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Synthesis and Antiproliferative Activity of Novel Quercetin-1,2,3-Triazole Hybrids using the 1,3-Dipolar Cycloaddition (Click) Reaction

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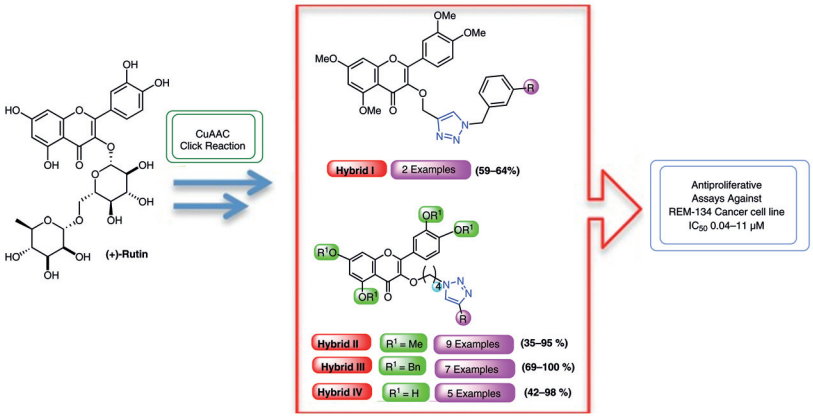

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Abstract Twenty-three new quercetin-1,2,3-triazole hybrids were synthesized in good to quantitative yields *via* Cu(I)-catalyzed azide-alkyne cycloaddition reaction under microwave irradiation. These new hybrids contain a 1,4-disubstituted 1,2,3-triazole ring at the 3-OH position of quercetin whilst the remaining hydroxyl groups were either protected as methyl or benzyl groups or left unprotected. All the quercetin-1,2,3-triazole hybrids **I–IV** were evaluated against REM-134 canine mammary cancer cell line, which is used as a translational model for human breast cancer. These new analogues exhibit potent antiproliferative activity against this cancer cell line. Furthermore, the results show that some of the new quercetin-1,2,3-triazole hybrids have better activity than quercetin. Our best inhibitors displayed IC_{50} values in the range of 41–180 nM, and undoubtedly will have an important impact on the treatment of both canine and human breast cancer.

Key words quercetin, 1,2,3-triazole, Huisgen reaction, molecular hybridization, anticancer, flavonoid

Quercetin (Quer), the most abundant polyphenolic flavonoid in our diet, has attracted attention over the last decades because of its recognized biological properties, such as antioxidant, anticancer, anti-Alzheimer, and anti-inflammatory action.[2] In spite of the interesting pharmacological properties of quercetin, it also presents some disadvantages, such as poor bioavailability and low solubility. Several efforts have been made to overcome these problems, principally by chemical modification of the quercetin structure. These include modifications based on the functionalization of the hydroxyl groups of quercetin with alkyl, aryl, ester, carboxylic acid and amino acids substituents, etc.[3] Quercetin and derivatives have proven beneficial effects against the proliferation of breast tumors.[4]

The 1,2,3-triazole unit is also a very important pharmacophore in medicinal chemistry, because it possesses several pharmacological properties, such as anticancer, antifungal, antibacterial, and anti-inflammatory action. This is probably due to its behavior as a bioisostere of several functional groups such as amides, carboxylic acids, esters and heterocycles, as well as chemical inertness, and the ability to interact through hydrogen bonding and dipole–dipole interactions.[5] Over the last decade, a wide diversity of 1,2,3-triazole hybrids have emerged, most of them with antitumor activity.[6] Recently, our research group has reported a variety of triazolyl hybrids, which have shown interesting antiproliferative activities.[7] Furthermore, the 1,2,3-triazole unit is easily synthesized using Cu(I)-catalyzed azide-alkyne cycloadditions (CuAAC), well known as the 'click' reaction, discovered independently by the groups of Sharpless and Meldal in 2002; this reaction has been used extensively for the preparation of new compounds with anticancer activity.[8]

In recent years, the molecular hybridization strategy has been adopted by researchers to prepare a wide variety of scaffolds with pharmacological properties. The hybridization between drugs, pharmacophores or natural products has given rise to numerous new molecules that can act as multifunctional agents.[9]

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Since natural flavonoids have diverse pharmacological properties, they have become very attractive structures for several chemical modifications in order to increase their potency. As in the case of flavonoid-1,2,3-triazole hybrids, a great diversity of these hybrids with several interesting biological properties have been reported.[10,11] Wang et al. reported the synthesis of the hybrid flavonoid triazolyl glycosides (apigenin, acacetin, 3′,4′,5,7-tetramethylquercetin), through CuAAC of terminal alkyne tethered flavonoids with acetylated sugar azides, which displayed potent antiproliferative activity against Hela, HCC1954 and SK-OV-3 cell lines.[11]

To enhance the anticancer properties of quercetin, it was decided to combine the flavonoid quercetin with the 1,2,3-triazole moiety. In this full paper we report the molecular hybridization between quercetin and 1,2,3-triazoles, describing four types of quercetin hybrids (**I–IV**; Figure 1), which have been fully characterized and evaluated in antiproliferative assays against REM-134 canine mammary carcinoma cell line. The use of this spontaneously occurring canine mammary tumor as a translational model for human breast cancer is advantageous (due to factors such as similar biological behavior, large body size, comparable responses to cytotoxic agents, and shorter life expectancy) and can simultaneously contribute to the improvement of human and canine breast cancer research.[12]

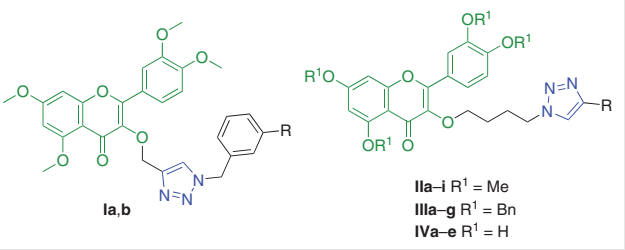
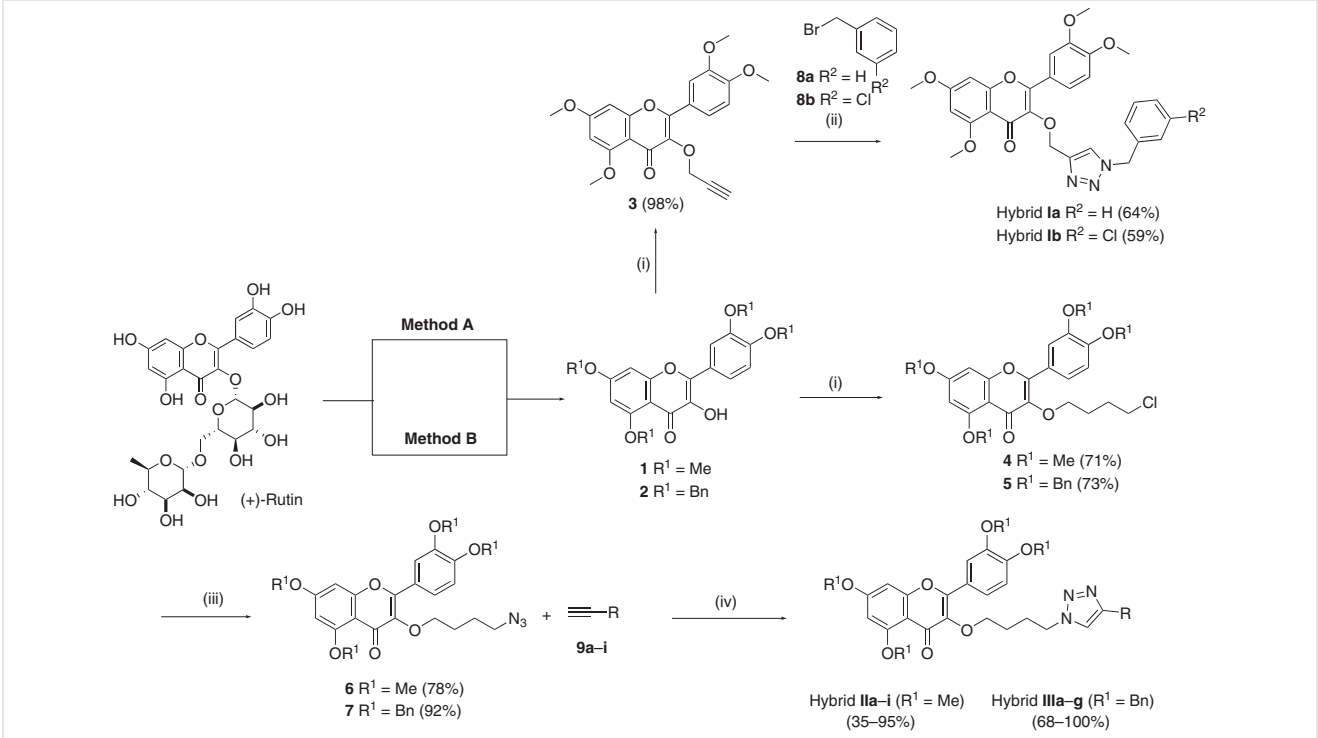


Figure 1 Quercetin-1,2,3-triazole hybrids **I–IV**

The synthetic approach used involved a series of reaction steps including alkylation, azidation, 1,3-cycloaddition and hydrogenolysis reactions (Scheme 1 and Scheme 2). All the hybrids have the 3-OH of the quercetin functionalized with a 1,4-disubstituted-1,2,3-triazole unit; the differences between them are the protection of the remaining four hydroxyl groups with alkyl or aryl substituents. Hybrids **I** and **II** have their four hydroxyls alkylated with methyl groups, in 3′,4′,5,7-tetramethylquercetin-1,2,3-triazole, and hybrids **III** have the hydroxyls protected as benzyl groups, giving



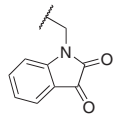
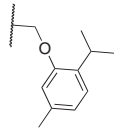
Scheme 1 Synthetic route for the synthesis of hybrids **I–III**. *Reagents and conditions*: Method A: (a) MeI, DMF, r.t., overnight; (b) HCl 5%, reflux, 3 h.[13a] Method B: (a) BnBr, DMF, r.t., overnight; (b) HCl (5% in methanol), reflux, 3 h.[13b] (i) propargyl bromide (1.5 equiv) or $Br(CH_2)_4Cl$ (1.5 equiv), K_2CO_3 (1.5 equiv), acetone, reflux, overnight; (ii) $Cu(OAc)_2{\cdot}H_2O$ (5 mol%), sodium L-ascorbate (20 mol%), 1,10-phenanthroline (5 mol%), aryl bromides **8a–b** (1 equiv), sodium azide (1.2 equiv), EtOH/H_2O (1:1), 90 °C, MW, 0.5–1 h; (iii) Sodium azide (1.5 equiv), DMF, 120 °C, MW, 1 h; (iv) $CuSO_4{\cdot}5H_2O$ (5 or 10 mol%), sodium L-ascorbate or L-ascorbic acid (20 mol%), alkyne **9a–i** (1 equiv), DMF, 90 °C, MW 0.5 h.

