Structure–activity relationship of C-5-curcuminoids and synthesis of their molecular probes thereof

ARTICLE *in* BIOORGANIC & MEDICINAL CHEMISTRY · FEBRUARY 2010

Impact Factor: 2.79 · DOI: 10.1016/j.bmc.2009.12.045 · Source: PubMed

8 AUTHORS, INCLUDING:

Hiroyuki Yamakoshi
Nagoya City University
32 PUBLICATIONS **541** CITATIONS
SEE PROFILE

Naoki Kanoh
Tohoku University
87 PUBLICATIONS **1,312** CITATIONS
SEE PROFILE

Hiroyuki Shibata
Akita University
62 PUBLICATIONS **1,649** CITATIONS
SEE PROFILE

Bioorganic & Medicinal Chemistry 18 (2010) 1083–1092

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry

journal homepage: www.elsevier.com/locate/bmc

Structure–activity relationship of C_5-curcuminoids and synthesis of their molecular probes thereof

Hiroyuki Yamakoshi [a], Hisatsugu Ohori [b], Chieko Kudo [b], Atsuko Sato [b], Naoki Kanoh [a], Chikashi Ishioka [b], Hiroyuki Shibata [c], Yoshiharu Iwabuchi [a,*]

[a] Graduate School of Pharmaceutical Sciences, Tohoku University, 6-3 Aobayama, Sendai, Japan
[b] Department of Clinical Oncology, Institute of Development, Aging and Cancer, Tohoku University, Sendai, Japan
[c] Department of Clinical Oncology, Akita University Hospital, Akita, Japan

ARTICLE INFO

Article history:
Received 1 October 2009
Revised 16 December 2009
Accepted 17 December 2009
Available online 23 December 2009

Keywords:
Curcumin
C_5-curcumin
Bis(arylmethylidene)acetones
Cytotoxicity
Cancer chemotherapy
Molecular probe

ABSTRACT

A series of novel analogues of 1,5-bis(4-hydroxy-3-methoxyphenyl)-penta-(1*E*,4*E*)-1,4-dien-3-one (C_5-curcumin), which is a natural analogue of curcumin isolated from the rhizomes of *Curcuma domestica* Val. (Zingiberacea), were synthesized and evaluated for their cytotoxicities against human colon cancer cell line HCT-116 to conclude the SAR of C_5-curcuminoids for further development of their use in cancer chemotherapy: (1) Bis(arylmethylidene)acetone serves as a promising skeleton for eliciting cytotoxicity. (2) The 3-oxo-1,4-pentadiene structure is essential for eliciting cytotoxicity. (3) As for the extent of the aromatic substituents, hexasubstituted compounds exhibit strong activities, in which 3,4,5-hexasubstitution results in the highest potency. (5) The symmetry between two aryl rings is not an essential requirement for bis(arylmethylidene)acetones to elicit cytotoxicity. (6) *para*-Positions allows the installation of additional functional groups for use as molecular probes. By taking advantage of the SAR diagram, we have elaborated several advanced derivatives having GI_{50} of single-digit micromolar potencies that will function as molecular probes to target and/or report key biomolecules interacting with curcumin and C_5-curcumin.

1. Introduction

Turmeric, a yellow powder derived from the rhizome of the herb *Curcuma longa* L., has long been used as an essential spice and a traditional medicine in China and India. Over a long period of study, its major active constituent curcumin has been found to exhibit various biological and pharmacological activities including anti-inflammatory, antioxidant, antimicrobial, antiviral, chemopreventive, antiangiogenic, and anticancer activities,[1] through interactions with various biomolecules and biochemical pathways[2] including transcriptional factors (e.g., NF-κB),[3] cell proliferation pathways (e.g., cyclin D1, and c-myc),[4,5] cell survival pathways (e.g., Bcl-2, Bcl-xL, and cFLIP),[6] caspase activation pathways (e.g., caspase-8, caspase-3, and caspase-9),[7] tumor suppressor pathways (e.g., p53 and p21),[8] death receptor pathways (e.g., DR4 and DR5),[9] mitochondrial pathways, and protein kinase pathways (e.g., JNK, Akt, and AMPK).[10,11]

The multitargeting feature of curcumin has been considered to be of special merit for cancer chemoprevention and pharmacotherapy in light of the evidence that curcumin acts on numerous biochemical cascades leading to apoptosis, where the cellular targets of curcumin acquire enhanced sensitivity by oncological transformation.[2] However, clinical trials on the oral administration of curcumin have revealed the low bioavailability of curcumin owing to its poor absorption.[12,13] Hence, much effort has been devoted to developing useful derivatives to not only circumvent its low bioavailability while maintaining its low toxicity, but also enhance its selectivity and potency for addressing the pathological diversity of human cancer.[14–18]

Previously, we conducted a screening of an in-house library of synthetic compounds to obtain clues to enhancing the potential of dietary phytochemicals, and found two interesting compounds, namely, GO-035 and GO-949, from a curcumin panel (Fig. 1): GO-035 exhibits a high cytotoxicity against the human colon cancer line DLD-1 with a GI_{50} of 2.0 μM, which was four times more potent than curcumin (GI_{50}, 8 μM), whereas GO-949 shows an attenuated GI_{50} >50 μM, which is less than 1/5 that of curcumin.[19]

We were particularly interested in the fact that a small difference of just one C_1 unit at both the peripherals of 1,5-diaryl-3-oxo-1,4-pentadiene [bis(arylmethylidene)acetone] brings about such a significant (>20-fold) difference between their potencies.

Another important fact to emphasize is that GO-035 (1,5-bis(3,4-dimethoxyphenyl)-(1*E*,4*E*)-1,4-pentadien-3-one) is a close derivative of a natural five-carbon analogue of curcumin, namely 1,5-bis(4-hydroxy-3-methoxyphenyl)-(1*E*,4*E*)-1,4-pentadien-3-one

* Corresponding author.
E-mail address: iwabuchi@mail.pharm.tohoku.ac.jp (Y. Iwabuchi).

0968-0896/$ - see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmc.2009.12.045

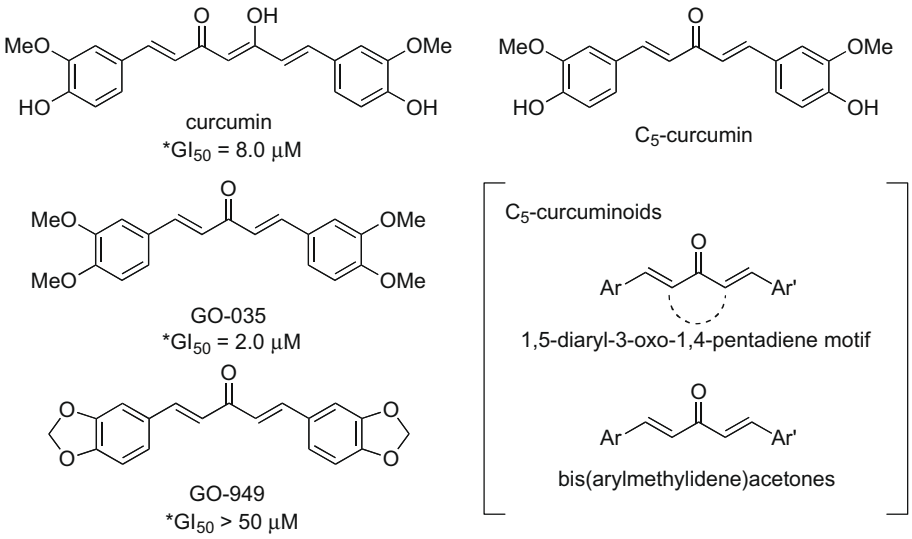


Figure 1.

(Fig. 1), of which the isolation from the rhizome of *Curcuma domestica* Val. and the antioxidative and anti-inflammatory activities were reported in 1993 by Masuda et al.;[20] however, little is known about its anticancer activity. (In relation to diarylheptanoid curcumin, we refer to this natural diarylpentanoid, 1,5-bis(4-hydroxy-3-methoxyphenyl)-(1*E*,4*E*)-1,4-pentadien-3-one,[20,21] as 'C_5-curcumin' hereafter.) Encouraged by this information, we synthesized and tested the growth-suppressive ability of >50 synthetic analogues of C_5-curcumin to obtain potentially useful analogues, namely, GO-Y030 and GO-Y031 (Fig. 2):[19] both compounds inhibit the Wnt/β-catenin pathway, whereby they induce the downregulation of β-catenin, Ki-Ras, Cyclin D1, c-Myc, and ErbB-2 at 2.5 μM, which correspond to at least 1/8 the curcumin concentration.[19,22] Importantly, the oral administration of GO-Y030 has been confirmed to induce a significantly improved chemopreventive ability in the FAP (familial adenomatous polyposis) mouse with no apparent toxicity in vivo.[23]

The observation of quite a huge difference in cytotoxicity depending on the extent and/or position of the aromatic substituent encouraged us to pursue further synthetic investigation to clarify the comprehensive SAR of C_5-curcuminoids for further development. We also envisioned the development of molecular probes based on GO-Y030/GO-Y031 to search for possible specific cellular targets.

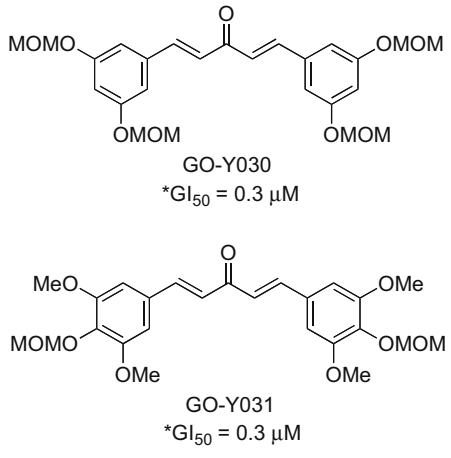


Figure 2.

In this work, we describe the comprehensive SAR of bis(arylmethylidene)acetones and the synthesis of molecular probes for future chemical biology studies.

2. Results and discussion

2.1. Chemistry

σ-Symmetric 1,5-diaryl-3-oxo-1,4-pentadienes were synthesized on the basis of the aldol condensation of modified benzaldehydes with acetone using established procedures (Scheme 1). The aldol condensation of a bicycloketone with arylaldehyde was attained by the phase transfer catalysis of hexadecyltrimethylammonium bromide. Asymmetric bis(arylmethylidene)acetones were synthesized in a two-step aldolization sequence via an aryl methyl ketone, of which the synthesis relied on Gupta's golden ratio employing 1:4 of aryl aldehyde/acetone.[24] The optimal monoaldolization of trimethoxybenzaldehydes with acetone was attained under Strauss's conditions using dimethylammonium dimethyl carbamate in CH_2Cl_2.[25] The monoenone GO-Y087 was synthesized by Saegusa oxidation[26] of GO-Y041.

