 4H).

4.1.3. 3,3a,4,5-Tetrahydro-1-(2-propenyl)-1,5-methano-1*H*,7*H*-furo[3,4-*d*]xanthene-7,13-dione (4), and 1,3a,4,11a-tetrahydro-1-(2-propenyl)-3*H*-1,4a-methano-10*H*-furo[3,4-*b*]xanthene-10,12-dione (5). A stirred solution of compound **9** (236 mg, 0.767 mmol) and diphenyl ether (3.0 mL) was refluxed in an oil bath at 190 °C for 11 h. The solution was cooled to room temperature and the product was purified twice by flash column chromatography (dichloromethane) to give compound **4** (28 mg, 12%) as white solids. ^{1}H NMR ($CDCl_3$): 7.95 (dd, J = 7.7, 1.7, 1H), 7.56 (ddd, J = 8.2, 7.1, 1.6, 1H), 7.34 (d, J = 7.1, 1H), 7.08 (m, 2H), 5.22 (m, 1H), 4.69 (m, 1H), 4.53 (m, 2H), 3.91 (d, J = 8.0, 1H), 3.53 (ddd, J = 6.1, 3.4, 2.1, 1H), 2.82 (dd, J = 13.3, 5.4, 1H), 2.63 (m, 1H), 2.51 (dd, J = 13.6, 9.5, 1H), 1.90 (m, 1H), 1.78 (ddd, J = 12.2, 10.4, 2.4, 1H); MS: ($M+H^+$), 309; and compound **5** (44 mg, 19%) as white solids. ^{1}H NMR ($CDCl_3$): 7.93 (dd, J = 8.0, 1.9, 1H), 7.56 (ddd, J = 8.2, 7.0, 1.8, 1H), 7.31 (d, J = 6.9, 1H), 7.19 (dd, J = 8.4, 1.0, 1H), 7.08 (td, J = 7.6, 1.1, 1H), 5.60 (m, 1H), 5.15 (s, 1H), 5.11 (m, 1H), 4.09 (dd, J = 8.3, 3.6, 1H), 3.97 (d, J = 8.2, 1H), 3.48 (dd, J = 6.9, 4.4, 1H), 2.63 (dd, J = 14.3, 6.6, 1H), 2.55 (m, 1H), 2.29 (dd, J = 12.5, 5.9, 1H), 2.23 (d, J = 5.8, 2H). Anal. Calcd. For $C_{19}H_{16}O_4$: C, 74.01; H, 5.23. Found: C, 73.62; H, 5.55.

4.1.4. 3,3a,4,5,6,6a-Hexahydro-1-(2-propenyl)-1,5-methano-1*H*,7*H*-furo[3,4-*d*]xanthene-7,13-dione (10). To a stirring solution of **4** (29 mg, 0.094 mmol) in tetrahydrofuran (15.0 mL) in a dry ice bath under argon was added dropwise 1.0 M L-Selectride in THF (150 μL, 0.15 mmol) and the solution was stirred for 25 min. The dry ice bath was removed and the solution was stirred for 20 min. The solution was concentrated by rotary evaporation and the residue was purified by column chromatography (2:1 hexanes/ethyl acetate) to yield compound **10** (11 mg, 39%) as white solids. ^{1}H NMR ($CDCl_3$): 7.91 (dd, J = 8.1, 1.8, 1H), 7.54 (ddd, J = 8.2, 7.0, 1.5, 1H), 7.08 (m, 2H), 5.86 (m, 1H), 5.27 (m, 1H), 5.12 (dt, J = 10.2, 1.5, 1H), 4.16 (dd, J = 8.0, 4.1, 1H), 3.53 (d, J = 8.0, 1H), 3.40 (dd, J = 11.5, 3.3, 1H), 3.06 (dd, J = 13.5, 6.0, 1H), 2.87 (dd, J = 13.3, 8.9, 1H), 2.82 (dt, J = 14.3, 3.6, 1H), 2.74 (dd, J = 9.9, 4.4, 1H), 2.44 (m, 1H), 2.01 (dd, J = 13.5, 10.4, 1H), 1.78 (ddt, J = 14.2, 11.7, 2.7, 1H), 1.67 (dt, J = 14.1, 3.5, 1H). MS: ($M+H^+$), 311.