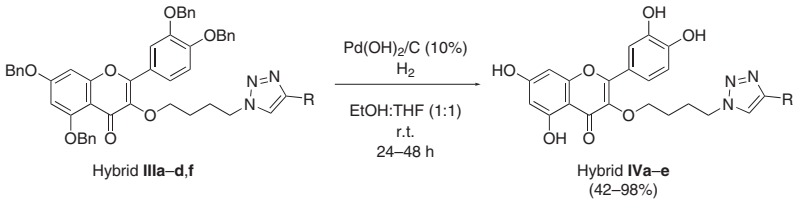
3′,4′,5,7-tetrabenzylquercetin-1,2,3-triazole. Hybrids **IV** have the four unprotected hydroxyls, existing as the quercetin-1,2,3-triazole. Our primary goal was to introduce a 1,4-disubstituted 1,2,3-triazole moiety only in the 3-OH position of the quercetin; to achieve this, the key intermediates **1** and **2** were prepared selectively using (+)-rutin (quercetin-3-*o*-rutinoside) as starting material in very good yields, using reported procedures.[13] Firstly, the hydroxyl groups of the (+)-rutin were alkylated (with iodomethane or benzyl bromide), then the rutinoside substituent was removed by acidic hydrolysis, furnishing the desired product. The hybrids **Ia–b** differ from the others because they have the quercetin core in the 4-position of the 1,2,3-triazole instead of the 1-position. For this reason, the synthesis of hybrids **I** differed from those of hybrids **II** and **III**. The first step consisted of the alkylation of quercetin derivative **1** with propargyl bromide using K_2CO_3 in acetone and furnished the desired 3-(prop-2-yn-1-yloxy)-3′,4′,5,7-tetramethylquercetin **3** in 98% yield, without purification (Scheme 1).[11] With the alkyne derivative **3** in hand, the 1,2,3-triazole moiety was introduced through a click multicomponent reaction under microwave (MW) irradiation, which combined the azidation and click reactions in one pot. The reaction was carried out between alkyne **3**, sodium azide, aryl bromide derivatives **8a–b** (benzyl bromide **8a** or 3-chlorobenzylbromide **8b**) catalyzed by $Cu(OAc)_2{\cdot}H_2O$ in the presence of L-ascorbic acid (reducing agent) and 1,10-phenylphenanthroline (which is a Cu(I) stabilizing agent) using ethanol/water (1:1) as solvent under microwave irradiation.[14]

The hybrids **Ia–b** were prepared with good yields, up to 64%. In the case of the hybrids **II**, the 3-OH unit of **2** was functionalized with a four-carbon containing linker, via alkylation with 1-bromo-4-chlorobutane and K_2CO_3 in acetone overnight, to give the 3-(4-chlorobutoxy)-3′,4′,5,7-tetramethylquercetin product **4** with very good yield (71%). The three-component click reaction, the method used for the preparation of hybrids **Ia–b**, was the first approach used for the synthesis of hybrids **II**, but, unfortunately, it was unsuccessful, probably because the chloro intermediate **4** is less reactive than the benzyl bromide substrates (**8a–b**). As an alternative, we adopted a stepwise strategy to introduce the 1,2,3-triazole moiety (Scheme 1). This methodology has already been successful for the synthesis of 1,2,3-triazole-dihydropyrimidinone hybrids.[7a] The azidation of intermediate **4** was carried out with sodium azide in DMF under MW conditions (30 minutes), yielding 3-(4-azidobutoxy)-3′,4′,5,7-tetramethylquercetin **6** with 78% yield. The nine 3′,4′,5,7-tetramethylquercetin-1,2,3-triazole hybrids **IIa–i** were prepared with moderate to excellent yields (Table 1), using 3-(4-azidobutoxy)-3′,4′,5,7-tetramethylquercetin **6**, terminal alkynes **9a–i**, $CuSO_4{\cdot}5H_2O$ (5 mol%) as catalyst and sodium L-ascorbate (20 mol%) as a reducing agent in DMF under MW conditions (10 minutes). The synthesis of the hybrids **IIIa–g** was the same as for hybrids **II**, but the catalyst loading was increased to 10 mol%, L-ascorbic acid was used instead of sodium L-ascorbate and the reaction time was increased (30 minutes). The yields obtained were good to excellent (Table 1).

Hybrids **IV** were easily prepared through debenzylation of hybrids **III** (Scheme 2), which involved hydrogenolysis catalyzed by $Pd(OH)_2$/activated carbon in THF/ethanol (1:1) under a H_2 atmosphere at room temperature. The querce-

Table 1 Yields for the Synthesis of Hybrids **II–IV**

Alkyne (**9**)	R	Hybrid	Yield (%)	Hybrid	Yield (%)	Hybrid	Yield (%)
a	Phenyl	**IIa**	92	**IIIa**	100	**IVa**	98
b	cyclopropyl	**IIb**	63	**IIIb**	100	**IVb**	95
c	1-hydroxycyclopentyl	**IIc**	52	**IIIc**	100	**IVc**	92
d	1-hydroxymethyl	**IId**	90	**IIId**	96	–	–
e	2-hydroxypropan-2-yl	**IIe**	90	**IIIe**	98	**IVd**	65
f		**IIf**	94	**IIIf**	78	–	–
g		**IIg**	95	**IIIg**	68	**IVe**	42
h	propanyl	**IIh**	35	–	–	–	–
i	2-aminopropan-2-yl	**IIi**	55	–	–	–	–



Scheme 2 Debenzylation of hybrids **III** via catalytic hydrogenolysis

tin-1,2,3-triazole hybrids **IVa–e** were obtained with good to excellent yields (Table 1).

All the new hybrids **I–IV** were fully characterized by ^{1}H and ^{13}C NMR and mass spectrometry analyses.

Antiproliferative Activity

The new quercetin-1,2,3-triazole hybrids **I–IV** synthesized in this work were screened at a concentration of 100 µM against REM-134 canine mammary carcinoma cell line. Quer and suberoylanilide hydroxamic acid (SAHA) were also evaluated for their antiproliferative activity. SAHA was used as a positive control, displaying an inhibitory concentration of 50% (IC_{50}) value of 1.0 µM. Interestingly, Quer did not show antiproliferative activity at 100 µM concentration (IC_{50} value >100 µM) nor did hybrids **III**, possessing the hydroxyl groups protected with benzyl groups. This may have been due to negative steric interactions with their biological target, which unfortunately is not known at the current time. Solubility issues were another factor. Nevertheless, hybrids **IV** and **I–II**, with either free hydroxyl groups or protected with methyl groups were antiproliferative.

Table 2 Antiproliferative Activity (IC_{50}, µM) against REM-134 Canine Mammary Carcinoma Cell Line

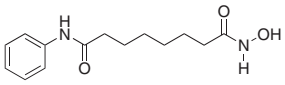
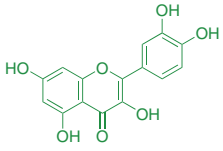
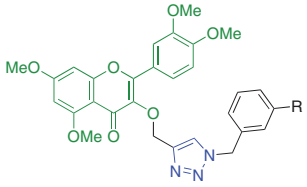
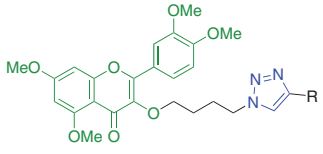
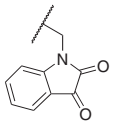
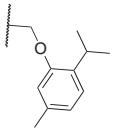
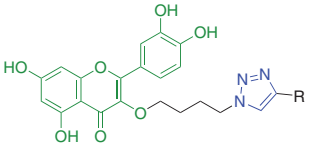
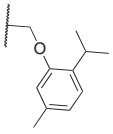
Compounds			IC_{50} (µM)
Structure	R	Code	
	–	SAHA	1
	–	Quer	>100
	H	**Ia**	$0.1 < IC_{50} < 10$
	Cl	**Ib**	0.62
	phenyl	**IIa**	0.12
	cyclopropyl	**IIb**	11
	1-hydroxycyclopentanyl	**IIc**	$10 < IC_{50} < 100$
	1-hydroxymethyl	**IId**	>100
	2-hydroxypropan-2-yl	**IIe**	$10 < IC_{50} < 100$

Table 2 (continued)

Compounds Structure	R	Code	IC_{50} (μM)
		**IIf**	0.11
		**IIg**	0.3
	propanyl	**IIh**	7.1
	2-aminopropan-2-yl	**IIi**	ca. 10
	phenyl	**IVa**	0.075
	cyclopropyl	**IVb**	0.041
	1-hydroxycyclopentanyl	**IVc**	0.16
	2-hydroxypropan-2-yl	**IVd**	>100
		**IVe**	0.18

Most hybrids **I**, **II** and **IV** exhibited inhibition of cell proliferation above 50% at 100 μM concentration. To determine the IC_{50} values, these hybrids were evaluated in the range of concentrations 10^{-9} to 10^{-5} M (at five concentrations; Table 2).

By comparing hybrids **Ia** and **Ib**, which have a very similar structure, we found the best inhibitor to be hybrid **Ib** (IC_{50}= 0.62 μM), having a chloro in the 3-position of the phenyl substituent, which enhanced the activity. However, hybrids **I** showed a lower antiproliferative effect than hybrids **II**, and this was probably due to the size of the linker, which was much shorter than the four-carbon-chain linker in the case of hybrids **II**. The role of the position-4 substituents in the 1,2,3-triazole ring of the hybrids **II** was also analyzed. We observed that the bulkier groups, 1-hydroxycyclopentanyl (**IIc**), 1-hydroxymethyl (**IId**), 2-hydroxypropan-2-yl (**IIe**) (which is a saturated sp^3 carbon-rich appendage) showed lower activities (>100 μM). However, substrates with cyclopropyl (**IIb**), 2-aminopropan-2-yl (**IIi**) or propanyl (**IIh**) substituents showed a moderate antiproliferative effect (10 μM). On the other hand, aromatic substituents such as phenyl (**IIa**), isatin (**IIf**), and thymol (**IIg**), delivered the highest activities (<1 μM). This may be a consequence of bearing unsaturated aromatic units and a planar structure, leading to more favorable interactions with the molecular target.

Generally, hybrids **IV** (quercetin-1,2,3-triazole) were stronger inhibitors, except for the hybrid **IVd**, which possessed a bulky saturated substituent at the 4-position of the 1,2,3-triazole ring (>100 μM). Among the hybrids **IV**, the most active compounds were **IVb** and **IVa**, bearing cyclopropyl and phenyl ring in the triazole side chain (IC_{50} values of 0.041 and 0.075 μM, respectively). Indeed, hybrids **IV**, with free hydroxyl groups in the quercetin unit, are more active than hybrids **II** (with methoxyl groups). A possible explanation is that the former may be able to form critical hydrogen bonds with their biological target. Furthermore, it should be noted that some hybrids are cytotoxic, at high concentrations; for instance, both **IVa** and **IVb** are cytotoxic at concentrations of >10 μM. Hybrid **IIg** is cytotoxic at concentrations >1 μM.

In this work 23 new quercetin-1,2,3-triazole hybrids were synthesized with moderate to excellent yields. These new hybrids were easily obtained by using the CuAAC methodology in conjunction with MW conditions. Generally, hybrids **I**, **II**, and **IV** exhibited antiproliferative effects against the REM-134 tumor cell line. Hybrids **I** and **II**, with the hydroxyls protected with methyl groups, presented very good IC_{50} values in the range 0.11–10 μM. Hybrids **IVa** and **IVb**, with IC_{50} values of 75 and 41 nM, respectively, were the best inhibitors, indicating that perhaps the free hydroxyls in the quercetin unit are important for biological activity. Functionalization of Quer in the 3-OH position with a 1,2,3-triazole moiety enhanced its antiproliferative effect in this cancer cell line.