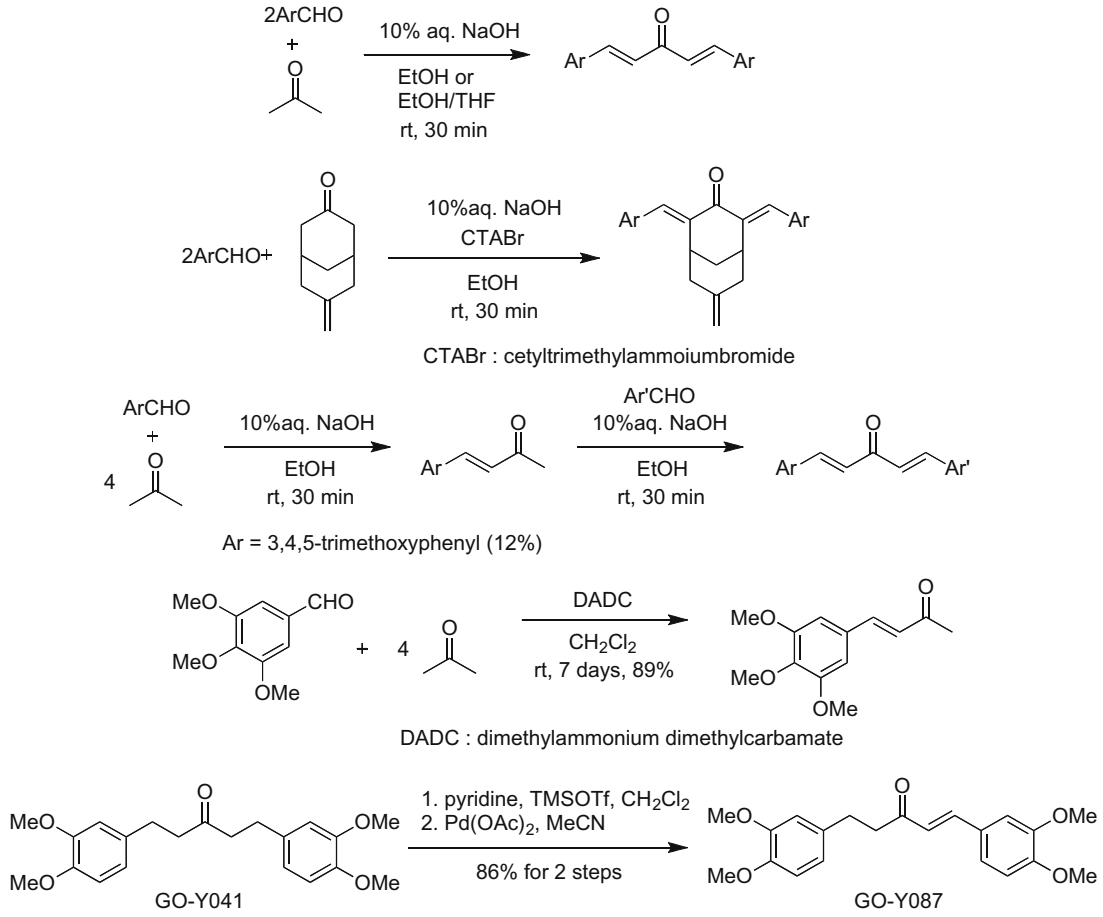
2.2. Pharmacological evaluation

The anticancer activities of the synthesized compounds were evaluated from the cell viability of the human colon cancer line HCT-116 with the quantitation of the uptake and digestion of 2-(2-methoxy-4-nitrophenyl)-3-(4-nitrophenyl)-5-(2,4-disulfophenyl)-2*H*-tetrazolium monosodium salt in accordance with the manufacturer's instructions (see Section 4).

2.3. SAR of C_5-curcuminoids

2.3.1. Preliminary SAR of C_5-curcumin

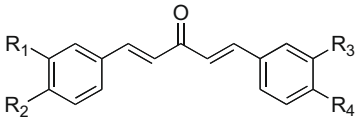
Turmeric contains several diarylheptanoids in which curcumin, demethoxycurcumin, and bisdemethoxycurcumin, featuring a phenolic group and the 1,7-diaryl-3,5-dioxo-1,6-heptadiene skeleton,



Scheme 1.

are the major active constituents responsible for the antioxidative and anti-inflammatory activities. In 2002, Lee et al. reported that synthetic 4,4′-dimethylcurcumin exhibits a marked cytotoxicity on human prostate cancer cell lines, indicating that the ethereal modification of the phenolic groups exerts a significant impact on the cytotoxic property of curcuminoids.[27] In this regard, questions were raised: (i) how such a significant effect was produced in the GO-035 by the dimethylation of natural C_5-curcumin; and (ii) what significant effect would dimethyl ether derivatives of C_5-curcumins exert on the anticancer activity in comparison with the dimethyl ether derivative of C_7-curcumin. To address the first question, a panel of related C_5-curcuminoids, namely, C_5-curcumin (GO-Y022), GO-Y023, GO-Y050, and GO-Y051, was synthesized and their cytotoxicities were compared with that of GO-035 (Table 1). It was confirmed that GO-035 acquired enhanced potency compared with natural C_5-curcumin (GO-Y022) through methyl etherification. Interestingly, both the regioisomeric GO-Y023 and the monomethylated C_5-curcumin GO-Y051 showed enhanced activities compared with C_5-curcumin, indicating the importance of *para*-etherification in cytotoxicity enhancement. Note that Lee et al. reported in 2006[28] the reversed potencies of C_5-curcumin and dimethylated C_5-curcumin (GO-035) determined on the basis of the anti-prostate cancer activities of these compounds: C_5-curcumin was shown to inhibit the growth of PC-3 and LNCaP cells by 50% at concentrations of 2.4 μM and 1.4 μM, respectively, whereas dimethylated C_5-curcumin (GO-035) was shown to inhibit their growth by 50% at concentrations of 3.8 μM and 3.5 μM, indicating the difference in intrinsic activity between tumor cell lines.

Table 1

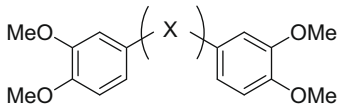


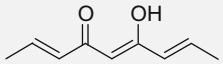
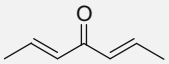
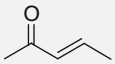
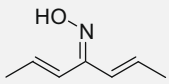
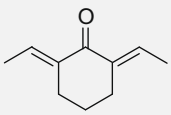
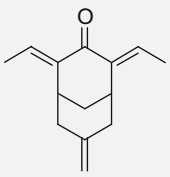
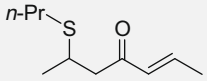
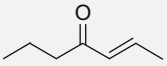
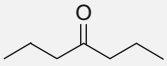
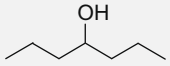
Compound	R_1	R_2	R_3	R_4	GI_{50} (μM)
GO-035	OMe	OMe	OMe	OMe	1.5
GO-Y022	OMe	OH	OMe	OH	15
GO-Y023	OH	OMe	OH	OMe	0.8
GO-Y050	OH	OMe	OMe	OMe	1.5
GO-Y051	OMe	OH	OMe	OMe	0.7

2.3.2. SAR of central tether moiety: C_5- versus C_7-curcuminoids

The second question regarding the correlation between C_7-curcuminoids and C_5-curcuminoids with respect to cytotoxicity was addressed using a panel of compounds carrying two 3,4-dimethoxybenzene rings at both edges of their alkyl tether, which were synthesized and evaluated (Table 2). It was found that GO-035 featuring a 3-oxo-1,4-pentadiene tether exhibited the highest activity among the panel. 4,4′-Dimethylcurcumin (GO-Y025) featuring the 3,5-dioxo-2,6-heptadiene tether exhibited a similar GI_{50} of 2.0 μM to that of GO-035. GO-Y034 featuring the 1,3-diaryl-3-oxo-2-propene skeleton showed a decreased GI_{50} of 7.0 μM, showing interesting contrast to several previously reported examples with antiangiogenic activities.[14] GO-Y032 that has a 3-oxo-1,4-pentadiene moiety merged within a cyclohexanone framework exhibited no cytotoxicity. The oxime GO-Y010, the monoenone GO-Y087,

Table 2



X				
Compound	GO-Y025	GO-Y035	GO-Y034	
GI_{50} (μM)	2.0	1.5	7.0	
X				
Compound	GO-Y010	GO-Y032	GO-Y037	
GI_{50} (μM)	>50	>50	>50	
X				
Compound	GO-Y066	GO-Y087	GO-Y041	GO-Y042
GI_{50} (μM)	22	>50	>50	>50

the saturated ketone GO-Y041, and the alcohol GO-Y042 were completely inactive, clearly indicating that 3-oxo-1,4-pentadiene plays indispensable roles in cytotoxicity induction. Interestingly, the monosulfide GO-Y066 exhibited a moderate GI_{50} of 22 μM, suggesting the reversible nature of the thiol adduct. On the basis of these data, the bis(arylmethylidene)acetone skeleton of C_5-curcuminoids was shown to be a reliable platform for the development of derivatives with an enhanced anticancer activity, and the 3-oxo-1,4-pentadine structure is essential for C_5-curcuminoids to induce cytotoxicity.

2.3.3. SAR of aromatic rings: Methoxy scanning

To obtain a comprehensive view of the effect of the aromatic substituent on C_5-curcuminoids, we carried out a methoxy scanning of bis(arylmethylidene)acetones, synthesizing and evaluating a panel of symmetrically/asymmetrically methoxy-substituted aryl analogues (Table 3). Generally, cytotoxicity increased as the number of methoxy substituents increased to culminate into hexamethoxylated bis(arylmethylidene)acetones, but decreased when the number of methoxy groups reached eight, as in GO-Y094.

Regarding tetramethoxylated compounds, the σ-symmetric series (cf. GO-035 and GO-Y067) exhibited higher activities than the asymmetric series (cf. GO-Y049 and GO-Y107). Among the σ-symmetric series, 2,4-methoxylated GO-Y103, 2,5-methoxylated GO-Y100, and 2,6-methoxylated GO-Y101 showed attenuated cytotoxicities, suggesting a disruptive effect of an *ortho*-methoxyl group on C_5-curcuminoids.