4.1.5. 3,4-Bis-(1,1-dimethyl-prop-2-ynyloxy)-9*H*-xanthen-9-one (11). A solution of compound **8** (1.25 g, 5.47 mmol), cupric chloride (30.2 mg, 0.225 mmol), 3-chloro-3-methyl-1-butyne (3.36 mL, 29.9 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (2.00 mL, 13.3 mmol) in acetonitrile (100 mL) was stirred at room temperature for 11 h under argon. The solution was then heated at 75 °C for 2 h and cooled to room temperature. The solution was partitioned between ethyl acetate (100 mL) and water (75 mL). The ethyl acetate layer was dried over sodium sulfate and was concentrated by rotary evaporation. The product was purified by flash column chromatography (10:1 hexanes/ethyl acetate) to yield compound **11** (496 mg, 25%) as light yellow solids. ^{1}H NMR ($CDCl_3$): 8.33 (dd, J = 8.0, 1.7, 1H), 8.07 (d, J = 9.1, 1H), 7.71 (ddd, J = 8.2, 7.1, 1.6, 1H), 7.65 (d, J = 9.1, 1H), 7.52 (dd, J = 8.5, 0.6, 1H), 7.38 (ddd, J = 8.0, 7.2, 0.6, 1H), 2.66 (s, 1H), 2.30 (s, 1H), 1.84 (s, 6H), 1.77 (s, 6H).

4.1.6. 3,4-Bis-(1,1-dimethyl-allyloxy)-9*H*-xanthen-9-one (12). To a solution of compound **11** (318 mg, 0.882 mmol) in methanol (25 mL) was added Lindlar's catalyst (Pd, 5 wt% on calcium carbonate, 75 mg) under hydrogen (1 atm). The mixture was stirred at room temperature for 1 h, then the mixture was filtered through a syringe filter and the solvent was evaporated. The residue was purified by column chromatography (SiO_2, EtOAc:hexanes/10–25%) to give compound **12** (249 mg, 77%) as white solids. ^{1}H NMR ($CDCl_3$): 8.31 (dd, J = 8.1, 1.8, 1H), 7.93 (d, J = 9.0, 1H), 7.70 (m, 1H), 7.50 (dd, J = 8.7, 0.9, 1H), 7.37 (m, 1H), 7.13 (d, J = 9.0, 1H), 6.30 (dd, J = 17.7, 10.8, 1H), 6.20 (dd, J = 17.1, 11.1, 1H), 5.25–5.16 (m, 3H), 5.03 (dd, J = 10.5, 0.9, 1H), 1.59 (s, 6H), 1.58 (s, 6H).

4.1.7. 3,3a,4,5-Tetrahydro-3,3-dimethyl-1-(3-methyl-2-butenyl)-1,5-methano-1*H*,7*H*-furo[3,4-*d*]xanthene-7,13-dione (13), and 1,3a,4,11a-tetrahydro-3,3-dimethyl-1-(3-methyl-2-butenyl)-3*H*-1,4a-methano-10*H*-furo[3,4-*b*]xanthene-10,12-dione (14). A solution of compound **12** (229 mg, 0.587 mmol) in toluene (10 mL) was refluxed under argon for 2 h. The solvent was evaporated and the residue was purified by column chromatography (SiO_2, EtOAc:hexanes/10–30%) to give compound **13** (145 mg, 63%) as white solids. ^{1}H NMR ($CDCl_3$): 7.95 (dd, J = 7.8, 1.5, 1H), 7.53 (ddd, J = 8.1, 7.2, 1.5, 1H), 7.44 (dd, J = 7.2, 0.6, 1H), 7.07 (m, 2H), 4.42 (m, 1H), 3.50 (dd, J = 6.9, 4.5, 1H), 2.65–2.61 (m, 2H), 2.46 (d, J = 9.3, 1H), 2.35 (dd, J = 12.6, 4.2, 1H), 1.73 (s, 3H), 1.31 (m, 1H), 1.31 (s, 6H), 0.92 (s, 3H); ^{13}C NMR ($CDCl_3$): 202.8, 176.3, 159.5, 136.1, 134.8, 134.7, 133.6, 126.8, 121.8, 119.0, 118.9, 118.0, 90.3, 84.6, 83.5, 48.8, 46.8, 30.4, 29.2, 25.4, 25.2, 16.8; MS: ($M+H^+$), 365; and compound **14** (18 mg, 8%) as white solids. ^{1}H NMR ($CDCl_3$): 7.92 (dd, J = 8.1, 1.8, 1H), 7.55 (ddd, J = 8.7, 7.2, 1.8, 1H), 7.26 (d, J = 6.9, 1H), 7.20 (dd, J = 8.4, 0.6, 1H), 7.07 (td, J = 7.2, 1.2, 1H), 5.03 (m, 1H), 3.77 (dd, J = 6.9, 4.5, 1H), 2.56 (d, J = 13.2, 1H), 2.50 (dd, J = 15.3, 6.9, 1H), 2.17 (dd, J = 9.6, 4.5, 1H), 2.09 (dd, J = 14.7, 8.4, 1H), 1.88 (dd, J = 13.2, 9.9, 1H), 1.72 (s, 3H), 1.60 (s, 3H), 1.39 (s, 3H), 1.35 (s, 3H); ^{13}C NMR ($CDCl_3$): 199.7, 175.4, 160.2, 136.5, 136.1, 135.9, 134.9, 127.0, 122.0, 119.2, 118.3, 117.3, 84.1, 83.7, 78.8, 44.8, 42.1, 33.1, 30.2, 29.7, 26.8, 26.0, 18.2. MS: ($M+H^+$), 365.