Most of these new quercetin-1,2,3-triazole hybrids **I**, **II**, and **IV** have much potential for use as chemotherapeutic agents for human and veterinary (dogs) applications. All hybrids will be evaluated for their anti-Alzheimer's and antibacterial properties in due course.

(+)-Rutin trihydrate 95% 1-bromo-4-chlorobutane 99%, sodium azide 99%, benzyl bromide 99%, sodium L-ascorbate 99%, 1,10-Phenantroline 99%, and phenylacetylene 98+% were purchased from Alfa Aesar. K_2CO_3 99% and silica gel 70–200 mesh for chromatography were purchased from Carlo Erba. Propargyl bromide solution, 3-chlorobenzyl bromide 97%, cyclopropylacetylene 97%, 1-ethynylcyclopentanol 98%, 2-propyn-1-ol 99%, 2-methyl-3-butyn-2-ol 98%, and 2-methyl-3-butyn-2-amine 95%, were purchased from Sigma–Aldrich. Pent-1-yne 99% was purchased from ACROS. $Cu(OAc)_2{\cdot}H_2O$ (99%), L-ascorbic acid, TLC plates (silica gel 60 F254), ethyl acetate (anhydrous, purity ≥99%), acetone, methanol, tetrahydrofuran (THF), ethanol, *n*-hexane (anhydrous, purity ≥99.5%) and $CuSO_4{\cdot}5H_2O$ (99%) were obtained from Merck. Deuterated solvents, $CDCl_3$, DMSO-d_6 and MeOD, were purchased from Cambridge Isotope Laboratories. All chemicals were used without further purification.

The products were analyzed by thin-layer chromatography (TCL) performed on F-254 silica gel coated aluminum plates from Merck. Column chromatography was performed on silica gel 60, 70–200 μm. Plates were visualized either by UV light or with phosphomolybdic acid in ethanol. ^{1}H and ^{13}C APT NMR spectra were recorded with a Bruker Avance III at 400 and 100 MHz, respectively. Chemical shifts were quoted in parts per million (ppm) and referenced to the appropriate solvent peak. Mass spectra (MS) ESI-TOF were obtaind by the mass spectrometry service of the University of Salamanca, Spain. Analysis (HRMS) was performed with a Thermo Orbitrap Q-exactive focus at a resolution of 70000. ESI was used as the ionization method, and an alternating method between positive and negative modes was applied. The method with best signal was used for the determination of the exact mass. Samples were dissolved in methanol. All microwave irradiation experiments were performed with a Biotage reactor in a sealed vessel. Melting points were measured with a Barnead Electrothermal™ 9100 Series melting-point apparatus. All readings for the bioassays were obtained with an Absorbance Microplate Spectrophotometry (TriStar® S LB 942 model) instrument at 460 nm wavelength.

The key intermediates 5,7-bismethoxyl-2-(3,4-bismethoxyphenyl)-3-hydroxyl-4*H*-chromen-4-one (**1**) and 5,7-bisbenzyloxy-2-(3,4-bisbenzyloxyphenyl)-3-hydroxyl-4*H*-chromen-4-one (**2**) were synthesized by following reported procedures.[13] 1-(Prop-2-yn-1-yl)isatin (**9f**) was prepared using a reported method.[15] 1-Isopropyl-4-methyl-2-(prop-2-ynyloxy)benzene (**9g**) was prepared by a reported method.[16]

Alkylation of Intermediates 1 and 2; General Procedure

Compound **1** or **2** (1.5 equiv) and K_2CO_3 (1.5 equiv) were dissolved in anhydrous acetone and then propargyl bromide or 1-bromo-4-chlorobutane (1.2 equiv) was added slowly to the reaction mixture. The reaction was heated at reflux overnight, and then the solvent was removed under vacuum. CH_2Cl_2 and H_2O were added, and the crude reaction product was extracted twice with CH_2Cl_2, the organic phases were combined, dried with anhydrous $MgSO_4$, filtered, and the solvent was removed under vacuum. When necessary, the crude products were purified by silica gel column chromatography.

2-(3,4-Dimethoxyphenyl)-5,7-dimethoxy-3-(prop-2-yn-1-yloxy)-4*H*-chromen-4-one (3)

Obtained by using the general procedure described above, with compound **1** (0.5 g, 1.4 mmol), K_2CO_3 (0.193 g) and propargyl bromide (0.21 mL) in acetone (10 mL). The title compound was obtained without further purification, as a light-yellow solid.

Yield: 98% (0.542 g).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.82 (d, *J* = 2 Hz, CHQuer), 7.73 (dd, *J* = 2, 8.5 Hz, 1 H, CHQuer), 6.97 (d, *J* = 8.6 Hz, 1 H, CHQuer), 6.52 (d, *J* = 2 Hz, 1 H, CHQuer), 6.36 (d, *J* = 2 Hz, 1 H, CHQuer), 4.97 (d, *J* = 2.4 Hz, 2 H, CH_2), 3.99 (s, 3 H, OCH_3), 3.98 (s, 3 H, OCH_3), 3.96 (s, 3 H, OCH_3), 3.90 (s, 3 H, OCH_3), 2.35 (t, *J* = 2 Hz, 1 H, CHalkyne).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 174.0, 164.1, 161.1, 158.9, 153.7, 151.0, 148.6, 138.6, 123.4, 122.5, 121.9, 112.0, 110.7, 96.0, 92.6, 79.3, 75.9, 59.3, 56.6, 56.3, 56.1, 56.0.

MS (ESI): *m*/*z* (%) = 397.24 (100) $[M + 1]^+$.

3-(4-Chlorobutoxy)-2-(3,4-dimethoxyphenyl)-5,7-dimethoxy-4*H*-chromen-4-one (4)

Obtained by using the general procedure described above, with compound **1** (1 g, 2.8 mmol), K_2CO_3 (0.583 g) and 1-bromo-4-chlorobutane (0.49 mL) in acetone (30 mL). The crude product was purified using SiO_2 gel and EtOAc as solvent to give the title compound as a white solid.

Yield: 71% (0.888 g); R_f = 0.63 in EtOAc; mp 131–132 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.66–7.69 (m, 2 H, CHQuer), 6.97 (d, *J* = 8 Hz, 1 H, CHQuer), 6.49 (d, *J* = 2 Hz, 1 H, CHQuer), 6.34 (d, *J* = 2 Hz, 1 H, CHQuer), 4.03 (t, *J* = 6 Hz, 2 H, CH_2-O), 3.96 (s, 6 H, 2×OMe), 3.95 (s, 3 H, OMe), 3.90 (s, 3 H, OMe), 3.61 (t, *J* = 6.4 Hz, 2 H, CH_2-Cl), 1.93–2.00 (m, 2 H, CH_2), 1.83–1.90 (m, 2 H, CH_2).

^{13}C APT NMR ($CDCl_3$, 100 MHz): δ = 174.1, 164.0, 161.1, 158.9, 153.0, 150.9, 148.7, 140.2, 123.5, 121.8, 111.4, 110.8, 109.5, 95.9, 92.5, 71.2, 56.5, 56.2, 56.1, 55.9, 45.1, 29.3, 27.6.

MS (ESI): *m*/*z* (%) = 449.20 (100) $[M + 1]^+$.

5,7-Bis(benzyloxy)-2-(3,4-bis(benzyloxy)phenyl)-3-(4-chlorobutoxy)-4*H*-chromen-4-one (5)

Obtained by using the general procedure described above, with compound **2** (1.2 g, 1.8 mmol), K_2CO_3 (0.30 g) and 1-bromo-4-chlorobutane (0.310 mL) in acetone (60 mL). The crude product was purified by washing with n-hexane/EtOAc (2:1) and dried under vacuum to give the title product as a slightly yellow solid.

Yield: 73% (0.997 g); mp 119–120 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.73 (d, *J* = 2 Hz, 1 H, CHQuer), 7.62 (dd, *J* = 2, 8.6 Hz, 1 H, CHQuer), 7.60 (d, *J* = 7.6 Hz, 2 H, CHAr), 7.49 (t, *J* = 7 Hz, 4 H, CHAr), 7.28–7.43 (m, 14 H, CHAr),7.03 (d, *J* = 8.6 Hz, 1 H, CHQuer), 6.52 (d, *J* = 2 Hz, 1 H, CHQuer), 6.45 (d, *J* = 2 Hz, 1 H, CHQuer), 5.26 (s, 2 H, CH_2Ph), 5.25 (s, 2 H, CH_2Ph), 5.24 (s, 2 H, CH_2Ph), 5.09 (s, 2 H, CH_2Ph), 4.00 (t, *J* = 6 Hz, 2 H, CH_2), 3.521 (t, *J* = 6 Hz, 2 H, CH_2), 1.840–1.893 (m, 2 H, CH_2), 1.780–1.83 (m, 2 H, CH_2).

^{13}C APT NMR ($CDCl_3$, 100 MHz): δ = 173.9, 162.8, 159.9, 158.8, 153.0, 150.9, 148.5, 140.3, 137.2, 136.9, 136.5, 135.8, 128.9, 128.7, 128.7 (2×CH), 128.6, 128.1, 128.0, 127.8, 127.7, 127.5, 127.3, 126.8, 124.0, 122.6, 115.4, 114.0, 110.2, 98.2, 94.0, 71.7, 71.5, 71.1, 70.9, 70.6, 45.0, 29.3, 27.5.

MS (ESI): *m*/*z* (%) = 753.30 (64) $[M]^+$.

Synthesis of Azide Derivatives 6 and 7; General Procedure

The reaction was carried out in a Biotage microwave reactor in a 5 or 20 mL vial equipped with a magnetic stirrer. Added to the vial were the chloro intermediates **4** or **5**, DMF and NaN_3 (1.5 equiv). The sealed vial was placed in the reactor, under the following conditions: 60 min, 120 °C, pre-stirring 60 s, normal adsorption. When the reaction was complete, H_2O and EtOAc and were added to the reaction mixture and it was extracted with H_2O. The organic layer was dried with $MgSO_4$, filtered, and concentrated under vacuum.

3-(4-Azidobutoxy)-2-(3,4-dimethoxyphenyl)-5,7-dimethoxy-4*H*-chromen-4-one (6)

Obtained by using the general procedure described above, with compound **4** (0.455 g, 1.0 mmol), and NaN_3 (0.099 g) in DMF (1 mL).

Yield: 78% (0.380 g); white solid; mp 98.0–99.0 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.66–7.69 (m, 2 H, CHQuer), 6.97 (d, *J* = 9 Hz, 1 H, CHQuer), 6.49 (d, *J* = 2 Hz, 1 H, CHQuer), 6.33 (d, *J* = 2 Hz, 1 H, CHQuer), 4.02 (t, *J* = 6 Hz, 2 H, CH_2-O), 3.95 (s, 6 H, 2×OMe), 3.95 (s, 3 H, OMe), 3.90 (s, 3 H, OMe), 3.33 (t, *J* = 6 Hz, 2 H, CH_2-N_3), 1.76–1.70 (m, 4 H, 2×CH_2).

^{13}C APT NMR ($CDCl_3$, 100 MHz): δ = 174.1, 164.0, 161.1, 158.9, 153.0, 150.9, 148.7, 140.2, 123.5, 121.8, 111.4, 110.8, 109.5, 95.8, 92.5, 71.4, 56.5, 56.2, 56.1, 55.9, 51.3, 27.5, 25.8.

MS (ESI): *m*/*z* (%) = 456.26 (100) $[M + 1]^+$.