Among hexamethoxylated bis(arylmethylidene)acetones, 3,4,5-methoxylated GO-Y016 showed the highest potency. The other compounds exhibited comparable cytotoxicities to GO-035 including the σ-symmetric and asymmetric analogues, indicating that symmetry is not an essential factor for cytotoxicity.

Overall, the methoxy scanning indicated the following: (1) The 3,4,5-methoxylated form is the most potent substitution pattern. (2) The number of methoxyl groups for potentiating the cytotoxicity is within 4–6, except in the cases of *ortho*-substituted analogues. (3) Symmetry between two aryl rings is not an essential requirement for bis(arylmethylidene)acetones to elicit cytotoxicity.

2.3.4. Advanced SAR of tetra- and hexasubstituted analogues

Having established a fundamental SAR guideline by methoxy scanning, we next investigated advanced SAR by adding extra substituents into tetrasubstituted bis(arylmethylidene)acetones (Table 4) and hexasubstituted bis(arylmethylidene) acetones (Table 5) with a hope to gain insight into the target biomolecules.

Table 3

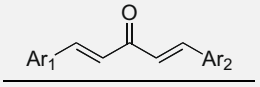
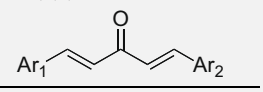
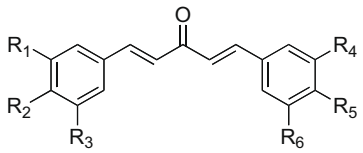
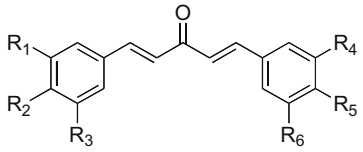
Compound	*n*	 $Ar_1 = Ar_2$		GI_{50} (μM)
GO-Y019	2	2-OMe-Ph		4.0
GO-Y091		3-OMe-Ph		9.1
GO-Y013		4-OMe-Ph		9.0
GO-Y015	4	2,3-OMe-Ph		1.3
GO-Y103		2,4-OMe-Ph		>50
GO-Y100		2,5-OMe-Ph		8.1
GO-Y101		2,6-OMe-Ph		9.0
GO-035		3,4-OMe-Ph		1.5
GO-Y067		3,5-OMe-Ph		2.0
GO-Y020	6	2,3,4-OMe-Ph		3.5
GO-Y106		2,3,6-OMe-Ph		2.3
GO-Y021		2,4,5-OMe-Ph		2.0
GO-Y104		2,4,6-OMe-Ph		2.3
GO-Y016		3,4,5-OMe-Ph		0.3
GO-Y094	8	2,3,4,6-OMe-Ph		>50
Compound	*n*	 Ar_1	Ar_2	GI_{50} (μM)
GO-Y110	3	Ph	3,4,5-OMe-Ph	4.4
GO-Y047		4-OMe-Ph	3,4-OMe-Ph	4.0
GO-Y049	4	4-OMe-Ph	3,4,5-OMe-Ph	3.0
GO-Y107		3-OMe-Ph	3,4,5-OMe-Ph	6.9
GO-Y046	5	3,4-OMe-Ph	3,4,5-OMe-Ph	0.4
GO-Y092	6	2,3,4-OMe-Ph	3,4,5-OMe-Ph	1.9
GO-Y093		2,4,5-OMe-Ph	3,4,5-OMe-Ph	3.3

Table 4



Compound	R_1	R_2	R_3	R_4	R_5	R_6	GI_{50} (μM)
Symmetric (3,4-substituted)							
GO-035	OMe	OMe	H	OMe	OMe	H	1.5
GO-Y040	OMOM	OMOM	H	OMOM	OMOM	H	0.8
GO-Y022	OMe	OH	H	OMe	OH	H	15
GO-Y023	OH	OMe	H	OH	OMe	H	0.8
Symmetric (3,5-substituted)							
GO-Y038	OH	H	OH	OH	H	OH	1.5
GO-Y067	OMe	H	OMe	OMe	H	OMe	2.0
GO-Y030	OMOM	H	OMOM	OMOM	H	OMOM	0.3
Asymmetric (3,4,5,3′-substituted)							
GO-Y098	OMe	OMe	OMe	OH	H	H	0.9
GO-Y107	OMe	OMe	OMe	OMe	H	H	6.9
GO-Y108	OMe	OMe	OMe	OMOM	H	H	4.0
GO-Y097	OMe	OMe	OMe	OCH(Me)OEt	H	H	1.4
GO-Y111	OMe	OMe	OMe	Cl	H	H	17
GO-Y109	OMe	OMe	OMe	OTf	H	H	2.4
GO-Y112	OMe	OMe	OMe	CCPh	H	H	8.1
GO-Y099	OMe	OMe	OMe	OTr	H	H	8.5
GO-Y102	OMe	OMe	OMe	OC(O)Ad	H	H	7.6
GO-Y105	OMe	OMe	OMe	$OC_{14}H_{29}$	H	H	>50

Table 5



Compound	R_1	R_2	R_3	R_4	R_5	R_6	GI_{50} (μM)
Symmetric (3,4,5-substituted)							
GO-Y026	OMe	OH	OMe	OMe	OH	OMe	0.8
GO-Y031	OMe	OMOM	OMe	OMe	OMOM	OMe	0.3
GO-Y039	OMe	OMEM	OMe	OMe	OMEM	OMe	0.4
GO-Y044	OMe	OCH_2CH_2OH	OMe	OMe	OCH_2CH_2OH	OMe	0.5
Asymmetric (3,4,5-substituted)							
GO-Y078	OMe	OMe	OMe	OMe	OH	OMe	0.8
GO-Y073	OMe	OMe	OMe	OMe	OCH_2CH_2OH	OMe	1.7
GO-Y082	OMe	OMe	OMe	OMe	OCH_2CO_2H	OMe	38
GO-Y081	OMe	OMe	OMe	OMe	OCH_2CO_2Me	OMe	7.0
GO-Y079	OMe	OMe	OMe	OMe	OCH(Me)OEt	OMe	1.5
GO-Y016	OMe	OMe	OMe	OMe	OMe	OMe	0.3

Since the fundamental SAR indicated that an *ortho*-substituent considerably reduced cytotoxicity, we focused on the *meta*- and *para*-substituted analogues.

As shown in Table 4, all the σ-symmetric, 3,4-substituted- and 3,5-substituted analogues showed significant cytotoxicities. Note that methoxymethylated analogues, namely, GO-Y040 and GO-Y030, exhibited enhanced cytotoxicities compared with the prototypic methoxylated counterpart, namely, GO-Y035 and GO-Y067, respectively, indicating there being a bit loose space around the binding sites for the aromatic peripherals. The attitude of tolerance towards the steric size of substituents was surveyed using a panel of 3,4,5-trimethoxy-3′-substituted derivatives, in which a variety of substituents were accepted, including adamantanecarboxyl (GO-Y102) and triphenylmethyl (GO-Y112) derivatives to retain moderate cytotoxicities, except long alkyloxy derivative (GO-Y105).

Table 5 highlights the advanced SAR of hexasubstituted analogues, indicating the introduction of various functional groups at the *para*-position, except for a carboxyl group (cf. GO-Y082), where the σ-symmetric and asymmetric compounds retained their potent cytotoxicities. These results also encouraged us to synthesize molecular probes employing the hexasubstituted C_5-curcuminoid platform.

2.3.5. Outline of SAR of C_5-curcuminoids

The following conclusions about SAR were drawn: (1) Bis(arylmethylidene)acetone serves as the most promising skeleton for eliciting cytotoxicity. (2) The 3-oxo-1,4-pentadiene structure is essential for eliciting cytotoxicity. (3) Hexasubstituted compounds exhibit strong activities. (4) 3,4,5-Hexasubstitution results in the highest potency. (5) The symmetry between two aryl rings is important for tetrasubstituted analogues but not a requirement

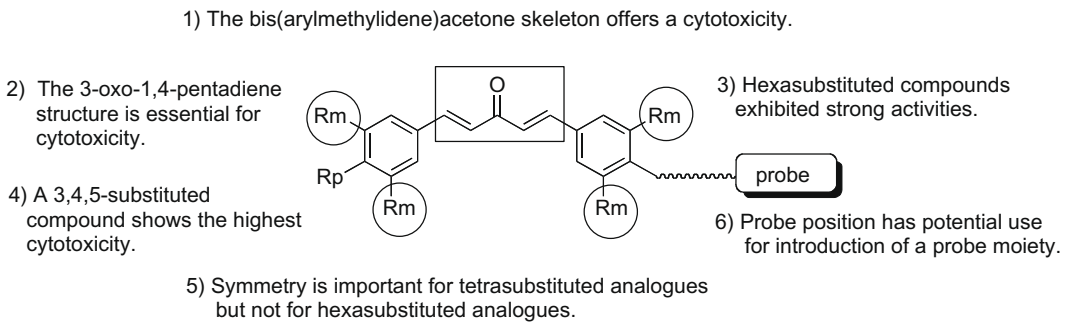


Figure 3.

for hexasubstituted analogues. (6) *para*-Positions are allowed to introduce of additional functional groups for use as molecular probes. These results are summarized in Figure 3. It would be interesting to point out that installation of methoxymethy groups instead of methoxy groups conferred bis(arylmethylidene)acetones improved water solubilities.

2.4. Development of molecular probes of C_5-curcuminoid

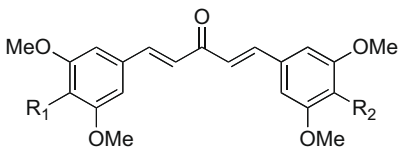
To date, many lines of evidence have been accumulated confirming that α,β-unsaturated ketones are excellent thiol alkylators via the Michael reaction. Dimmock and co-workers successfully demonstrated that bis(arylmethylidene)acetones have the highest efficiency as 'Michael alkylators' for thiols.[29] Considering the highly potent cytotoxicity of these compounds reaching GI_{50} values down to the submicromolar level, it would be reasonable to expect that GO-Y016, GO-Y030, and GO-Y031 interact with key biomolecules, playing crucial roles in cells via specific *S*-alkylation. The identification and characterization of such biomolecules which C_5-curcumin targets should provide useful information for cancer chemotherapy development. With this concept in mind, we envisioned the development of molecular probes based on C_5-curcuminoids, where we define the criterion for the probe as having a GI_{50} of single-digit micromolar potency.