4.1.8. 7,8-Bis-(1,1-dimethyl-prop-2-ynyloxy)-2-phenyl-4*H*-chromen-4-one (16). To a suspension of 7,8-dihydroxy-2-phenyl-4*H*-chromen-4-one (510 mg, 2 mmol) and $CuCl_2$ (16 mg, 0.12 mmol) in acetonitrile (3 mL) were added 3-chloro-3-methyl-1-butyne (0.5 mL, 4.56 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (0.78 mL, 5.2 mmol) slowly at 0 °C. The dark mixture was stirred at 0 °C for 5 h and then at room temperature overnight. The solvent was evaporated and the residue was purified by column chromatography (SiO_2, EtOAc:hexanes/10–50%) to give compound **16** (540 mg, 69%) as white solids. ^{1}H NMR ($CDCl_3$): 8.02 (m, 2H), 7.96 (d, J = 9.0, 1H), 7.69 (d, J = 9.0, 1H), 7.53 (m, 3H), 6.78 (s, 1H), 2.66 (s, 1H), 2.26 (s, 1H), 1.81 (s, 6H), 1.76 (s, 6H).

4.1.9. 7,8-Bis-(1,1-dimethyl-allyloxy)-2-phenyl-4*H*-chromen-4-one (17). To a solution of compound **16** (98 mg, 0.254 mmol) in methanol (20 mL) was added Lindlar's catalyst (Pd, 5 wt% on calcium carbonate, 25 mg) under hydrogen (1 atm). The mixture was stirred at room temperature for 50 min, then it was filtered through a syringe filter and the solvent was evaporated. The residue was purified by column chromatography (SiO_2, EtOAc:hexanes/10–25%) to give compound **17** (72 mg, 73%) as white solids. ^{1}H NMR ($CDCl_3$): 7.98 (m, 2H), 7.81 (dd, J = 9.0, 0.9, 1H), 7.52 (m, 3H), 7.16 (dd, J = 9.0, 0.6, 1H), 6.75 (d, J = 0.6, 1H), 6.22 (m, 2H), 5.24–5.12 (m, 3H), 4.98 (dd, J = 10.2, 1.2, 1H), 1.56 (s, 6H), 1.55 (s, 6H).

4.1.10. 6,7,7a,8-Tetrahydro-8,8-dimethyl-10-(3-methyl-2-butenyl)-2-phenyl-6,10-methano-4*H*,10*H*-furo[3,4-*i*]-1-benzopyran-4,11-dione (18), and 5a,6,8a,9-Tetrahydro-8,8-dimethyl-6-(3-methyl-2-butenyl)-2-phenyl-8*H*-6,9a-Methano-4*H*-furo[3,4-*g*]-1-benzopyran-4,10-dione (19). A solution of compound **17** in diphenyl ether (2 mL) was stirred at 120 °C under argon for 3 h. The reaction mixture was cooled to room temperature and the product was purified by column chromatography (SiO_2, EtOAc:hexanes/10–30%) to give compound **18** (45 mg, 52%) as white solids. ^{1}H NMR ($CDCl_3$): 7.85–7.82 (m, 2H), 7.57–7.46 (m, 3H), 7.30 (d, J = 6.9, 1H), 6.13 (s, 1H), 4.69 (m, 1H), 3.48 (dd, J = 6.9, 4.5, 1H), 2.67–2.56 (m, 2H), 2.52 (d, J = 9.3, 1H), 2.34 (dd, J = 13.5, 4.5, 1H), 1.69 (s, 3H), 1.40 (s, 3H), 1.36 (m, 1H), 1.31 (s, 6H); ^{13}C NMR ($CDCl_3$): 203.0, 177.1, 168.4, 134.5, 134.1, 132.9, 131.7, 131.2, 128.8, 126.5, 117.9, 100.8, 92.7, 84.3, 83.2, 49.2, 46.5, 30.4, 29.1, 29.0, 25.7, 25.0, 17.8; MS: ($M+H^+$), 391; and compound **19** (21 mg, 24%) as white solids. ^{1}H NMR ($CDCl_3$): 7.91–7.87 (m, 2H), 7.55–7.43 (m, 3H), 7.06 (d, J = 6.6, 1H), 6.09 (s, 1H), 5.07 (m, 1H), 3.77 (dd, J = 6.9, 4.5, 1H), 2.69 (d, J = 13.2, 1H), 2.53 (dd, J = 15.3, 6.6, 1H), 2.16 (dd, J = 9.3, 4.2, 1H), 2.11 (dd, J = 15.0, 8.7, 1H), 1.91 (dd, J = 13.2, 9.9, 1H), 1.74 (s, 3H), 1.61 (s, 3H), 1.40 (s, 3H), 1.36 (s, 3H); ^{13}C NMR ($CDCl_3$): 198.7, 175.9, 169.6, 136.1, 135.3, 132.8, 131.8, 131.1, 128.6, 126.8, 117.2, 101.3, 86.0, 83.7, 78.7, 44.5, 41.6, 32.8, 30.2, 29.6, 26.8, 26.0, 18.3; MS: ($M+H^+$), 391.