3-(4-Azidobutoxy)-5,7-bis(benzyloxy)-2-(3,4-bis(benzyloxy)phenyl)-4*H*-chromen-4-one (7)

Obtained by using the general procedure described above, with compound **5** (0.997 g, 1.3 mmol) and NaN_3 (0.13 g) in DMF (10 mL).

Yield: 92 % (0.91 g); white solid; mp 125–126 °C.

^{1}H NMR ($CDCl_3$, 400.0 MHz): δ = 7.72 (d, *J* = 2 Hz, 1 H, CHQuer), 7.65 (dd, *J* = 2, 8.6 Hz, 1 H, CHQuer), 7.59 (d, *J* = 7.5 Hz, 2 H, CHAr), 7.47–7.50 (m, 4 H, CHAr), 7.28–7.43 (m, 14 H, CHAr), 7.03 (d, *J* = 8.6 Hz, 1 H, CHQuer), 6.52 (d, *J* = 2 Hz, CHQuer), 6.45 (d, *J* = 2 Hz, 1 H, CHQuer), 5.26 (s, 4 H, 2×CH_2Ph), 5.24 (s, 2 H, CH_2Ph), 5.09 (s, 2 H, CH_2Ph), 3.99 (t, *J* = 6 Hz, 2 H, CH_2), 3.25 (t, *J* = 6.5 Hz, 2 H, CH_2), 1.65–1.75 (m, 4 H, 2×CH_2).

^{13}C APT NMR ($CDCl_3$, 100 MHz): δ = 173.9, 162.8, 159.9, 153.0, 150.9, 148.5, 140.3, 137.2, 136.9, 136.5, 135.8, 128.7, 128.9, 128.7 (2xCH), 128.6, 128.1, 128.0, 127.8, 127.7, 127.5, 127.3, 126.8, 124.0, 122.6, 115.4, 113.9, 110.2, 98.2, 94.0, 71.7, 71.7, 71.1, 70.9, 70.6, 51.3, 27.4, 25.7.

MS (ESI): *m*/*z* (%) = 760.33 (100) $[M + 1]^+$.

Synthesis of Hybrids Ia-b; General Procedure

The reaction was carried out in a Biotage microwave reactor in a 3 mL vial equipped with a magnetic stirring bar. To the vial, $Cu(OAc)_2{\cdot}H_2O$ (5 mol%), sodium ascorbate (20 mol%), 1,10-phenantroline (5 mol%) and EtOH/H_2O (1:1, 4 mL) were added and stirred for 5 minutes at room temperature. Afterwards, propargyl derivative **3** (1 equiv), sodium azide (1.2 equiv), and benzyl bromide derivatives **8a–b** (1.2 equiv) were added to the reaction mixture, which was heated at 90 °C for 30–60 min. Subsequently, H_2O (15 mL) was added and the reaction mixture was extracted with CH_2Cl_2 (3×15 mL). The organic phases were combined and dried with $MgSO_4$, filtered, and the solvent was evaporated under vacuum. The crude product was purified by column chromatography.

3-((1-Benzyl-1*H*-1,2,3-triazol-4-yl)methoxy)-2-(3,4-dimethoxyphenyl)-5,7-dimethoxy-4*H*-chromen-4-one (Ia)

By following the general procedure, with propargyl derivative **3** (0.250 g, 0.63 mmol) and benzyl bromide **8a** (0.09 mL, 0.76 mmol) the reaction was heated for 1 h. The crude product was purified with SiO_2 gel using EtOAc as solvent.

Yield: 64 % (0.334 g); yellow solid; R_f = 0.38 (EtOAc); mp 165.7–166.7 °C.

^{1}H NMR ($CDCl_3$, 400.0 MHz): δ = 7.78 (s, 1 H, CHtrzl), 7.67–7.34 (m, 2 H, 2×CHQuer), 7.32–7.34 (m, 2 H, CHAr), 7.21–7.23 (m, 2 H, CHAr), 6.93 (d, *J* = 8.5 Hz, 1 H, CHQuer), 6.50 (d, *J* = 2 Hz, 1 H, CHQuer), 6.34 (d, *J* = 2 Hz, 1 H, CHQuer), 5.47 (s, 2 H, CH_2), 5.20 (s, 2 H, CH_2), 3.95 (s, 3 H, OCH_3), 3.94 (s, 3 H, OCH_3), 3.90 (s, 3 H, OCH_3), 3.89 (s, 3 H, OCH_3).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 174.1, 164.1, 161.0, 158.9, 153.4, 151.0, 148.8, 144.8, 139.5, 134.6, 129.2, 128.8, 128.2, 124.3, 123.2, 121.8, 111.4, 110.8, 109.4, 96.0, 92.6, 65.0, 56.6, 56.3, 56.1, 55.9, 54.2.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{29}H_{28}N_3O_7$: 530.1922; found: 530.1914.

3-((1-(3-Chlorobenzyl)-1*H*-1,2,3-triazol-4-yl)methoxy)-2-(3,4-dimethoxyphenyl)-5,7-dimethoxy-4*H*-chromen-4-one (Ib)

By following the general procedure, with propargyl derivative **3** (0.125 g, 0.32 mmol) and 3-chlorobenzyl bromide **8b** (0.06 mL, 0.47 mmol), the reaction was heated for 30 minutes. The crude product was purified with SiO_2 gel using EtOAc as solvent.

Yield: 59 % (0.106 g); slightly yellow solid; R_f = 0.5 (EtOAc); mp 149.5–150.5 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.85 (s, 1 H, CHtrzl), 7.68–7.70 (m, 2 H, CHQuer), 7.29–7.32 (m, 1 H, CHAr), 7.24–7.27 (m, 2 H, CHAr), 7.10 (d, *J* = 7 Hz, 1 H, CHAr), 6.94 (d, *J* = 8 Hz, 1 H, CHQuer), 6.51 (d, *J* = 2 Hz, CHQuer), 6.36 (d, *J* = 2 Hz, CHQuer), 5.45 (s, 2 H, CH_2), 5.20 (s, 2 H, CH_2), 3.96 (s, 3 H, OCH_3), 3.94 (s, 3 H, OCH_3), 3.91 (s, 3 H, OCH_3), 3.90 (s, 3 H, OCH_3).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 174.1, 164.1, 161.0, 158.9, 153.4, 151.1, 148.8, 145.1, 139.6, 136.6, 135.1, 130.5, 129.1, 128.3, 126.2, 124.4, 123.1, 121.8, 111.4, 110.9, 109.4, 96.0, 92.6, 65.1, 56.6, 56.3, 56.1, 55.9, 53.5.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{29}H_{27}{}^{35}ClN_3O_7$: 564.1532; found: 564.1523.

Synthesis of Hybrids II; General Procedure

The reaction was carried out in a Biotage microwave reactor in a 5 mL vial equipped with a magnetic stirring bar. To the vial, $CuSO_4{\cdot}5H_2O$ (5 mol%), sodium L-ascorbate or L-ascorbic acid (20 mol%), DMF (3 mL), azide derivatives **6** (1 equiv) and alkynes **9a–i** (1 equiv) were added.

The sealed vial was placed in the reactor, under the following conditions: 10 minutes, 90 °C, pre-stirring 60 seconds, normal adsorption. When the reaction was complete, EtOAc (5 mL) and H_2O (5 mL) were added to the reaction mixture and this was extracted twice with EtOAc. The organic phase was collected and dried with $MgSO_4$, filtered, and concentrated under vacuum. The crude product was purified by column chromatography or recrystallization, if necessary.

2-(3,4-Dimethoxyphenyl)-5,7-dimethoxy-3-(4-(4-phenyl-1*H*-1,2,3-triazol-1-yl)butoxy)-4*H*-chromen-4-one (IIa)

By following the general procedure described above, the precursor **6** (130 mg, 0.28 mmol), $CuSO_4{\cdot}5H_2O$ (3.5 mg, 0.014 mmol), L-ascorbic acid (10 mg, 0.056 mmol) and phenylacetylene **9a** (30 µL, 0.28 mmol) were added to a vial and allowed to react.

Yield: 92% (0.143 g); slightly yellow solid; mp 143–144 °C.

^{1}H NMR (DMSO-d_6, 400 MHz): δ = 8.58 (s, 1 H, CHtrzl), 7.84 (d, *J* = 8 Hz, 2 H, CHAr), 7.65 (dd, *J* = 2, 8.5 Hz, 1 H, CHQuer), 7.63 (s, 1 H, CHQuer), 7.44 (t, *J* = 8 Hz, 2 H, CHAr), 7.33 (t, *J* = 7 Hz, 1 H, CHAr), 7.07 (d, *J* = 8.5 Hz, 1 H, CHQuer), 6.80 (d, *J* = 2 Hz, 1 H, CHQuer), 6.47 (d, *J* = 2 Hz, 1 H, CHQuer), 4.47 (t, *J* = 7 Hz, 2 H, CH_2-trzl), 3.94 (t, *J* = 6 Hz, 2 H, CH_2-O), 3.88 (s, 3 H, OCH_3), 3.83 (s, 3 H, OCH_3), 3.79 (s, 3 H, OCH_3), 3.78 (s, 3 H, OCH_3), 1.97–2.04 (m, 2 H, C*H*$_2$CH$_2$-trzl), 1.62–1.69 (m, 2 H, C*H*$_2$CH$_2$O-).

^{13}C APT NMR (DMSO-d_6, 100 MHz): δ = 172.2, 163.7, 160.3, 158.2, 151.9, 150.6, 148.3, 146.3, 139.3, 130.9, 128.9, 127.8, 125.1, 122.6, 121.4, 121.3, 111.3, 111.1, 108.4, 95.9, 93.0, 70.6, 56.1, 56.0, 55.6, 55.5, 49.2, 26.5.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{31}H_{32}N_3O_7$: 558.2235; found: 558.2224.

2-(3,4-Dimethoxyphenyl)-3-(4-(4-cyclopropyl-1*H*-1,2,3-triazol-1-yl)butoxy)-5,7-dimethoxy-4*H*-chromen-4-one (IIb)

By following the general procedure described above, the precursor **6** (170 mg, 0.37 mmol), $CuSO_4{\cdot}5H_2O$ (4.6 mg, 0.018 mmol), sodium ascorbate (14.7 mg, 0.074 mmol) and cyclopropylacetylene **9b** (31 µL, 0.37 mmol) were added to a vial and allowed to react. The crude product was purified by column chromatography with SiO_2 gel using EtOAc as eluent.

Yield: 63% (0.121 g); slightly yellow solid; R_f 0.35 in EtOAc; mp 98–100 °C.

^{1}H NMR (DMSO-d_6, 400 MHz): δ = 7.78 (s, 1 H, CHtrzl), 7.65 (dd, *J* = 2, 8.4 Hz, 1 H, CHQuer), 7.62 (s, 1 H, CHQuer), 7.10 (d, *J* = 8.6 Hz, 1 H, CHQuer), 6.79 (d, *J* = 2 Hz, 1 H, Quer), 6.47 (d, *J* = 2 Hz, 1 H, CHQuer), 4.31 (t, *J* = 7 Hz, 2 H, CH_2-trzl), 3.90 (t, *J* = 6 Hz, 2 H, CH_2-O), 3.88 (s, 3 H, OCH_3), 3.84 (s, 3 H, OCH_3), 3.83 (s, 3 H, OCH_3), 3.80 (s, 3 H, OCH_3), 1.86–1.94 (m, 3 H, C*H*$_2$CH$_2$-trzl and CH-Cyclopropyl), 1.55–1.62 (m, 2 H, C*H*$_2$CH$_2$O-), 0.85–0.90 (m, 2 H, CH_2-Cyclopropyl), 0.67–0.70 (m, 2 H, CH_2-Cyclopropyl).