From our SAR of C_5-curcuminoids, the direction of modification was set to the *para*-position of 3,3′,4,4′,5,5′-substituted compounds. Results are shown in Table 6. As expected, almost all the compounds exhibited strong cell growth inhibition, involving a large substituent (GO-Y061), azides (e.g., GO-Y085 and GO-Y065), alkynes (e.g., GO-Y060 and GO-048) and polar triazole (e.g., GO-Y074 and GO-Y083). Because azides and alkynes have versatile functions for the preparation of molecular probes,[30] several molecules retaining cytotoxicity will find good use in chemical biological studies of C_5-curcuminoids. We also obtained cytotoxic C_5-curcumin derivatives linked to a fluorescent dye[31] that provide useful insight into the molecular targets of C_5-curcuminoids for further development of anticancer medicines.

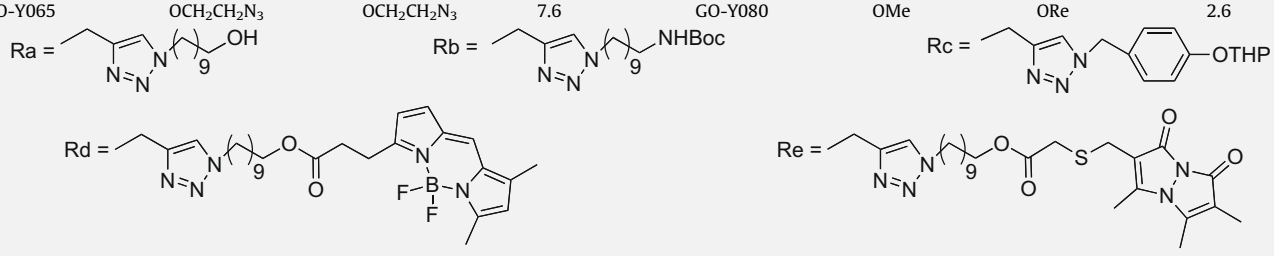
3. Conclusion

We determined the SAR of C_5-curcuminoids to gain useful insight into the molecular basis of their biological activities and fabricated molecular probes. From the SAR diagram, we have obtained several potential molecular probes that will target key biomolecules of C_5-curcuminoids. The SAR diagram will not only provide useful insight into the chemical biology of C_5-curcuminoids, but also encourage medicinal chemists to design useful derivatives for cancer chemotherapy. From these findings, we have obtained useful molecular probes that can form covalent bonds with their target proteins. The result of our study of such molecular probes will be reported elsewhere.

Table 6



Compound	R_1	R_2	GI_{50} (μM)	Compound	R_1	R_2	GI_{50} (μM)
GO-Y060	OMe	OCH_2CCH	1.8	GO-Y074	OMe	ORa	0.8
GO-Y085	OMe	$OCH_2CH_2N_3$	9.7	GO-Y083	OMe	ORb	0.8
GO-Y063	OMOM	OCH_2CCH	2.4	GO-Y061	OMe	ORc	0.3
GO-Y048	OCH_2CCH	OCH_2CCH	0.3	GO-Y076	OMe	ORd	15
GO-Y065	$OCH_2CH_2N_3$	$OCH_2CH_2N_3$	7.6	GO-Y080	OMe	ORe	2.6



4. Experimental

4.1. Chemical synthesis

Melting point was determined using a Yazawa BY-2 melting point apparatus and reported uncorrected. Infrared spectra were obtained on a JASCO *FT/IR*-410 Fourier Transform Infrared Spectrophotometer at a 4.0 cm^{-1} resolution and reported in wave numbers. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded using JEOL JMN-AL400 (400 MHz), and JEOL JNM-ECP-500 (500 MHz) spectrometers. Chemical shift (δ) is reported in parts per million (ppm) downfield, relative to tetramethylsilane (TMS). Coupling constant (J) is reported in hertz. Multiplicities are reported using the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; br, broad. Carbon-13 nuclear magnetic resonance (^{13}C NMR) spectra were recorded using JEOL JMN-AL400 (100 MHz) and JEOL JNM-ECP-500 (125 MHz) spectrometers. Chemical shift is reported in ppm relative to the center of $CDCl_3$ or CD_3OD. Low- and high-resolution mass spectra were recorded on a JEOL JMS-DX303 or JMS-700 using electron impact (EI). FAB mass spectra were recorded on a JEOL-JMS700 spectrometer using 3-nitrobenzyl alcohol as a matrix. Elemental analysis was performed using a Yanaco CHN CORDER MT-6. The synthesis and spectral properties of compounds **GO-Y011**-**Y051** were reported in our previous paper.[19] The synthesis schemes for **GO-Y010**-**Y112** and characterization data other than GO-Y compounds are provided in Supplementary data. All reactions were carried out in an atmosphere of argon unless otherwise specified. Anhydrous solvents were transferred via a syringe to flame-dried glassware, which had been cooled under a stream of dry nitrogen. Ethereal solvents and dichloromethane (anhydrous; Kanto Chemical Co., Inc.) were used as received. All other solvents were dried and distilled by standard procedures. Yields refer to chromatographically and spectroscopically (^{1}H NMR) homogeneous materials unless otherwise stated. Reagents of the highest commercial quality were purchased and used without further purification.

4.1.1. (1*E*,4*E*)-1-(3,5-Dimethoxy-4-(prop-2-ynyloxy)phenyl)-5-(3,4,5-trimethoxy-phenyl)-penta-1,4-dien-3-one (GO-Y060)

Yellow needle (AcOEt/hexane = 1:1): mp 118–120 °C. IR ($CHCl_3$): 3258, 2360, 1649, 1618, 1583, 1501, 1455, 1419, 1317, 1278, 1244, 1127 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (2H, d, J = 15.7 Hz), 6.98 (1H, d, J = 15.7 Hz), 6.97 (1H, d, J = 15.7 Hz), 6.85 (4H, s), 4.79 (2H, d, J = 2.4 Hz), 3.92 (12H, s), 3.90 (3H, s), 2.45 (1H, t, J = 2.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.4, 153.8, 153.5, 143.4, 143.2, 140.5, 137.8, 131.0, 130.2, 125.0, 124.8, 105.7, 105.6, 79.1, 75.1, 61.0, 60.1, 56.3, 56.2. MS (EI) *m/z*: 438 (M^+). HRMS (EI) Calcd for $C_{25}H_{26}O_7$: 438.1679. Found: 438.1670. Anal. Calcd for $C_{25}H_{26}O_7$: C, 68.48; H, 5.98. Found: C, 68.29; H, 6.04.

4.1.2. (1*E*,4*E*)-1-(3,5-Dimethoxy-4-((1-(4-(tetrahydro-2*H*-pyran-2-yloxy)benzyl)-1*H*-1,2,3-triazol-4-yl)methoxy)phenyl)-5-(3,4,5-trimethoxyphenyl)penta-1,4-dien-3-one (GO-Y061)

Yellow oil. IR ($CHCl_3$): 2940, 1649, 1682, 1503, 1455, 1419, 1277, 1241, 1126 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (1H, d, J = 15.9 Hz), 7.63 (1H, d, J = 15.7 Hz), 7.58 (1H, s), 7.18 (2H, d, J = 8.5 Hz), 7.04 (2H, d, J = 8.5 Hz), 6.98 (1H, d, J = 15.9 Hz), 6.97 (1H, d, J = 15.7 Hz), 6.85 (2H, s), 6.78 (2H, s), 5.43 (2H. s), 5.43 (1H, m), 5.23 (2H, s), 3.91 (6H, s), 3.90 (3H, s), 3.86 (1H, m), 3.79 (6H, s), 3.61 (1H, m), 1.96 (2H, m), 1.85 (2H, m), 1.67 (2H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.4, 157.3, 153.5, 153.4, 143.2, 143.1, 140.4, 138.4, 130.6, 130.2, 129.5, 127.4, 124.8, 124.7, 122.7, 116.9, 105.6, 105.4, 96.2, 66.4, 61.9, 60.9, 60.2, 56.1, 56.0, 53.6, 30.1, 25.0, 20.9, 18.5, 14.1. MS (EI) *m/z*: 587 ([M−THP$^+$]). HRMS (EI) Calcd for $C_{32}H_{33}N_3O_8$: 587.2268. Found: 587.2261.

4.1.3. (1*E*,4*E*)-1-(3,5-Dimethoxy-4-(methoxymethoxy)phenyl)-5-(3,5-dimethoxy-4-(prop-2-ynyloxy)phenyl)penta-1,4-dien-3-one (GO-Y063)

Yellow plate (AcOEt/hexane = 2:1): mp 122–124 °C. IR ($CHCl_3$): 3268, 2938, 1649, 1618, 1583, 1500, 1455, 1419, 1277, 1154, 1126 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (1H, d, J = 15.9 Hz), 7.66 (1H, d, J = 15.9 Hz), 6.98 (1H, d, J = 15.9 Hz), 6.97 (1H, d, J = 15.9 Hz), 6.85 (4H, s), 5.18 (2H, s), 4.78 (2H, d, J = 2.4 Hz), 3.92 (6H, s), 3.91 (6H, s), 3.61 (3H, s), 2.45 (1H, t, J = 2.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.4, 153.8, 153.6, 143.4, 143.2, 137.8, 137.0, 131.0, 130.7, 125.0, 124.9, 105.6, 98.2, 79.1, 75.1, 60.0, 57.2, 56.3, 56.2. MS (EI) *m/z*: 468 (M^+). HRMS (EI) Calcd for $C_{26}H_{28}O_8$: 468.1784. Found: 468.1786. Anal. Calcd for $C_{26}H_{28}O_8$: C, 66.66; H, 6.02. Found: C, 66.43; H, 6.16.

4.1.4. (1*E*,4*E*)-1,5-Bis(4-(2-azidoethoxy)-3,5-dimethoxyphenyl)penta-1,4-dien-3-one (GO-Y065)

Yellow styloid ($CHCl_3$/hexane = 1:2): mp 107–109 °C. IR ($CHCl_3$): 2938, 2105, 1650, 1617, 1583, 1502, 1454, 1419, 1278, 1244, 1128 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) *d* 7.67 (2H, d, J = 15.8 Hz), 6.98 (2H, d, J = 15.8 Hz), 6.85 (4H, s), 4.20 (4H, t, J = 5.3 Hz), 3.92 (12H, s), 3.57 (4H, t, J = 5.3 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) *d* 188.4, 153.5, 143.3, 138.8, 130.7, 124.9, 105.5, 71.7, 56.2, 51.1. MS (FAB) *m/z*: 524 (M^+). HRMS (FAB) Calcd for $C_{25}H_{29}N_6O_7$: 525.2106. Found: 525.2106. Anal. Calcd for $C_{25}H_{28}N_6O_7$: C, 57.25; H, 5.38; N, 16.02. Found: C, 57.02; H, 5.68; N, 16.03.