4.1.11. 3,4-Bis-allyloxy-benzophenone (21). To a suspension of 3,4-dihydroxybenzophenone (2.14 g, 10 mmol) and cesium carbonate (7.01 g, 21.6 mmol) in dry acetone (50 mL) was added allylbromide (5.3 mL, 60 mmol). The mixture was stirred at 60 °C for 6 h and additional allybromide (3.0 mL, 34.7 mmol) and cesium carbonate (3.00 g, 9.2 mmol) were added. The mixture was stirred for 3 h, cooled to room temperature, filtered and washed with EtOAc. The filtrate was evaporated under reduced pressure. The crude product was partitioned between EtOAc (50 mL) and H_2O (15 mL). The EtOAc phase was separated and evaporated to give compound **21** (2.9 g, 99%) as a light yellow oil. ^{1}H NMR ($CDCl_3$): 7.77 (m, 1H), 7.74 (m, 1H), 7.57 (m, 1H), 7.50–7.44 (m, 3H), 7.38 (ddd, J = 8.7, 2.4, 0.9, 1H), 6.91 (d, J = 8.4, 1H), 6.08 (m, 2H), 5.47 (m, 1H), 5.41 (m, 1H), 5.32 (m, 2H), 4.68 (m, 4H).

4.1.12. (2,5-Diallyl-3,4-dihydroxy)-benzophenone (22). A solution of compound **21** (1.51 g, 5.1 mmol) in diphenyl ether (3 mL) was stirred at 200 °C for 2 h. The reaction mixture was cooled and it was purified by column chromatography (SiO_2, 30% EtOAc in hexanes) to give compound **22** (0.84 g, 56%) as a light yellow oil. ^{1}H NMR ($CDCl_3$): 7.79 (m, 2H), 7.57 (m, 1H), 7.44 (t, J = 7.8, 2H), 6.78 (s, 1H), 6.16–5.86 (m, 3H), 5.60 (br s, 1H), 5.12 (m, 4H), 3.51 (d, J = 6.0, 2H), 3.39 (d, J = 6.6, 2H).

4.1.13. (2,5-Diallyl-3,4-bis-allyloxy)-benzophenone (23). A suspension of compound **22** (840 mg, 2.85 mmol), cesium carbonate (2.78 g, 8.55 mmol) and allybromide (1.5 mL, 17.3 mmol) was stirred at 60 °C for 20 h. The mixture was filtered and washed with EtOAc. The filtrate was evaporated and the crude product was purified by col-

umn chromatography (SiO_2, 10–30% EtOAc:hexanes) to give compound **23** (880 mg, 83%) as a light yellow oil. ^{1}H NMR ($CDCl_3$): 7.81–7.77 (m, 2H), 7.57 (tt, J = 7.2, 1.5, 1H), 7.47–7.41 (m, 2H), 6.90 (s, 1H), 6.10 (m, 2H), 5.89 (m, 2H), 5.43 (m, 1H), 5.38 (m, 1H), 5.27 (m, 1H), 5.24 (m, 1H), 5.04 (m, 1H), 5.00 (m, 1H), 4.88 (m, 1H), 4.83 (dq, J = 10.2, 1.5, 1H), 4.57–4.51 (m, 4H), 3.50 (dt, J = 6.3, 1.5, 2H), 3.89 (dt, J = 6.6, 1.2, 2H).