^{13}C APT NMR (DMSO-d_6, 100 MHz): δ = 172.2, 163.7, 160.3, 158.2, 151.9, 150.7, 148.9, 148.3, 139.3, 122.6, 121.4, 120.5, 111.4, 111.1, 108.4, 95.9, 93.0, 70.6, 63.1, 56.1, 56.0, 55.6, 48.8, 26.6, 7.6, 6.6.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{28}H_{32}N_3O_7$: 522.2235; found: 522.2225.

2-(3,4-Dimethoxyphenyl)-3-(4-(4-(1-hydroxycyclopentyl)-1*H*-1,2,3-triazol-1-yl)butoxy)-5,7-dimethoxy-4*H*-chromen-4-one (IIc)

By following the general procedure described above, the precursor **6** (180 mg, 0.4 mmol), $CuSO_4{\cdot}5H_2O$ (5.0 mg, 0.02 mmol), sodium L-ascorbate (15.9 mg, 0.08 mmol) and 1-ethynylcyclopentanol **9c** (44 µL, 0.4 mmol) were added to a vial and allowed to react. The crude product was purified by column chromatography with SiO_2 gel using EtOAc as eluent.

Yield: 52% (0.117 g); yellow oil; R_f 0.11 in EtOAc.

^{1}H NMR (DMSO-d_6, 400 MHz): δ = 7.87 (s, 1 H, CHtrzl), 7.64–7.68 (m, 2 H, 2×CHQuer), 7.12 (d, *J* = 8.6 Hz, 1 H, CHQuer), 6.81 (d, *J* = 2 Hz, 1 H, CHQuer), 6.48 (d, *J* = 2 Hz, 1 H, CHQuer), 4.97 (s, 1 H, OH), 4.36 (t, *J* = 7 Hz, 2 H, CH_2), 3.90 (t, *J* = 6 Hz, 2 H, CH_2), 3.89 (s, 3 H, OCH_3), 3.84 (s, 3 H, OCH_3), 3.83 (s, 3 H, OCH_3), 3.81 (s, 3 H, OCH_3), 1.91–1.97 (m, 4 H, CH_2), 1.78–1.85 (m, 4 H, CH_2), 1.61–1.69 (m, 4 H, CH_2).

^{13}C NMR (DMSO-d_6, 100 MHz): δ = 172.2, 163.7, 160.3, 158.2, 154.4, 152.0, 150.7, 148.3, 139.3, 122.6, 121.4, 121.1, 111.4, 111.1, 108.4, 95.9, 93.0, 77.5, 70.6, 59.8, 56.1, 56.0, 55.6, 55.6, 48.8, 40.7, 26.7, 26.6, 23.3.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{30}H_{36}N_3O_8$: 566.2497; found: 566.2489.

2-(3,4-Dimethoxyphenyl)-3-(4-(4-(hydroxymethyl)-1*H*-1,2,3-triazol-1-yl)butoxy)-5,7-dimethoxy-4*H*-chromen-4-one (IId)

By following the general procedure described above, the precursor **6** (180 mg, 0.4 mmol), $CuSO_4{\cdot}5H_2O$ (5.0 mg, 0.02 mmol), sodium L-ascorbate (15.9 mg, 0.08 mmol) and prop-2-yn-1-ol **9d** (44 µL, 0.4 mmol) were added to a vial and allowed to react.

Yield: 90% (0.185 g); white solid; mp 117–118 °C.

^{1}H NMR (DMSO-d_6, 400 MHz): δ = 7.95 (s, 1 H, CHtrzl), 7.65 (dd, *J* = 2, 8.4 Hz, 1 H, CHQuer), 7.63 (s, 1 H, CHQuer), 7.10 (d, *J* = 8.5 Hz, 1 H, CHQuer), 6.80 (d, *J* = 2 Hz, 1 H, CHQuer), 6.47 (d, *J* = 2 Hz, 1 H, CHQuer), 5.17 (t, *J* = 5.6 Hz, 1 H, CH_2OH), 4.51 (d, *J* = 5.4 Hz, 2 H, C*H*$_2$OH), 4.38 (t, *J* = 7 Hz, 2 H, CH_2-trzl), 3.90 (t, *J* = 7 Hz, 2 H, CH_2-O), 3.89 (s, 3 H, OCH_3), 3.84 (s, 3 H, OCH_3), 3.83 (s, 3 H, OCH_3), 3.80 (s, 3 H, OCH_3), 1.90–1.97 (m, 2 H, C*H*$_2$CH$_2$-trzl), 1.58–1.65 (m, 2 H, C*H*$_2$CH$_2$O-).

^{13}C APT NMR (DMSO-d_6, 100 MHz): δ = 172.6, 164.1, 160.7, 158.6, 152.4, 151.1, 148.8, 148.4, 139.7, 123.0, 122.9, 121.9, 111.8, 111.5, 108.9, 96.3, 93.5, 71.0, 56.5, 56.5, 56.0, 55.5, 49.3, 27.1, 27.0.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{26}H_{30}N_3O_8$: 512.2027; found: 512.2020.

2-(3,4-Dimethoxyphenyl)-3-(4-(4-(2-hydroxypropan-2-yl)-1*H*-1,2,3-triazol-1-yl)butoxy)-5,7-dimethoxy-4*H*-chromen-4-one (IIe)

By following the general procedure described above, the precursor **6** (180 mg, 0.4 mmol), $CuSO_4{\cdot}5H_2O$ (5.0 mg, 0.02 mmol), sodium L-ascorbate (15.9 mg, 0.08 mmol) and 2-methyl-3-butyn-2-ol **9e** (39 µL, 0.4 mmol) were added to a vial and allowed to react.

Yield: 90% (0.185 g); white solid; mp 99–100 °C.

^{1}H NMR (DMSO-d_6, 400 MHz): δ = 7.86 (s, 1 H, CHtrzl), 7.64–7.67 (m, 2 H, 2×CHQuer), 6.80 (d, *J* = 2 Hz, 1 H, CHQuer), 6.47 (d, *J* = 2 Hz, 1 H, CHQuer), 5.08 (s, 1 H, OH), 4.36 (t, *J* = 7 Hz, 2 H, CH_2-trzl), 3.81–3.92 (m, 14 H, 4×OMe, CH_2-O), 1.91–1.95 (m, 2 H, CH_2), 1.61–1.65 (m, 2 H, CH_2), 1.45 (s, 6 H, 2×CH_3).

^{13}C APT NMR (DMSO-d_6, 100 MHz): δ = 172.2, 163.7, 160.3, 158.2, 155.8, 151.9, 150.7, 148.3, 139.3, 122.6, 121.4, 120.4, 111.4, 111.1, 108.4, 95.9, 93.0, 70.6, 67.0, 56.1, 56.0, 55.6, 48.8, 30.7, 26.7, 26.6.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{28}H_{34}O_8N_3$: 540.2340; found: 540.2333.

1-((1-(4-((2-(3,4-Dimethoxyphenyl)-5,7-dimethoxy-4-oxo-4*H*-chromen-3-yl)oxy)butyl)-1*H*-1,2,3-triazol-4-yl)methyl)indoline-2,3-dione (IIf)

By following the general procedure described above, the precursor **6** (180 mg, 0.4 mmol), $CuSO_4{\cdot}5H_2O$ (5.0 mg, 0.02 mmol), sodium L-ascorbate (15.9 mg, 0.08 mmol) and 1-(prop-2-yn-1-yl)isatin **9f** (74 mg, 0.4 mmol) were added to a vial and allowed to react.

Yield: 94% (0.241 g); orange solid; mp 116–117 °C.

^{1}H NMR (DMSO-d_6, 400 MHz): δ = 8.15 (s, 1 H, CH-trzl), 7.59–7.64 (m, 3 H, CHQuer and CHIsatin), 7.54 (d, *J* = 7 Hz, 1 H, CHIsatin), 7.08–7.16 (m, 3 H, CHQuer and CHIsatin), 6.80 (d, *J* = 2 Hz, 1 H, CHQuer), 6.77 (d, *J* = 2 Hz, 1 H, CHQuer), 4.37 (t, *J* = 7 Hz, 2 H, CH_2-trzl), 3.79–3.88 (m, 14 H, 4×OMe, CH_2-O), 1.89–1.95 (m, 2 H, CH_2), 1.58–1.63 (m, 2 H, CH_2).

^{13}C APT NMR (DMSO-d_6, 100 MHz): δ = 183.1, 172.1, 163.7, 160.3, 158.2, 157.8, 151.9, 150.7, 150.2, 148.3, 141.4, 139.3, 138.1, 124.4, 123.5, 123.3, 122.5, 121.4, 117.6, 111.4, 111.2, 111.1, 108.4, 95.9, 93.0, 70.5, 56.1, 56.0, 55.6, 55.6, 49.1, 26.5, 26.5.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{34}H_{33}N_4O_9$: 641.2242; found: 641.2230.

2-(3,4-Dimethoxyphenyl)-3-(4-(4-((2-isopropyl-5-methylphenoxy)methyl)-1*H*-1,2,3-triazol-1-yl)butoxy)-5,7-dimethoxy-4*H*-chromen-4-one (IIg)

By following the general procedure described above, the precursor **6** (80 mg, 0.18 mmol), $CuSO_4{\cdot}5H_2O$ (2.2 mg, 0.008 mmol), L-ascorbic acid (3 mg, 0.017 mmol) and 1-isopropyl-4-methyl-2-(prop-2-yn-1-yloxy) **9g** (33.1 mg, 0.18 mmol) were added to a vial and allowed to react. The crude product was purified by column chromatography with SiO_2 gel using the gradient EtOAc/n-hexane (2:1) and (4:1) as eluent.

Yield: 95% (0.107 g); colorless solid; R_f 0.38 in EtOAc/n-hexane (4:1); mp 98–100 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.64–7.68 (m, 3 H, 2×CHQuer + CHtrzl), 7.08 (d, *J* = 8 Hz, 1 H, CH), 6.96 (d, *J* = 8 Hz, 1 H, CH), 6.78 (s, 1 H, CH), 6.75 (d, *J* = 8 Hz, 1 H, CHQuer), 6.51 (d, *J* = 2 Hz, 1 H, CHQuer), 6.35 (d, *J* = 2 Hz, 1 H, CHQuer), 5.18 (s, 2 H, CH_2), 4.55 (t, *J* = 7 Hz, 2 H, CH_2), 4.00 (t, *J* = 6 Hz, 2 H, CH_2), 3.96 (s, 3 H, OCH_3), 3.94 (s, 3 H, OCH_3), 3.91 (s, 3 H, OCH_3), 3.90 (s, 3 H, OCH_3), 3.22–3.29 (m, 1 H, C*H*$(CH_3)_2$), 2.31 (s, 3 H, CH_3), 2.17–2.24 (m, 2 H, CH_2), 1.72–1.79 (m, 2 H, CH_2), 1.16 (s, 3 H, CH_3), 1.14 (s, 3 H, CH_3).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 174.2, 164.1, 161.1, 159.0, 155.5, 153.2, 151.0, 148.8, 140.1, 136.5, 134.4, 126.1, 123.4, 122.8, 121.9, 121.8, 113.0, 111.3, 110.9, 109.5, 95.9, 92.6, 77.2, 71.0, 62.7, 56.6, 56.2, 56.1, 55.9, 50.1, 27.3, 27.0, 26.6, 22.9 (2×CH_3), 21.5.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{36}H_{42}N_3O_8$: 644.2966; found: 644.2955.