4.1.5. (*E*)-1,5-Bis(3,4-dimethoxyphenyl)-5-(propylthio)pent-1-en-3-one (GO-Y066)

Yellow oil. IR ($CHCl_3$): 2959, 1655, 1593, 1513, 1463, 1420, 1262, 1139, 1024 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) *d* 7.46 (1H, d, J = 16.0 Hz), 7.09 (1H, dd, J = 8.5, 1.9 Hz), 7.02 (1H, d, J = 1.9 Hz), 6.98 (1H, d, J = 2.2 Hz), 6.92 (1H, dd, J = 8.5, 2.2 Hz), 6.86 (1H, d, J = 8.2 Hz), 6.78 (1H, d, J = 8.2 Hz), 6.55 (1H, d, J = 16.0 Hz), 4.42 (1H, t, J = 7.1 Hz), 3.91 (3H, s), 3.91 (3H, s), 3.90 (3H, s), 3.85 (3H, s), 3.17 (2H, d, J = 7.1 Hz), 2.24–2.38 (2H, m), 1.54 (2H, m), 0.91 (3H, t, J = 7.5 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) *d* 196.9, 151.4, 149.2, 148.9, 148.1, 143.1, 127.2, 124.2, 123.1, 120.0, 111.0, 110.8, 110.7, 109.7, 55.9, 55.9, 55.8, 55.8, 47.6, 44.5, 33.5, 22.5, 13.4. MS (EI) *m/z*: 430 (M^+). HRMS (EI) Calcd for $C_{24}H_{30}O_5S$: 430.1814. Found: 430.1824.

4.1.6. (1*E*,4*E*)-1-(4-(2-Hydroxyethoxy)-3,5-dimethoxyphenyl)-5-(3,4,5-trimethoxy-phenyl)penta-1,4-dien-3-one (GO-Y073)

Yellow oil. IR ($CHCl_3$): 3511, 2940, 1650, 1617, 1582, 1503, 1454, 1419, 1318, 1278, 1244, 1127 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (2H, d, J = 15.7 Hz), 6.99 (1H, d, J = 15.7 Hz), 6.98 (1H, d, J = 15.7 Hz), 6.86 (2H, s), 6.85 (2H, s), 4.18 (2H, t, J = 4.4 Hz), 3.92 (6H, s), 3.92 (6H, s), 3.90 (3H, s), 3.75 (2H, m), 3.35 (1H, t, J = 6.3 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.3, 153.5, 153.4, 143.4, 143.0, 140.4, 138.6, 130.7, 130.2, 125.0, 124.7, 105.6, 105.4, 75.5, 61.4, 60.9, 56.2. MS (EI) *m/z*: 444 (M^+). HRMS (EI) Calcd for $C_{24}H_{28}O_8$: 444.1784. Found: 444.1787.

4.1.7. (1*E*,4*E*)-1-(4-((1-(10-Hydroxydecyl)-1*H*-1,2,3-triazol-4-yl)methoxy)-3,5-di-methoxyphenyl)-5-(3,4,5-trimethoxyphenyl)penta-1,4-dien-3-one (GO-Y074)

Yellow amorphous. IR ($CHCl_3$): 3408, 2930, 1650, 1617, 1583, 1502, 1455, 1419, 1318, 1278, 1245, 1127 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (1H, s), 7.65 (2H, d, J = 16.0 Hz), 6.99 (1H, d, J = 15.7 Hz), 6.98 (1H, d, J = 16.0 Hz), 6.85 (2H, s), 6.83 (2H, s), 5.25 (2H, s), 4.33 (2H, m), 3.91 (6H, s), 3.90 (6H, s), 3.88 (3H, s), 3.62 (2H, s), 2.20 (1H, s), 1.88 (2H, m), 1.55 (2H, m), 1.27–1.30 (12H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.3, 153.4, 153.2, 144.4, 143.2, 143.0, 140.2, 138.4, 130.5, 124.7, 124.6,

122.6, 105.5, 105.4, 66.3, 62.5, 60.7, 56.0, 56.0, 50.1, 32.5, 30.0, 29.2, 29.1, 29.0, 28.7, 26.2, 25.5. MS (EI) *m/z*: 637 (M^+). HRMS (EI) Calcd for $C_{35}H_{47}N_3O_8$: 637.3363. Found: 637.3354.

4.1.8. GO-Y076

Orange oil. IR ($CHCl_3$): 2931, 1729, 1649, 1605, 1501, 1277, 1247, 1128 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.68 (1H, s), 7.65 (1H, d, J = 15.9 Hz), 7.64 (1H, d, J = 15.9 Hz), 7.07 (1H, s), 6.97 (2H, d, J = 15.9 Hz), 6.87 (1H, d, J = 4.1 Hz), 6.85 (2H, s), 6.83 (2H, s), 6.26 (1H, d, J = 4.1 Hz), 6.10 (1H, s), 5.25 (2H, s), 4.33 (2H, t, J = 7.4 Hz), 4.08 (2H, t, J = 6.6 Hz), 3.92 (6H, s), 3.90 (3H, s), 3.89 (6H, s), 3.29 (2H, t, J = 7.5 Hz), 2.75 (2H, t, J = 7.5 Hz), 2.56 (3H, s), 2.24 (3H, s), 1.89 (2H, m), 1.61 (2H, m), 1.23–1.31 (12H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.5, 172.6, 160.4, 157.3, 153.7, 153.5, 144.7, 143.8, 143.4, 143.3, 140.5, 138.7, 133.3, 130.7, 130.3, 128.8, 128.1, 124.9, 124.8, 123.8, 122.7, 120.4, 116.7, 105.7, 105.6, 66.7, 64.7, 61.0, 56.2, 56.2, 50.3, 33.4, 30.3, 29.3, 29.3, 29.1, 29.0, 28.6, 26.5, 25.8, 24.0, 14.9, 11.3. MS (FAB) *m/z*: 912 ($[M+H]^+$). HRMS (FAB) Calcd for $C_{49}H_{61}BF_2N_5O_9$: 912.4530. Found: 912.4502.

4.1.9. (1*E*,4*E*)-1-(4-Hydroxy-3,5-dimethoxyphenyl)-5-(3,4,5-trimethoxyphenyl)-penta-1,4-dien-3-one (GO-Y78)

Yellow amorphous. IR ($CHCl_3$): 3389, 2939, 1645, 1583, 1505, 1455, 1421, 1283, 1153, 1125 cm^{-1}. UV ($CHCl_3$) 380 nm. ^1H NMR (400 MHz, $CDCl_3$) δ 7.66 (1H, d, J = 15.7 Hz), 7.65 (1H, d, J = 15.9 Hz), 6.98 (1H, d, J = 15.7 Hz), 6.94 (1H, d, J = 15.9 Hz), 5.99 (1H, s), 3.93 (6H, s), 3.91 (6H, s), 3.90 (3H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.4, 153.4, 147.2, 143.7, 142.9, 140.3, 137.5, 130.3, 126.2, 124.8, 123.4, 105.5, 105.4, 60.9, 56.3, 56.1. MS (EI) *m/z*: 400 (M^+). HRMS (EI) Calcd for $C_{22}H_{24}O_7$: 400.1522. Found: 400.1502.

4.1.10. (1*E*,4*E*)-1-(4-(1-Ethoxyethoxy)-3,5-dimethoxyphenyl)-5-(3,4,5-trimethoxy-phenyl)penta-1,4-dien-3-one (GO-Y079)

Yellow oil. IR ($CHCl_3$): 2938, 1650, 1617, 1582, 1501, 1419, 1277, 1244, 1128 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.66 (2H, d, J = 15.7 Hz), 6.98 (2H, d, J = 15.7 Hz), 6.85 (4H, s), 5.33 (1H, q, J = 5.1 Hz), 3.94 (6H, s), 3.91 (3H, s), 3.90 (6H, s), 3.82 (1H, m), 3.64 (1H, m), 1.51 (3H, d, J = 5.1 Hz), 1.19 (3H, t, J = 7.3 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.4, 153.5, 153.4, 143.3, 143.2, 140.4, 137.5, 130.3, 130.2, 124.8, 124.7, 105.6, 105.6, 103.3, 62.9, 60.9, 56.2, 56.0, 20.9, 15.1. MS (EI) *m/z*: 472 (M^+). HRMS (EI) Calcd for $C_{26}H_{31}O_8$: 471.2008.

4.1.11. 10-(4-((2,6-Dimethoxy-4-((1*E*,4*E*)-3-oxo-5-(3,4,5-trimethoxyphenyl)penta-1,4-dienyl)phenoxy)methyl)-1*H*-1,2,3-triazol-1-yl)decyl 2-((3,5,6-trimethyl-1,7-di-oxo-1,7-dihydropyrazolo[1,2-*a*]pyrazol-2-yl)methylthio)ethanoate (GO-Y080)

Yellow oil. IR ($CHCl_3$): 2931, 1742, 1582, 1502, 1418, 1277, 1229, 1126 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.69 (1H, s), 7.66 (1H, d, J = 16.1 Hz), 7.65 (1H, d, J = 16.1 Hz), 6.98 (2H, d, J = 16.1 Hz), 6.86 (2H, s), 6.84 (2H, s), 5.24 (2H, s), 4.35 (2H, t, J = 7.1 Hz), 4.13 (2H, t, J = 6.8 Hz), 3.92 (6H, s), 3.90 (3H, s), 3.89 (6H, s), 3.83 (2H, s), 3.26 (2H, s), 2.41 (3H, s), 1.89 (3H, s), 1.83 (3H, s), 1.62–1.64 (4H, m), 1.27–1.31 (12H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.5, 169.6, 160.6, 160.0, 153.7, 153.5, 146.1, 144.8, 144.4, 143.4, 143.3, 140.5, 138.7, 130.8, 130.3, 125.0, 124.8, 122.8, 115.1, 112.8, 105.7, 105.6, 66.7, 66.1, 61.0, 56.3, 56.2, 56.2, 50.3, 32.7, 30.3, 29.3, 29.3, 29.1, 28.9, 28.5, 26.4, 25.8, 25.3, 11.7, 7.1, 6.9. MS (FAB) *m/z*: 902 ($[M+H]^+$). HRMS (FAB) Calcd for $C_{47}H_{60}N_5O_{11}S$: 902.4010. Found: 902.4011.