4.1.14. 4-Benzoyl-2,3,3a,7a-tetrahydro-3a,6,7-tri-(2-propenyl)-3,6-methanobenzofuran-7(6*H*)-one (24), and 5-benzoyl-2,3,3a,7a-tetrahydro-3a,6,7a-tri-(2-propenyl)-3,6-methanobenzofuran-7(6*H*)-one (25). A solution of compound **23** (474 mg, 1.27 mmol) in diphenyl ether (3 mL) was stirred at 200 °C for 2 h. The reaction mixture was cooled to room temperature and the product was purified by column chromatography (SiO_2, CH_2Cl_2) to give compound **24** (190 mg, 35%) as solids. ^{1}H NMR ($CDCl_3$): 7.80–7.75 (m, 2H), 7.59 (m, 1H), 7.48–7.43 (m, 2H), 6.23 (s, 1H), 5.85–5.58 (m, 2H), 5.36 (m, 1H), 5.21–5.06 (m, 3H), 5.02–4.91 (m, 3H), 4.14 (dd, J = 8.7, 4.5, 1H), 3.72 (d, J = 8.4, 1H), 3.01 (dd, J = 13.8, 5.7, 1H), 2.93 (dd, J = 14.4, 7.2, 1H), 2.66–2.51 (m, 3H), 2.41–2.29 (m, 2H), 2.08 (dd, J = 13.2, 10.2, 1H), 1.70 (d, J = 13.5, 1H); ^{13}C NMR ($CDCl_3$): 204.4, 192.8, 141.6, 139.8, 136.5, 133.8, 133.2, 132.5, 132.0, 129.7, 128.3, 119.3, 118.8, 118.5, 83.5, 53.4, 51.1, 50.9, 39.6, 39.3, 34.3, 33.5, 32.7; MS: ($M+H^+$), 375; and compound **25** (79 mg, 14%) as solids. ^{1}H NMR ($CDCl_3$): 7.79–7.76 (m, 2H), 7.60 (tt, J = 6.6, 1.5, 1H), 7.50–7.44 (m, 2H), 6.33 (s, 1H), 5.98–5.73 (m, 2H), 5.60 (m, 1H), 5.16–4.95 (m, 6H), 4.18 (dd, J = 8.4, 4.5, 1H), 3.70 (d, J = 8.7, 1H), 3.49 (m, 1H), 2.81 (dd, J = 14.4, 8.7, 1H), 2.67 (dd, J = 9.9, 4.5, 1H), 2.56–2.50 (m, 2H), 2.45–2.37 (m, 1H), 2.24 (dd, J = 14.7, 9.3, 1H), 2.02 (dd, J = 12.9, 10.2, 1H), 1.69 (d, J = 13.8, 1H); ^{13}C NMR ($CDCl_3$) 205.5, 193.8, 141.2, 141.1, 137.3, 133.7, 133.3, 132.9, 132.0, 129.9, 128.3, 118.9, 118.7, 118.3, 82.7, 74.3, 53.2, 49.5, 39.7, 38.5, 35.3, 34.0, 30.6; MS: ($M+H^+$), 375.

4.2. Caspase activation assay (EC_{50})

The caspase assay was run as previously reported.[33] In brief, T47D, HCT116 and SNU398 cells were exposed continuously to test compound for 24 h. The caspase-3 fluorogenic substrate *N*-(Ac-DEVD)-*N*-ethoxycarbonyl-R110 in a caspase buffer was then added, followed by incubation at 37 °C for 2 h.

Calculation. The relative fluorescence unit (RFU) values measured on a Model Spectrafluor Plus Tecan Instrument were used to calculate the sample readings as follows: the activity of caspase activation was determined by the ratio of the net RFU value for the test compound to that of control samples. The EC_{50} (μM) was determined by a sigmoidal dose–response calculation (XLFit3, IDBS), as the concentration of compound that produces the 50% maximum response.

4.3. Cell growth inhibition assay (GI_{50})

The cell growth inhibition assay was run as previously reported.[34] In brief, T47D, HCT116 and SNU398 cells were exposed continuously to test compound for 48 h. CellTiter-Glo reagent (Promega) was added. The samples were mixed by agitation, incubated at room temperature for 10–15 min and then read using a luminescent plate reader (Model Spectrafluor Plus Tecan Instrument). The GI_{50} is defined as 50% inhibition of cell proliferation.

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