2-(3,4-Dimethoxyphenyl)-5,7-dimethoxy-3-(4-(4-propyl-1*H*-1,2,3-triazol-1-yl)butoxy)-4*H*-chromen-4-one (IIh)

By following the general procedure described above, the precursor **6** (180 mg, 0.4 mmol), $CuSO_4{\cdot}5H_2O$ (5.0 mg, 0.02 mmol), sodium L-ascorbate (15.9 mg, 0.08 mmol) and pent-1-yne **9h** (39.4 µL, 0.4 mmol) were added to a vial and allowed to react.

Yield: 35% (0.074 g); yellow oil; R_f 0.4 in EtOAc.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.63–7.67 (m, 2 H, CHQuer), 7.33 (s br, 1 H, CHtrzl), 6.95 (d, *J* = 8.5 Hz, 1 H, CHQuer), 6.49 (d, *J* = 2 Hz, 1 H, CHQuer), 6.34 (d, *J* = 2 Hz, 1 H, CHQuer), 4.00 (t, *J* = 6 Hz, 2 H CH_2-trzl), 3.95 (s, 3 H, OCH_3), 3.94 (s, 3 H, OCH_3), 3.91 (s, 3 H, OCH_3), 3.89 (s, 3 H, OCH_3), 2.66 (t, *J* = 7.6 Hz, 2 H, CH_2), 2.10–2.17 (m, 2 H, CH_2), 1.63–1.73 (m, 4 H, 2×CH_2), 0.94 (t, *J* = 7 Hz, 3 H, CH_3).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 174.2, 164.1, 161.0, 158.9, 153.2, 151.0, 148.7, 140.0, 128.2, 123.3, 121.8, 111.2, 110.9, 109.4, 95.9, 92.6, 71.1, 56.5, 56.2, 56.1, 55.9, 49.9, 27.7, 27.3, 27.0, 22.8, 13.9.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{28}H_{34}N_3O_7$: 524.2391; found: 524.2380.

3-(4-(4-(2-Aminopropan-2-yl)-1*H*-1,2,3-triazol-1-yl)butoxy)-2-(3,4-dimethoxyphenyl)-5,7-dimethoxy-4*H*-chromen-4-one (IIi)

By following the general procedure described above, the precursor **6** (180 mg, 0.4 mmol), $CuSO_4{\cdot}5H_2O$ (5.0 mg, 0.02 mmol), sodium L-ascorbate (15.9 mg, 0.08 mmol) and 2-methyl-3-butyn-2-amine **9i** (42 µL, 0.4 mmol) were added to a vial and allowed to react.

Yield: 55% (0.118 g); yellow solid.

^{1}H NMR (DMSO-d_6, 400 MHz): δ = 7.86 (s, 1 H, CHtrzl), 7.63–7.67 (m, 2 H, CHQuer), 7.11 (d, *J* = 8.6 Hz, 1 H, CHQuer), 6.80 (d, *J* = 2 Hz, 1 H, CHQuer), 6.47 (d, *J* = 2 Hz, CHQuer), 4.35 (t, *J* = 7 Hz, CH_2), 3.89–3.92 (m, 5 H, CH_2 and OCH_3), 3.83 (s, 3 H, OCH_3), 3.81 (s, 3 H, OCH_3), 3.35–3.38 (m, 2 H, NH_2), 1.89–1.96 (m, 2 H, CH_2), 1.61–1.67 (m, 2 H, CH_2), 1.36 (s, 6 H, 2×CH_3).

^{13}C NMR (DMSO-d_6, 100 MHz): δ = 172.2, 163.7, 160.3, 158.2, 151.9 (2×C), 150.7, 148.3, 139.3, 122.6, 121.4, 119.8, 111.4, 111.1, 108.4, 95.9, 93.0, 70.6, 56.1, 56.0, 55.6, 50.3, 48.8, 35.8, 26.6, 26.6.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{28}H_{35}N_3O_7$: 539.2500; found: 539.2494.

Synthesis of Hybrids III

The reaction was carried out in a Biotage microwave reactor in a 5 mL vial equipped with a magnetic stirring bar. To the vial, $CuSO_4{\cdot}5H_2O$ (10 mol%), L-ascorbic acid (20 mol%), DMF (3 mL), azide derivatives **7** (1 equiv) and alkynes **9a–g** (1 equiv) were added. The sealed vial was placed in the reactor, with the following conditions: 30 minutes, 90 °C, pre-stirring 60s, normal adsorption. When the reaction was complete, EtOAc (5 mL) and H_2O (5 mL) were added to the reaction mixture and this was extracted twice with EtOAc. The organic phase was collected and dried with $MgSO_4$, filtered and concentrated under vacuum. The crude product was purified by column chromatography or recrystallization (if necessary).

5,7-Bis(benzyloxy)-2-(3,4-bis(benzyloxy)phenyl)-3-(4-(4-phenyl-1*H*-1,2,3-triazol-1-yl)butoxy)-4*H*-chromen-4-one (IIIa)

By following the general procedure described above, the precursor **7** (250 mg, 0.33 mmol), $CuSO_4{\cdot}5H_2O$ (8.2 mg, 0.032 mmol), L-ascorbic acid (12 mg, 0.065 mmol) and phenylacetylene **9a** (36 µL, 0.33 mmol) were added to a vial and allowed to react.

Yield: 99% (0.280 g); mp 153–154 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.82 (s, 1 H, CHtrzl), 7.79–7.81 (m, 2 H, CHAr), 7.68 (d, *J* = 2 Hz, 1 H, CHQuer),7.58–7.64 (m, 3 H, CHAr and CHQuer), 7.29–7.47 (m, 21 H, CHAr), 7.00 (d, *J* = 8.6 Hz, 1 H, CHQuer), 6.52 (d, *J* = 2 Hz, 1 H, CHQuer), 6.46 (d, *J* = 2 Hz, 1 H, CHQuer), 5.26 (s, 2 H, CH_2Ph), 5.21 (s, 4 H, 2×CH_2Ph), 5.09 (s, 2 H, CH_2Ph), 4.46 (t, *J* = 7 Hz, 2 H, CH_2), 3.99 (t, *J* = 6 Hz, 2 H, CH_2), 2.05–2.13 (m, 2 H, CH_2), 1.65–1.72 (m, 2 H, CH_2).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 174.3, 163.3, 160.2, 159.2, 153.5, 151.8, 151.4, 148.8, 140.5, 137.4, 137.1, 136.7, 136.1, 129.3, 129.2, 129.1, 129.0, 128.9, 128.7, 128.7, 128.5, 128.4, 128.2, 128.1, 127.8, 127.7, 127.0, 126.3, 126.3, 126.2, 124.1, 122.9, 115.7, 114.2, 110.4, 98.5, 94.3, 72.0, 71.4, 71.3, 71.2, 71.0, 50.5, 27.6, 27.1.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{55}H_{47}N_3O_7$: 862.3487; found: 862.3469.

5,7-Bis(benzyloxy)-2-(3,4-bis(benzyloxy)phenyl)-3-(4-(4-cyclopropyl-1*H*-1,2,3-triazol-1-yl)butoxy)-4*H*-chromen-4-one (IIIb)

By following the general procedure described above, the precursor **7** (350 mg, 0.46 mmol), $CuSO_4$.5 H_2O (11.5 mg, 0.046 mmol), L-ascorbic acid (16 mg, 0.092 mmol) and cyclopropylacetylene **9b** (39 µL, 0.46 mmol) were added to a vial and allowed to react.

Yield: 100% (0.380 g); white solid; mp 124–125 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.68 (s, 1 H, CHtrzl), 7.58–7.64 (m, 3 H, CHQuer and CHAr), 7.29–7.49 (m, 19 H, CHAr), 7.03 (d, *J* = 8.6 Hz, 1 H, CHQuer), 6.53 (d, *J* = 2 Hz, 1 H, CHQuer), 6.46 (d, *J* = 2 Hz, 1 H, CHQuer), 5.26 (s, 2 H, CH_2Ph), 5.25 (s, 2 H, CH_2Ph), 5.22 (s, 2 H, CH_2Ph), 5.09 (s, 2 H, CH_2Ph), 1.99–2.06 (m, 2 H, CH_2), 1.88–1.94 (m, 1 H, CHcyclopropyl), 1.61–1.67 (m, 2 H, CH_2), 0.88–0.94 (m, 2 H, CHcyclopropyl), 0.81–0.86 (m, 2 H, CHcyclopropyl).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 173.9, 162.9, 159.9, 158.8, 153.1, 151.0, 149.7, 148.4, 140.1, 137.1, 136.8, 136.4, 135.7, 128.9, 128.7, 128.7, 128.7, 128.6, 128.1, 128.1, 127.9, 127.7, 127.4, 127.3, 126.7, 123.8, 122.6, 120.4, 115.3, 113.9, 110.1, 98.2, 94.0, 71.7, 71.1, 71.0, 70.9, 70.6, 50.1, 27.2, 26.8, 8.1, 6.6.

MS (ESI): *m*/*z* (%) = 826.41 (100) [M + 1]$^+$.

5,7-Bis(benzyloxy)-2-(3,4-bis(benzyloxy)phenyl)-3-(4-(4-(1-hydroxycyclopentyl)-1*H*-1,2,3-triazol-1-yl)butoxy)-4*H*-chromen-4-one (IIIc)

By following the general procedure described above, the precursor **7** (250 mg, 0.33 mmol), $CuSO_4$·5H_2O (8.2 mg, 0.033 mmol), L-ascorbic acid (12 mg, 0.066 mmol) and 1-ethynylcyclopentanol **9c** (37 µL, 0.33 mmol) were added to a vial and allowed to react.

Yield: 100% (0.286 g); white solid; mp 112–113 °C.

^{1}H NMR (DMSO-d_6, 400 MHz): δ = 7.85 (s, 1 H, CHtrzl), 7.72–7.59 (m, 4 H, CHQuer + CHAr), 7.50–7.47 (m, 5 H, CHAr), 7.44–7.30 (m, 13 H, CHAr), 7.24 (d, *J* = 8.8 Hz, 1 H, CHQuer), 6.90 (d, *J* = 1.5 Hz, 1 H, CHQuer), 6.68 (d, *J* = 1.5 Hz, 1 H, CHQuer), 5.24 (s, 2 H, CH_2Ph), 5.23 (s, 4 H, 2×CH_2Ph), 5.21 (s, 2 H, CH_2Ph), 4.96 (s, 1 H, OH), 4.32 (t, *J* = 7 Hz, 2 H, -OCH_2), 3.9 (t, *J* = 6 Hz, 2 H, -NCH_2), 1.96–1.80 (m, 8 H, 4×CH_2), 1.65–1.55 (m, 4 H, 2×CH_2(linker)).

^{13}C APT NMR (DMSO-d_6, 100 MHz): δ = 172.3, 162.6, 159.1, 158.1, 154.4, 151.9, 150.2, 147.7, 139.4, 137.1, 136.8, 136.8, 136.1, 128.5, 128.5, 128.4, 128.4, 128.2, 128.0, 128.0, 127.9, 127.9, 127.6, 127.5, 126.9, 122.9, 122.0, 121.0, 114.0, 113.7, 108.9, 97.8, 94.2, 77.5, 70.7, 70.4, 70.1, 69.9, 69.9, 48.8, 40.7, 26.5 (2×CH_2), 23.3.