4.1.12. Methyl 2-(2,6-dimethoxy-4-((1*E*,4*E*)-3-oxo-5-(3,4,5-trimethoxyphenyl)-penta-1,4-dienyl)phenoxy)ethanoate (GO-Y081)

Yellow amorphous. IR ($CHCl_3$): 2941, 1759, 1649, 1618, 1583, 1503, 1419, 1278, 1127 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) *d* 7.66 (1H, d, J = 15.7 Hz), 7.64 (1H, d, J = 15.9 Hz), 6.97 (1H, d, J = 15.7 Hz), 6.97 (1H, d, J = 15.9 Hz), 6.85 (2H, s), 6.84 (2H, s), 4.70 (2H, s), 3.92 (6H, s), 3.90 (9H, s), 3.81 (3H, s). ^{13}C NMR (100 MHz, $CDCl_3$) *d* 188.1, 169.3, 153.1, 152.5, 143.0, 142.7, 140.1, 138.0, 130.3, 129.9, 124.7, 124.5, 105.3, 69.1, 60.6, 55.9, 55.8, 51.7. MS (EI) *m/z*: 472 (M^+). HRMS (EI) Calcd for $C_{25}H_{28}O_9$: 472.1713.

4.1.13. 2-(2,6-Dimethoxy-4-((1*E*,4*E*)-3-oxo-5-(3,4,5-trimethoxyphenyl)-penta-1,4-dienyl)phenoxy)ethanoic acid (GO-Y082)

Yellow powder ($CHCl_3$/Et_2O): mp 208–210 °C. IR ($CHCl_3$): 3584, 1767, 1617, 1583, 1503, 1419, 1280, 1126 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.68 (1H, d, J = 16.0 Hz), 7.65 (1H, d, J = 15.9 Hz), 7.00 (1H, d, J = 16.0 Hz), 6.97 (1H, d, J = 15.9 Hz), 6.87 (2H, s), 6.85 (2H, s), 4.65 (2H, s), 3.97 (6H, s), 3.92 (6H, s), 3.91 (3H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.2, 170.1, 153.5, 152.1, 143.8, 142.5, 140.6, 138.0, 131.9, 130.0, 125.7, 124.6, 105.7, 105.3, 71.1, 61.0, 56.3, 56.2. MS (EI) *m/z*: 458 (M^+). HRMS (EI) Calcd for $C_{24}H_{26}O_9$: 458.1577. Found: 458.1540.

4.1.14. *tert*-Butyl 10-(4-((2,6-dimethoxy-4-((1*E*,4*E*)-3-oxo-5-(3,4,5-trimethoxy-phenyl)penta-1,4-dienyl)phenoxy)methyl)-1*H*-1,2,3-triazol-1-yl)decylcarbamate (GO-Y083)

Yellow amorphous. IR ($CHCl_3$): 3379, 1698, 1649, 1617, 1582, 1503, 1455, 1419, 1277, 1245, 1128 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.71 (1H, s), 7.66 (1H, d, J = 15.9 Hz), 7.65 (1H, d, J = 15.9 Hz), 6.99 (2H, d, J = 15.9 Hz), 6.85 (2H, s), 6.83 (2H, s), 5.24 (2H, s), 4.34 (2H, t, J = 7.2 Hz), 3.91 (6H, s), 3.91 (3H, s), 3.90 (6H, s), 3.09 (2H, m), 1.88 (2H, m), 1.43–1.46 (11H, m), 1.26–1.30 (12H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.2, 155.8, 153.4, 153.2, 144.4, 143.1, 143.0, 140.2, 138.4, 130.5, 130.0, 124.7, 124.6, 122.6, 105.4, 105.3, 66.3, 60.7, 56.0, 55.9, 50.0, 40.3, 30.1, 29.8, 29.1, 29.0, 28.9, 28.7, 28.2, 28.2, 26.5, 26.2. MS (FAB) *m/z*: 736 (M^+). HRMS (FAB) Calcd for $C_{40}H_{56}N_4O_9$: 736.4047. Found: 736.4046.

4.1.15. (1*E*,4*E*)-1-(4-(2-Azidoethoxy)-3,5-dimethoxyphenyl)-5-(3,4,5-trimethoxy-phenyl)penta-1,4-dien-3-one (GO-Y085)

Yellow oil. IR ($CHCl_3$): 2938, 2105, 1649, 1617, 1582, 1503, 1454, 1418, 1277, 1127 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.66 (2H, d, J = 15.9 Hz), 6.98 (1H, d, J = 15.9 Hz), 6.97 (1H, d, J = 15.9 Hz), 6.85 (4H, s), 4.19 (2H, t, J = 5.2 Hz), 3.92 (12H, s), 3.90 (3H, s), 3.56 (2H, t, J = 5.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.4, 153.5, 153.4, 143.4, 143.2, 140.4, 138.7, 130.7, 130.2, 124.9, 124.7, 105.6, 105.4, 71.6, 61.0, 56.2, 51.1. MS (FAB) *m/z*: 470 ($[M+H]^+$). HRMS (FAB) Calcd for $C_{24}H_{28}O_7N_3$: 470.1927. Found: 470.1940.

4.1.16. (*E*)-1,5-Bis(3,4-dimethoxyphenyl)pent-1-en-3-one (GO-Y087)

Pale yellow solid. IR ($CHCl_3$): 2935, 1682, 1653, 1594, 1513, 1234, 1139, 1024 cm^{-1}. UV ($CHCl_3$) 337 nm. ^1H NMR (400 MHz, $CDCl_3$) δ 7.49 (1H, d, J = 16.1 Hz), 7.10 (1H, d, J = 8.3 Hz), 7.04 (1H, s), 6.86 (1H, d, J = 8.3 Hz), 6.80–6.75 (3H, m), 6.61 (1H, d, J = 16.1 Hz), 3.90 (6H, s), 3.87 (3H, s), 3.87 (3H, s), 3.84 (3H, s), 2.96 (4H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.0, 151.1, 149.0, 148.7, 147.1, 142.5, 133.7, 127.2, 124.1, 122.8, 120.0, 111.7, 111.2, 110.9, 109.5, 55.9, 55.8, 55.8, 55.7, 42.4, 29.9. MS (EI) *m/z*: 418 (M^+). HRMS (EI) Calcd for $C_{23}H_{30}O_7$: 418.1992. Found: 418.2004.

4.1.17. (1*E*,4*E*)-1-(2,3,4-Trimethoxyphenyl)-5-(3,4,5-trimethoxyphenyl)penta-1,4-dien-3-one (GO-Y092)

Yellow oil. IR ($CHCl_3$): 2930, 1671, 1651, 1620, 1596, 1487, 1290, 1255, 1185, 1102, 1047 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.70 (2H, d, J = 15.9 Hz), 7.33 (2H, t, J = 8.0 Hz), 7.21 (2H, d,

J = 8.0 Hz), 7.13 (2H, t, J = 2.5 Hz), 7.06 (2H, d, J = 15.9 Hz), 6.96 (2H, dd, J = 8.0, 2.5 Hz), 3.86 (6H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.7, 159.8, 143.1, 136.1, 129.8, 125.5, 121.0, 116.2, 113.2, 55.2. MS (EI) m/z: 294 (M^+). HRMS (EI) Calcd for $C_{19}H_{18}O_3$: 294.1256. Found: 294.1241.

4.1.18. (1*E*,4*E*)-1-(2,4,5-Trimethoxyphenyl)-5-(3,4,5-trimethoxyphenyl)penta-1,4-dien-3-one (GO-Y093)

Yellow box (AcOEt/hexane = 1:2): mp 160–162 °C. IR ($CHCl_3$): 2928, 1681, 1593, 1462, 1250, 1212, 1101 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (1H, d, J = 16.0 Hz), 7.64 (1H, d, J = 16.0 Hz), 7.12 (1H, s), 7.01 (1H, d, J = 16.0 Hz), 6.99 (1H, d, J = 16.0 Hz), 6.84 (2H, s), 6.52 (1H, s), 3.94 (3H, s), 3.92 (6H, s), 3.91 (3H, s), 3.90 (6H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.9, 154.4, 153.4, 152.6, 143.3, 142.4, 140.2, 138.2, 130.5, 125.0, 123.7, 115.3, 110.9, 105.5, 98.8, 60.9, 56.5, 56.3, 56.2, 56.0. MS (EI) m/z: 414 (M^+). HRMS (EI) Calcd for $C_{23}H_{26}O_7$: 414.1679. Found: 414.1663. Anal. Calcd for $C_{23}H_{26}O_7$: C, 66.65; H, 6.32. Found: C, 66.36; H, 6.36.

4.1.19. (1*E*,4*E*)-1,5-Bis(2,3,4,6-tetramethoxyphenyl)penta-1,4-dien-3-one (GO-Y094)

Yellow box (AcOEt/hexane = 1:1): mp 171–173 °C. IR ($CHCl_3$): 2938, 1637, 1592, 1565, 1315, 1204, 1105 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (2H, d, J = 16.4 Hz), 7.50 (2H, d, J = 16.4 Hz), 6.30 (2H, s), 3.93 (6H, s), 3.92 (6H, s), 3.91 (6H, s), 3.83 (6H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.1, 156.4, 155.2, 154.5, 136.5, 133.5, 127.6, 111.1, 92.1, 61.1, 61.1, 56.0, 55.9. MS (EI) m/z: 474 (M^+). HRMS (EI) Calcd for $C_{25}H_{30}O_9$: 474.1890. Found: 474.1874. Anal. Calcd for $C_{25}H_{30}O_9$: C, 63.28; H, 6.37. Found: C, 63.07; H, 6.33.

4.1.20. (1*E*,4*E*)-1-(3-(1-Ethoxyethoxy)phenyl)-5-(3,4,5-trimethoxyphenyl)penta-1,4-dien-3-one (GO-Y097)

Yellow oil. IR ($CHCl_3$): 2976, 1650, 1619, 1581, 1504, 1320, 1127, 1102 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (1H, d, J = 15.8 Hz), 7.65 (1H, d, J = 15.8 Hz), 7.32 (1H, m), 7.26 (1H, m), 7.25 (1H, m), 7.08 (1H, d, J = 15.8 Hz), 7.06 (1H, m), 6.96 (1H, d, J = 15.8 Hz), 6.85 (2H, s), 5.44 (1H, q, J = 5.3 Hz), 3.92, (6H, s), 3.90 (3H, s), 3.79 (1H, m), 3.57 (1H, m), 1.54 (3H, d, J = 5.3 Hz), 1.23 (3H, t, J = 6.9 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.5, 157.2, 153.4, 143.4, 142.9, 140.3, 136.1, 130.1, 130.0, 125.3, 124.9, 122.0, 119.4, 116.7, 105.5, 99.4, 61.2, 61.0, 56.2, 20.2, 15.3. MS (EI) m/z: 412 (M^+). HRMS (EI) Calcd for $C_{24}H_{28}O_6$: 412.1886. Found: 412.1901.

4.1.21. (1*E*,4*E*)-1-(3-Hydroxyphenyl)-5-(3,4,5-trimethoxyphenyl)penta-1,4-dien-3-one (GO-Y098)

Yellow plate (AcOEt/hexane = 1:1): mp 137–139 °C. IR ($CHCl_3$): 3353, 1644, 1617, 1582, 1504, 1274, 1126 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (1H, d, J = 16.0 Hz), 7.67 (1H, d, J = 16.0 Hz), 7.29 (1H, t, J = 7.8 Hz), 7.20 (1H, d, J = 7.8 Hz), 7.16 (1H, s), 7.09 (1H, d, J = 16.0 Hz), 6.96 (1H, d, J = 16.0 Hz), 6.91 (1H, d, J = 7.8 Hz), 6.84 (2H, s), 5.79 (1H, br s), 3.92, (6H, s), 3.91 (3H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.0, 156.3, 153.5, 143.9, 143.3, 140.5, 136.3, 130.2, 130.2, 125.3, 125.0, 121.0, 117.8, 115.0, 105.7, 61.0, 56.2. MS (EI) m/z: 340 (M^+). HRMS (EI) Calcd for $C_{20}H_{20}O_5$: 340.1311. Found: 340.1295. Anal. Calcd for $C_{20}H_{20}O_5$: C, 70.57; H, 5.92. Found: C, 70.57; H, 6.07.

4.1.22. (1*E*,4*E*)-1-(3,4,5-Trimethoxyphenyl)-5-(3-(trityloxy)phenyl)penta-1,4-dien-3-one (GO-Y099)

Yellow amorphous. IR ($CHCl_3$): 3007, 1650, 1618, 1581, 1504, 1448, 1320, 1241, 1127 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (1H, d, J = 16.0 Hz), 7.48 (1H, d, J = 16.0 Hz), 7.46 (6H, m), 7.31–7.21 (9H, m), 7.05 (1H, d, J = 8.0 Hz), 7.00 (1H, t, J = 8.0 Hz), 6.96 (1H, d, J = 1.2 Hz), 6.88 (1H, d, J = 16.0 Hz), 6.83 (1H, d, J = 16.0 Hz), 6.83 (2H, s), 6.71 (1H, dd, J = 8.0, 1.2 Hz), 3.92, (6H, s), 3.90 (3H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.5, 156.6, 153.4, 143.7, 143.1, 142.9, 140.3, 135.1, 130.1, 128.8, 128.6, 127.7, 127.2, 125.1, 124.8, 123.0, 121.5, 120.6, 105.5, 90.7, 60.8, 56.0. MS (EI) m/z: 581 [$(M-H)^+$]. HRMS (EI) Calcd for $C_{39}H_{33}O_5$: 581.2328. Found: 581.2332.

4.1.23. (1*E*,4*E*)-1-(3-(Adamantane-1-carboxy)phenyl) 5-(3,4,5-trimethoxyphenyl)-penta-1,4-dien-3-one (GO-Y102)

Yellow oil. IR ($CHCl_3$): 2907, 1745, 1651, 1620, 1582, 1504, 1321, 1209, 1182, 1127, 1101, 1052 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (1H, d, J = 16.0 Hz), 7.66 (1H, d, J = 16.0 Hz), 7.43 (1H, dt, J = 7.8, 1.8 Hz), 7.40 (1H, t, J = 7.8 Hz), 7.34 (1H, t, J = 1.8 Hz), 7.09 (1H, dt, J = 7.8, 1.8 Hz), 7.08 (1H, d, J = 16.0 Hz), 6.94 (1H, d, J = 16.0 Hz), 6.85 (2H, s), 3.92, (6H, s), 3.90 (3H, s), 2.11–2.08 (9H, m), 1.82–1.75 (6H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.4, 175.9, 153.4, 151.5, 143.5, 142.0, 140.5, 136.3, 130.1, 129.8, 125.9, 125.9, 124.9, 123.5, 120.8, 105.6, 60.9, 56.1, 41.0, 38.7, 36.4, 27.8. MS (EI) m/z: 502 (M^+). HRMS (EI) Calcd for $C_{31}H_{34}O_6$: 502.2355. Found: 502.2344.

4.1.24. (1*E*,4*E*)-1-(3-(Tetradecyloxy)phenyl)-5-(3,4,5-trimethoxyphenyl)penta-1,4-dien-3-one (GO-Y105)

Yellow oil. IR ($CHCl_3$): 2923, 1651, 1619, 1581, 1504, 1267, 1244, 1128, 1102 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (1H, d, J = 15.8 Hz), 7.65 (1H, d, J = 15.8 Hz), 7.30 (1H, t, J = 7.9 Hz), 7.18 (1H, d, J = 7.9 Hz), 7.13 (1H, t, J = 2.3 Hz), 7.08 (1H, d, J = 15.8 Hz), 6.96 (1H, d, J = 15.8 Hz), 6.94 (1H, dd, J = 7.9, 2.3 Hz), 6.84 (2H, s), 3.98 (2H, t, J = 6.6 Hz), 3.91, (6H, s), 3.90 (3H, s), 1.80 (2H, m), 1.47 (2H, m), 1.35–1.26 (20H, m), 1.88 (3H, t, J = 6.9 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.6, 159.5, 153.5, 143.3, 143.2, 140.4, 136.1, 130.2, 129.8, 125.3, 125.0, 120.9, 116.7, 113.9, 105.6, 68.1, 60.9, 56.2, 31.9, 29.6, 29.6, 29.6, 29.6, 29.5, 29.3, 29.2, 26.0, 22.6, 14.0. MS (EI) m/z: 536 (M^+). HRMS (EI) Calcd for $C_{34}H_{48}O_5$: 536.3502. Found: 536.3494.

4.1.25. (1*E*,4*E*)-1,5-Bis(2,3,6-trimethoxyphenyl)penta-1,4-dien-3-one (GO-Y106)

Yellow needle (AcOEt/hexane = 1:1): mp. 116–118 °C. IR ($CHCl_3$): 2938, 1644, 1578, 1485, 1256, 1107 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (2H, d, J = 16.3 Hz), 7.64 (2H, d, J = 16.3 Hz), 6.90 (2H, d, J = 8.9 Hz), 6.62 (2H, d, J = 8.9 Hz), 3.87 (6H, s), 3.87 (6H, s), 3.85 (6H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.2, 153.8, 150.0, 147.1, 133.8, 130.1, 118.8, 114.4, 105.9, 60.9, 56.5, 56.0. MS (EI) m/z: 414 (M^+). HRMS (EI) Calcd for $C_{23}H_{26}O_7$: 414.1679. Found: 414.1673. Anal. Calcd for $C_{23}H_{26}O_7$: C, 66.65; H, 6.32. Found: C, 66.54; H, 6.37.

4.1.26. (1*E*,4*E*)-1-(3-Methoxyphenyl)-5-(3,4,5-trimethoxyphenyl)penta-1,4-dien-3-one (GO-Y107)

Yellow oil. IR ($CHCl_3$): 2939, 1650, 1619, 1581, 1504, 1319, 1267, 1245, 1126, 1102 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (1H, d, J = 15.9 Hz), 7.66 (1H, d, J = 15.9 Hz), 7.33 (1H, t, J = 8.0 Hz), 7.22 (1H, d, J = 8.0 Hz), 7.15 (1H, t, J = 2.0 Hz), 7.08 (1H, d, J = 15.9 Hz), 6.96 (1H, d, J = 15.9 Hz), 6.96 (1H, dd, J = 8.0, 2.0 Hz), 6.85 (2H, s), 3.92, (6H, s), 3.90 (3H, s), 3.86 (3H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.7, 160.0, 153.5, 143.5, 143.1, 140.5, 136.2, 130.3, 130.0, 125.5, 125.0, 121.1, 116.3, 113.4, 105.7, 61.0, 56.2, 55.4. MS (EI) m/z: 354 (M^+). HRMS (EI) Calcd for $C_{21}H_{22}O_5$: 354.1467. Found: 354.1454.

4.1.27. (1*E*,4*E*)-1-(3-(Methoxymethoxy)phenyl)-5-(3,4,5-trimethoxyphenyl)penta-1,4-dien-3-one (GO-Y108)

Yellow oil. IR ($CHCl_3$): 2939, 1650, 1619, 1582, 1504, 1321, 1243, 1151, 1127, 1103, 1007 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ

7.70 (1H, d, J = 15.9 Hz), 7.66 (1H, d, J = 15.9 Hz), 7.33 (1H, t, J = 7.6 Hz), 7.31 (1H, m), 7.26 (1H, d, J = 7.6 Hz), 7.09 (1H, m), 7.08 (1H, d, J = 15.9 Hz), 6.97 (1H, d, J = 15.9 Hz), 6.85 (2H, s), 5.22 (2H, s), 3.92, (6H, s), 3.90 (3H, s), 3.51 (3H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.7, 157.7, 153.5, 143.5, 143.0, 140.5, 136.3, 130.3, 130.0, 125.6, 125.0, 122.3, 118.6, 115.5, 105.6, 94.5, 61.0, 56.2, 56.1. MS (EI) m/z: 384 (M^+). HRMS (EI) Calcd for $C_{22}H_{24}O_6$: 384.1573. Found: 384.1555.

4.1.28. 3-((1*E*,4*E*)-3-Oxo-5-(3,4,5-trimethoxyphenyl)penta-1,4-dienyl)phenyl trifluoromethanesulfonate (GO-Y109)

Yellow amorphous. IR ($CHCl_3$): 1651, 1622, 1581, 1504, 1419, 1320, 1212, 1127 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (1H, d, J = 15.7 Hz), 7.68 (1H, d, J = 15.9 Hz), 7.62 (1H, d, J = 7.9 Hz), 7.53 (1H, m), 7.51 (1H, t, J = 7.9 Hz), 7.31 (1H, dd, J = 7.9, 2.2 Hz), 7.12 (1H, d, J = 15.9 Hz), 6.95 (1H, d, J = 15.7 Hz), 6.86 (2H, s), 3.93, (6H, s), 3.91 (3H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.9, 153.4, 149.8, 144.0, 140.6, 140.2, 137.5, 130.7, 129.9, 128.2, 127.1, 123.4, 122.5, 120.3, 118.6 (1C, q, J = 321.2 Hz), 105.6, 60.8, 56.0. MS (EI) m/z: 472 (M^+). HRMS (EI) Calcd for $C_{21}H_{19}F_3O_7S$: 472.4326. Found: 472.0775.