MS (ESI): *m*/*z* (%) = 852.43 (100) [M–OH]$^+$.

5,7-Bis(benzyloxy)-2-(3,4-bis(benzyloxy)phenyl)-3-(4-(4-(hydroxymethyl)-1*H*-1,2,3-triazol-1-yl)butoxy)-4*H*-chromen-4-one (IIId)

By following the general procedure described above, the precursor **7** (250 mg, 0.33 mmol), $CuSO_4$.5 H_2O (8.2 mg, 0.033 mmol), L-ascorbic acid (12 mg, 0.066 mmol) and prop-2-yn-1-ol **9d** (19 µL, 0.33 mmol) were added to a vial and allowed to react.

Yield: 96% (0.258 g); white solid; mp 92–93 °C.

^{1}H NMR (DMSO-d_6, 400 MHz): δ = 7.95 (s, 1 H, CHtrzl), 7.72–7.59 (m, 4 H, CHQuer + CHAr), 7.50–7.31 (m, 18 H, CHAr), 7.24 (d, *J* = 8.6 Hz, 1 H, CHQuer), 6.91 (s br, 1 H, CHQuer), 6.69 (s br, 1 H, CHQuer), 5.25 (s, 2 H, CH_2Ph), 5.24 (s, 4 H, 2×CH_2Ph), 5.21 (s, 2 H, CH_2Ph), 4.49 (s br, 2 H, CH_2OH), 4.34 (t, *J* = 7 Hz, 2 H, -OCH_2), 3.90 (t, *J* = 6 Hz, 2 H, -NCH_2), 1.90–1.87 (m, 2 H, CH_2), 1.58–1.55 (m, 2 H, CH_2).

^{13}C APT NMR (DMSO-d_6, 100 MHz): δ = 172.2, 162.6, 159.1, 158.1, 151.9, 150.3, 150.2, 147.7, 139.4, 137.0, 136.8, 136.7, 136.0, 128.5, 128.5, 128.4, 128.3, 128.2, 128.0, 127.9, 127.9, 127.6, 127.5, 126.9, 122.9, 122.0, 122.0, 114.0, 113.6, 108.9, 97.8, 94.2, 70.7, 70.4, 70.0, 69.9, 69.9, 55.1, 48.8, 26.5, 26.4.

MS (ESI): *m*/*z* (%) = 816.39 (100) [M + 1]$^+$.

5,7-Bis(benzyloxy)-2-(3,4-bis(benzyloxy)phenyl)-3-(4-(4-(2-hydroxypropan-2-yl)-1*H*-1,2,3-triazol-1-yl)butoxy)-4*H*-chromen-4-one (IIIe)

By following the general procedure described above, the precursor **7** (250 mg, 0.33 mmol), $CuSO_4$·5H_2O (8.2 mg, 0.033 mmol), L-ascorbic acid (12 mg, 0.066 mmol) and 2-methyl-3-butyn-2-ol **9e** (31 µL, 0.33 mmol) were added to a vial and allowed to react.

Yield: 98% (0.227 g); white solid; mp 146.8–147.8 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.68 (d, *J* = 2 Hz, 1 H, CHar), 7.63 (dd, *J* = 2, 8.6 Hz, 1 H, CHar), 7.58 (d, *J* = 8.6 Hz, 2 H, CHar), 7.46–7.48 (m, 4 H, CHar), 7.29–7.42 (m, 15 H, CHar), 7.03 (d, *J* = 8.6 Hz, 1 H, CHQuer), 6.52 (d, *J* = 2 Hz, 1 H, CHQuer), 6.45 (d, *J* = 2 Hz, 1 H, CHQuer), 5.26 (s, 2 H, CH_2Ph), 5.25 (s, 2 H, CH_2Ph), 5.22 (s, 2 H, CH_2Ph), 5.09 (s, 2 H, CH_2Ph), 4.38 (t, *J* = 7 Hz, 2 H, CH_2),3.94 (t, *J* = 6 Hz, 2 H, CH_2), 2.00–2.08 (m, 2 H, CH_2),1.64–1.71 (m, 2 H, CH_2), 1.59 (s, 6 H, 2×CH_3).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 173.9, 162.9, 159.9, 158.8, 155.7, 153.1, 151.0, 148.5, 140.2, 137.1, 136.8, 136.5, 135.8, 128.9, 128.7, 128.7 (2×CH), 128.6, 128.2, 128.1, 127.8, 127.7, 127.5, 127.4, 126.8, 124.0, 122.6, 119.4, 115.6, 114.1, 110.1, 98.3, 94.1, 71.8, 71.2, 71.1, 70.9, 70.6, 68.6, 50.0, 30.6 (2xCH_3), 27.1, 27.0.

MS (ESI): *m*/*z* (%) = 844.43 (77) [M + 1]$^+$.

1-((1-(4-((5,7-Bis(benzyloxy)-2-(3,4-bis(benzyloxy)phenyl)-4-oxo-4*H*-chromen-3-yl)oxy)butyl)-1*H*-1,2,3-triazol-4-yl)methyl)indoline-2,3-dione (IIIf)

By following the general procedure described above, the precursor **7** (350 mg, 0.46 mmol), $CuSO_4$·5H_2O (11.5 mg, 0.046 mmol), L-ascorbic acid (16 mg, 0.092 mmol) and 1-(prop-2-yn-1-yl)isatin **9f** (85 mg, 0.46 mmol) were added to a vial and allowed to react. The crude product was purified by column chromatography with SiO_2 gel using EtOAc/n-hexane (1:1) as eluent.

Yield: 78% (0.300 g); orange solid; R_f 0.35 in EtOAc/n-hexane (1:1); mp 78–79 °C.

^{1}H NMR ($CDCl_3$, 400.MHz): δ = 7.66 (d, *J* = 2 Hz, 1 H, CHar), 7.63 (s. 1 H, CHtrzl), 7.61 (dd, *J* = 2, 9 Hz, 1 H, CHar), 7.45–7.57 (m, 8 H, CHar), 7.25–7.42 (m, 15 H, CHar), 7.02–7.07 (m, 2 H, CHar), 6.51 (d, *J* = 2 Hz, CHQuer), 6.45 (d, *J* = 2 Hz, CHQuer), 5.26 (s, 2 H, CH_2Ph), 5.24 (s, 2 H, CH_2Ph), 5.21 (s, 2 H, CH_2Ph), 5.09 (s, 2 H, CH_2Ph), 4.94 (s, 2 H, CH_2-isatin), 4.38 (t, *J* = 7 Hz, 2 H, CH_2), 3.93 (t, *J* = 6 Hz, 2 H, CH_2), 1.98–2.06 (m, 2 H, CH_2), 1.59–1.65 (m, 2 H, CH_2).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 183.2, 173.9, 162.9, 159.9, 158.8, 158.0, 153.1, 151.0, 150.4, 148.4, 141.5, 140.1, 138.7, 137.1, 136.8, 136.4, 135.7, 128.9, 128.7 (2×CH), 128.7, 128.6, 128.1, 128.1, 127.8,

127.7, 127.4, 127.3, 126.7, 125.3, 124.0, 123.8, 123.2, 122.6, 117.6, 115.3, 113.9, 111.7, 110.0, 98.2, 94.0, 71.6, 71.0, 70.9, 70.9, 70.6, 50.1, 35.5, 27.0, 26.8.

MS (ESI): *m*/*z* (%) = 945.40 (100) $[M + 1]^+$.

5,7-Bis(benzyloxy)-2-(3,4-bis(benzyloxy)phenyl)-3-(4-(4-((2-isopropyl-5-methylphenoxy)methyl)-1*H*-1,2,3-triazol-1-yl)butoxy)-4*H*-chromen-4-one (IIIg)

By following the general procedure described above, the precursor **7** (250 mg, 0.33 mmol), $CuSO_4 \cdot 5H_2O$ (8.2 mg, 0.033 mmol), L-ascorbic acid (12 mg, 0.066 mmol) and 1-isopropyl-4-methyl-2-(prop-2-yn-1-yloxy) **9g** (64 mg, 0.33 mmol) were added to a vial and allowed to react. The crude product was purified by column chromatography with SiO_2 gel using EtOAc/n-hexane (1:2) as eluent.

Yield: 68% (0.212 g); colorless solid; R_f 0.21 in EtOAc/n-hexane (1:2); mp 98–100 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.57–7.68 (m, 5 H, CHAr), 7.27–7.48 (m, 18 H, CHAr), 7.09 (d, *J* = 8 Hz, 1 H, CH), 7.02 (d, *J* = 8.6 Hz, 1 H, CH),6.75–6.77 (m, 2 H, CHQuer and CH), 6.53 (d, *J* = 2 Hz, 1 H, CHQuer), 6.46 (d, *J* = 2 Hz, 1 H, CHQuer), 5.25 (s, 4 H, C*H*$_2$Ph and C*H*$_2$O), 5.22 (s, 2 H, C*H*$_2$Ph), 5.15 (s, 2 H, C*H*$_2$Ph), 5.09 (s, 2 H, C*H*$_2$Ph), 4.43 (t, *J* = 7 Hz, 2 H, CH_2), 3.97 (t, *J* = 6 Hz, 2 H, CH_2), 3.21–3.31 (m, 1 H, CH), 2.31 (s, 3 H, CH_3), 2.04–2.11 (m, 2 H, CH_2), 1.64–1.70 (m, 2 H, CH_2), 1.16 (s, 3 H, CH_3), 1.15 (s, 3 H, CH_3).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 173.9, 162.9, 159.9, 158.8, 155.5, 153.1, 151.0, 148.4, 144.6, 140.2, 137.1, 136.8, 136.5, 136.4, 135.7, 134.4, 128.9, 128.7, 128.7, 128.7, 128.6, 128.1, 128.1, 127.8, 127.7, 127.4, 127.3, 126.7, 126.1, 123.8, 122.7, 122.6, 121.9, 115.3, 113.9, 113.0, 110.1, 98.2, 94.0, 71.7, 71.1, 71.0, 70.9, 70.6, 62.5, 50.1, 27.1, 26.9, 26.6, 22.9 (2×CH_3), 21.5.

MS (ESI): *m*/*z* (%) = 948.49 (100) $[M + 1]^+$.

Synthesis of Hybrids IV: General Procedure

To a round-bottom flask with magnet stirrer was added the hybrid III, which was dissolved in a mixture of EtOH/THF (1:1, *v*/*v*), followed by the addition of palladium hydroxide/activated carbon (10%). The flask was fitted with a hydrogen balloon and the reaction was carried out over a 24–48 h period. The reaction mixture was then filtered on Celite/SiO_2 and washed with EtOH (30 mL). The residue obtained after evaporation of the solvent was purified by chromatography (if necessary).

2-(3,4-Dihydroxyphenyl)-5,7-dihydroxy-3-(4-(4-phenyl-1*H*-1,2,3-triazol-1-yl)butoxy)-4*H*-chromen-4-one (IVa)

By following the general procedure, the hybrid **IIIa** (100 mg, 0.12 mmol) was dissolved in 20 mL of a solvent mixture, and $Pd(OH)_2$/activated carbon (10 mg) was added. The reaction was conducted for 48 h.

Yield: 98% (0.059 g); slightly yellow solid; mp 115–116 °C.

^{1}H NMR (DMSO-d_6, 400 MHz): δ = 12.71 (s, 1 H, OH), 8.55 (s, 1 H, CHtrzl), 7.84 (d, *J* = 7.5 Hz, 2 H, CHQuer), 7.42–7.46 (m, 3 H, CHAr), 7.52 (s br, 1 H, CHAr), 7.31–7.34 (m, 1 H, CHAr), 6.89 (d, *J* = 8 Hz, 1 H, CHQuer), 6.39 (s br, 1 H, CHQuer), 6.18 (s br, 1 H, CHQuer), 4.44 (t, *J* = 7 Hz, 2 H, CH_2), 3.95 (t, *J* = 6 Hz, 2 H, CH_2), 1.97–2.05 (m, 2 H, CH_2), 1.64–1.70 (m, 2 H, CH_2).

^{13}C NMR (DMSO-d_6, 100 MHz): δ = 177.9, 164.3, 161.3, 156.4, 156.0, 148.7, 146.3, 145.2, 136.6, 130.9, 128.9, 127.8, 125.1, 121.3, 120.8, 120.7, 115.7, 115.4, 104.1, 98.6, 93.6, 71.1, 49.2, 26.4 (2×CH_2).

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{27}H_{24}N_3O_7$: 502.1609; found: 502.1599.

3-(4-(4-Cyclopropyl-1*H*-1,2,3-triazol-1-yl)butoxy)-2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-4*H*-chromen-4-one (IVb)

By following the general procedure, the hybrid **IIIb** (200 mg, 0.24 mmol) was dissolved in solvent mixture (50 mL) and $Pd(OH)_2$/activated carbon (20 mg) was added. The reaction was conducted for 48 h. The crude product was purified by column chromatography with SiO_2 gel using EtOAc/methanol (4:1) as eluent.

Yield: 95% (0.107 g); colorless semi-solid; R_f 0.84 in EtOAc/methanol (4:1).

^{1}H NMR (DMSO-d_6, 400 MHz): δ = 12.71 (s, 1 H, OH), 7.77 (s, 1 H, CHtrzl), 7.52 (d, *J* = 2 Hz, CHQuer), 7.43 (dd, *J* = 2, 8 Hz, 1 H, CHQuer), 6.89 (d, *J* = 8 Hz, 1 H, CHQuer), 6.41 (d, *J* = 2 Hz, 1 H, CHQuer), 6.19 (d, *J* = 2 Hz, 1 H, CHQuer), 4.29 (t, *J* = 7 Hz, 2 H, CH_2), 3.92 (t, *J* = 6 Hz, 2 H, CH_2), 1.86–1.94 (m, 2 H, CH_2), 1.56–1.64 (m, 2 H, CH_2), 0.85–0.89 (m, 2 H, CH_2), 0.68–0.70 (m, 2 H CH_2).

^{13}C NMR (DMSO-d_6, 100 MHz): δ = 178.0, 164.3, 161.3, 156.4, 156.0, 149.0, 148.7, 145.2, 136.6, 120.9, 120.8, 120.5, 115.7, 115.5, 104.2, 98.6, 93.6, 71.2, 48.9, 26.5, 26.4, 7.6, 6.6.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{24}H_{24}N_3O_7$: 466.1609; found: 466.1601.

2-(3,4-Dihydroxyphenyl)-5,7-dihydroxy-3-(4-(4-(1-hydroxycyclopentyl)-1*H*-1,2,3-triazol-1-yl)butoxy)-4*H*-chromen-4-one (IVc)

By following the general procedure, the hybrid **IIIc** (180 mg, 0.21 mmol) was dissolved in solvent mixture (50 mL) and $Pd(OH)_2$/activated carbon (18 mg) was added. The reaction was conducted for 24 h. The crude product was purified by column chromatography with SiO_2 gel using EtOAc/methanol (9:1) as eluent.

Yield: 92% (0.097 g); colorless semi-solid; R_f 0.55 in EtOAc/methanol (9:1).

^{1}H NMR (DMSO-d_6, 400 MHz): δ = 12.71 (s, 1 H, OH), 7.87 (s, 1 H, CHtrzl), 7.52 (d, *J* = 2 Hz, 1 H, CHQuer), 7.44 (dd, *J* = 2, 8 Hz, 1 H, CHQuer), 6.88 (d, *J* = 8 Hz, 1 H, CHQuer), 6.40 (s br, 1 H, CHQuer), 6.18 (s br, 1 H, CHQuer), 4.34 (t, *J* = 7 Hz, 2 H, CH_2), 3.92 (t, *J* = 6 Hz, 2 H, CH_2), 1.97–1.89 (m, 4 H, 2×CH_2), 1.83–2.80 (m, 4 H, 2×CH_2), 1.68–1.58 (m, 2 H, 2×CH_2).

^{13}C NMR (DMSO-d_6, 100 MHz): δ = 177.9, 164.4, 161.3, 156.4, 156.0, 154.4, 148.8, 145.3, 136.6, 121.1, 120.9, 120.7, 115.7, 115.4, 104.1, 98.6, 93.6, 77.5, 71.2, 48.8, 40.7, 26.6, 26.5, 23.3.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{26}H_{28}N_3O_8$: 510.1871; found: 510.1867.

2-(3,4-Dihydroxyphenyl)-5,7-dihydroxy-3-(4-(4-(2-hydroxypropan-2-yl)-1*H*-1,2,3-triazol-1-yl)butoxy)-4*H*-chromen-4-one (IVd)

By following the general procedure, the hybrid **IIId** (174 mg, 0.21 mmol) was dissolved in solvent mixture (50 mL) and $Pd(OH)_2$/activated carbon (18 mg) was added. The reaction was conducted for 24 h. The crude product was purified by column chromatography with SiO_2 gel using EtOAc/methanol (9:1) as eluent.

Yield: 65% (0.065 g); dark white semi-solid; R_f 0.34 in EtOAc/methanol (9:1).

^{1}H NMR (DMSO-d_6, 400 MHz): δ = 1.45 (s, 6 H, 2×CH_3), 1.60–1.67 (m, 2 H, CH_2), 1.90–1.97 (m, 2 H, CH_2), 3.93 (t, *J* = 6 Hz, 2 H, CH_2), 4.35 (t, *J* = 7 Hz, 2 H, CH_2), 5.07 (s, 1 H, OH), 6.19 (d, *J* = 2 Hz, CHQuer), 6.40 (d, *J* = 2 Hz, CHQuer), 6.89 (d, *J* = 8 Hz, CHQuer), 7.44 (dd, *J* = 2, 8 Hz, 1 H,

CHQuer), 7.52 (d, *J* = 2 Hz, 1 H, CHQuer), 7.86 (s, 1 H, CHQuer), 9.40 (s, 1 H, OH), 9.77 (s, 1 H, OH), 10.85 (s, 1 H, CHQuer), 12.71 (s, 1 H, CHQuer).

^{13}C NMR (DMSO-d_6, 100 MHz): δ = 26.5, 26.5, 30.7, 48.8, 67.0, 71.2, 93.6, 98.5, 104.2, 115.4, 115.7, 120.4, 120.7, 120.9, 136.6, 145.2, 148.7, 155.8, 156.0, 156.4, 161.3, 164.1, 178.0.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{24}H_{26}N_3O_8$: 484.1714; found: 484.1705.

2-(3,4-Dihydroxyphenyl)-5,7-dihydroxy-3-(4-(4-((2-isopropyl-5-methylphenoxy)methyl)-1*H*-1,2,3-triazol-1-yl)butoxy)-4*H*-chromen-4-one (IVe)

Following the general procedure, the hybrid **IIIg** (137 mg, 0.14 mmol) was dissolved in solvent mixture (30 mL) and $Pd(OH)_2$/activated carbon (14 mg) was added. The reaction was conducted for 24 h. The crude product was purified by column chromatography with SiO_2 gel using EtOAc/n-hexane (1:1) as eluent.

Yield: 42% (0.035 g); slightly yellow solid; R_f 0.48 in EtOAc/n-hexane (1:1); mp 69–70 °C.

^{1}H NMR (DMSO-d_6, 400 MHz): δ = 12.71 (s, 1 H, OH), 10.84 (s, 1 H, OH), 9.77 (s, 1 H, OH), 9.39 (s, 1 H, OH), 8.16 (s, 1 H, CHtrzl), 7.51 (d, *J* = 2 Hz, 1 H, CHQuer), 7.43 (dd, *J* = 2, 8 Hz, 1 H, CHQuer), 7.04 (d, *J* = 8 Hz, CHAr), 6.94 (s, 1 H, CHAr), 6.89 (d, *J* = 8 Hz, 1 H, CHAr), 6.71 (d, *J* = 8 Hz, 1 H, CHQuer), 6.40 (d, *J* = 2 Hz, 1 H, CHQuer), 6.19 (d, *J* = 2 Hz, 1 H, CHQuer), 5.11 (s, 2 H, CH_2), 4.42 (t, *J* = 7 Hz, 2 H, CH_2), 3.93 (t, *J* = 6 Hz, 2 H, CH_2), 3.10–3.17 (m, 1 H, C*H*$(CH_3)_2$), 2.26 (s, 3 H, CH_3), 1.91–2.01 (m, 2 H, CH_2), 1.60–1.67 (m, 2 H, CH_2), 1.08 (s, 3 H, CH_3), 1.07 (s, 3 H, CH_3).

^{13}C NMR (DMSO-d_6, 100 MHz): δ = 178.0, 164.2, 161.3, 156.4, 156.0, 155.1, 148.7, 145.2, 143.1, 136.6, 135.9, 133.4, 125.6, 124.1, 121.4, 120.9, 120.7, 115.7, 115.4, 113.1, 104.2, 98.6, 93.6, 71.1, 61.6, 49.0, 26.5, 26.4, 26.0, 22.7, 21.0.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{32}H_{34}N_3O_8$: 588.2340; found: 588.2332.

Methodology for Antiproliferative Assays

Test-Solution Preparation

The synthesized compounds were first dissolved in dimethyl sulfoxide (DMSO) at a concentration of 4×10^{-2} M. They were then diluted in cell growth media (EMEM) (supplemented with FBS 10%) with 0.25% DMSO to assess the 'test-solutions' at 10^{-9} M to 10^4 M range. All the 'test-solutions' were stored in a fridge (4 °C) until further analysis.

Antiproliferative Assay

REM-134 (canine mammary carcinoma cell line) was the cell line used to investigate the antiproliferative activity of the synthesized compounds. REM-134 cells were cultured in Eagle's Minimum Essential Medium (EMEM) supplemented with 10% fetal bovine serum (FBS) and 1% Strep-Pen (100 g/L Streptomycin; 100U/mL Penicillin). The cells were grown in a 5% CO_2 atmosphere at 37 °C.

For the proliferative and/or cytotoxic evaluation assays, 5.000 cells/well were seeded in a 96-well plate. After 24 h, the medium was removed and 100 µL of the test solutions were applied in triplicate. Negative and positive controls were prepared, incubating cells in culture media (maximal cellular proliferation expected), and with 2.5×10^{-5} M of the chemotherapeutic agent SAHA (maximal anti-proliferative action expected), respectively. Additionally, control samples without cells were carried out. The cells were then incubated during a period of 72 h in a 5% CO_2 incubator at 37 °C. Subsequently, the number of cells was calculated, using the Cell Counting Kit-8 method (Sigma–Aldrich) according to the manufacturer instructions.

Conflict of Interest

The authors declare no conflict of interest.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0040-1719928.

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