4.1.29. (1*E*,4*E*)-1-Phenyl-5-(3,4,5-trimethoxyphenyl)penta-1,4-dien-3-one (GO-Y110)

Yellow oil. IR ($CHCl_3$): 2938, 1650, 1619, 1583, 1504, 1451, 1419, 1325, 1281, 1186, 1127, 1001 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (1H, d, J = 15.9 Hz), 7.66 (1H, d, J = 15.9 Hz), 7.63 (2H, m), 7.42 (3H, m), 7.11 (1H, d, J = 15.9 Hz), 6.97 (1H, d, J = 15.9 Hz), 6.85 (2H, s), 3.92, (6H, s), 3.90 (3H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.7, 153.5, 143.4, 143.2, 140.5, 134.8, 130.5, 130.3, 129.0, 128.4, 125.2, 125.1, 105.6, 61.0, 56.2. MS (EI) m/z: 324 (M^+). HRMS (EI) Calcd for $C_{20}H_{20}O_4$: 324.1362. Found: 324.1340.

4.1.30. (1*E*,4*E*)-1-(3-Chlorophenyl)-5-(3,4,5-trimethoxyphenyl)penta-1,4-dien-3-one (GO-Y111)

Yellow plate (AcOEt/hexane = 1:4): mp 102–104 °C. IR ($CHCl_3$): 2938, 1651, 1620, 1581, 1504, 1418, 1318, 1126, 1102 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66 (2H, d, J = 15.8 Hz), 7.62 (1H, t, J = 1.7 Hz), 7.48 (1H, dd, J = 8.0, 1.7 Hz), 7.38 (1H, dd, J = 8.0, 1.7 Hz), 7.35 (1H, t, J = 8.0 Hz), 7.11 (1H, d, J = 15.8 Hz), 6.93 (1H, d, J = 15.8 Hz), 6.85 (2H, s), 3.92, (6H, s), 3.91 (3H, s). ^{13}C NMR (125 MHz, $CDCl_3$) δ 188.3, 153.6, 143.8, 141.5, 140.7, 136.7, 135.0, 130.3, 130.2, 130.1, 127.8, 126.8, 126.2, 125.1, 105.7, 61.0, 56.3. MS (EI) m/z: 358 (M^+). HRMS (EI) Calcd for $C_{20}H_{19}ClO_4$: 358.0972. Found: 358.0949. Anal. Calcd for $C_{20}H_{19}ClO_4$: C, 66.95; H, 5.34. Found: C, 66.93; H, 5.33.

4.1.31. (1*E*,4*E*)-1-(3-(Phenylethynyl)phenyl)-5-(3,4,5-trimethoxyphenyl)penta-1,4-dien-3-one (GO-Y112)

Yellow oil. IR ($CHCl_3$): 2938, 1651, 1619, 1582, 1504, 1418, 1322, 1127, 1101 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (1H, m), 7.72 (1H, d, J = 15.9 Hz), 7.67 (1H, d, J = 15.9 Hz), 7.65–7.54 (4H, m), 7.42–7.36 (4H, m), 7.15 (1H, d, J = 15.9 Hz), 6.96 (1H, d, J = 15.9 Hz), 6.86 (2H, s), 3.92, (6H, s), 3.91 (3H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.5, 153.5, 143.6, 142.1, 140.6, 135.1, 133.3, 131.6, 131.0, 130.2, 129.0, 128.5, 128.4, 128.3, 125.7, 125.1, 124.2, 122.9, 105.7, 90.2, 88.5, 61.0, 56.2. MS (EI) m/z: 424 (M^+). HRMS (EI) Calcd for $C_{28}H_{24}O_4$: 424.1675. Found: 424.1663.

4.2. Cell growth suppression analysis

HCT116 was obtained from the Cell Resource Center for Biomedical Research (Institute of Development, Aging and Cancer, Tohoku University, Sendai, Japan). The growth suppressive effects of the compounds were measured for 48 h. Cell viability was assayed by quantifying the uptake and digestion of 2-(2-methoxy-4-nitrophenyl)-3-(4-nitrophenyl)-5-(2,4-disulfophenyl)-2*H*-tetrazolium monosodium salt in accordance with the manufacturer's instructions (Dojindo Laboratories, Kumamoto, Japan) using a 96-well plate reader, MPR-4Ai (Tosoh Corp., Tokyo, Japan). The percentage cell growth of the control, which was treated with 1% DMSO alone, was calculated and plotted, and then mean growth inhibitory concentration (GI_{50}) was determined.

Acknowledgements

This work was partly supported by a Grant-in Aid for the Research Fellowship for Young Scientists (H.Y) and Grant-in-Aid for the Grobal COE Program for 'International Center of Research & Education for Molecular Complex Chemistry' from Ministry of Education, Culture, Sports, Science, and Technology, Japan.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmc.2009.12.045.

References and notes

1. Surh, Y. J. *Nat. Rev. Cancer* **2003**, *3*, 768.
2. Ravindran, J.; Prasad, S.; Aggarwal, B. B. *AAPS J.* **2009**, *11*, 495.
3. Singh, S.; Aggarwal, B. B. *J. Biol. Chem.* **1995**, *270*, 24995.
4. Dorai, T.; Aggarwal, B. B. *Cancer Lett.* **2004**, *215*, 129.
5. Mukhopadhyay, A.; Banerjee, S.; Stafford, L. J.; Xia, C.; Liu, M.; Aggarwal, B. B. *Oncogene* **2002**, *21*, 8852.
6. Aggarwal, S.; Ichikawa, H.; Takada, Y.; Sandur, S. K.; Shishodia, S.; Aggarwal, B. B. *Mol. Pharmacol.* **2006**, *69*, 195.
7. Shikora, E.; Bielak-Żmijewska, A.; Magalska, A.; Piwocka, K.; Mosieniak, G.; Kalinowska, M.; Widlak, P.; Cymerman, I. A.; Bujnicki, J. M. *Mol. Cancer Ther.* **2006**, *5*, 927.
8. Choudhuri, T.; Pal, S.; Agwarwal, M. L.; Das, T.; Sa, G. *FEBS Lett.* **2002**, *512*, 334.
9. Jung, E. M.; Lim, J. H.; Lee, T. J.; Park, J.-W.; Choi, K. S.; Kwon, T. K. *Carcinogenesis* **2005**, *26*, 1905.
10. Woo, J.-H.; Kim, Y.-H.; Lee, K.-S.; Bae, J. H.; Min, D. S.; Chang, J.-S.; Jeong, Y.-J.; Lee, Y. H.; Park, J.-W.; Kwon, T. K. *Carcinogenesis* **2003**, *24*, 1199.
11. Siwak, D. R.; Shishodia, S.; Aggarwal, B. B.; Kurzrock, R. *Cancer* **2005**, *104*, 879.
12. Sarkar, F. H.; Li, Y. *Cancer Treat. Rev.* **2009**, *35*, 597.
13. Anand, P.; Kunnumakkara, A. B.; Newman, R. A.; Aggarwal, B. B. *Mol. Pharm.* **2007**, *4*, 807.
14. Robinson, T. P.; Ehlers, T.; Hubbard, R. B., IV; Bai, X.; Arbiser, J. L.; Goldsmith, D. J.; Bowen, J. P. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 115.
15. Robinson, T. P.; Hubbard, R. B., IV; Ehlers, T. J.; Arbiser, J. L.; Goldsmith, D. J.; Bowen, J. P. *Bioorg. Med. Chem.* **2005**, *13*, 4007.
16. Adams, B. K.; Ferstl, E. M.; Davis, M. C.; Herold, M.; Kurtkaya, S.; Camalier, R. F.; Hoollingshead, M. G.; Kaur, G.; Sausville, E. A.; Rickles, F. R.; Snyder, J. P.; Liotta, D. C.; Shoji, M. *Bioorg. Med. Chem.* **2004**, *12*, 3871.
17. Sun, A.; Shoji, M.; Lu, Y. J.; Liotta, D. C.; Snyder, J. P. *J. Med. Chem.* **2006**, *49*, 3153.
18. Thomas, S. L.; Zhong, D.; Zhou, W.; Malik, S.; Liotta, D.; Snyder, J. P.; Hamel, E.; Giannakakou, P. *Cell Cycle* **2008**, *7*, 2409.
19. Ohori, H.; Yamakoshi, H.; Tomizawa, M.; Shibuya, M.; Kakudo, U.; Takahashi, A.; Takahashi, S.; Kato, S.; Suzuki, T.; Ishioka, C.; Iwabuchi, Y.; Shibata, H. *Mol. Cancer Ther.* **2006**, *5*, 2563.
20. Masuda, T.; Jitoe, A.; Isobe, J.; Nakatani, N.; Yonemori, S. *Phytochemistry* **1993**, *32*, 1557.
21. Park, S.-Y.; Kim, D. S. H. L. *J. Nat. Prod.* **2002**, *65*, 1227.
22. Hutzen, B.; Friedman, L.; Sobo, M.; Lin, L.; Cen, L.; Angelis, S.; Yamakoshi, H.; Shibata, H.; Iwabuchi, Y.; Lin, J. *Int. J. Oncol.* **2009**, *35*, 867.
23. Shibata, H.; Yamakoshi, H.; Sato, A.; Ohori, H.; Kakudo, Y.; Kudo, C.; Takahashi, Y.; Watanabe, M.; Takano, H.; Ishioka, C.; Noda, T.; Iwabuchi, Y. *Cancer Sci.* **2009**, *100*, 956.
24. Paul, S.; Gupta, M. *Synth. Commun.* **2005**, *35*, 213.
25. Kreher, U. P.; Rosamilia, A. E.; Raston, C. L.; Scott, J. L.; Strauss, C. R. *Org. Lett.* **2003**, *5*, 3107.
26. Ito, Y.; Hirao, T.; Saegusa, T. *J. Org. Chem.* **1978**, *43*, 1011.
27. Ohtsu, H.; Xiao, Z.; Ishida, J.; Nagai, M.; Wang, H.-K.; Itokawa, H.; Su, C.-Y.; Shih, C.; Chiang, T.; Chang, E.; Lee, Y.; Tsai, M.-Y.; Chang, C.; Lee, K.-H. *J. Med. Chem.* **2002**, *45*, 5037.
28. Lin, L.; Shi, Q.; Nyarko, A. K.; Bastow, K. F.; Wu, C.-C.; Su, C.-Y.; Shih, C. C.-Y.; Lee, K.-H. *J. Med. Chem.* **2006**, *49*, 3963.
29. Das, U.; Sharma, R. K.; Dimmock, J. R. *Curr. Med. Chem.* **2009**, *16*, 2001.
30. Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2001**, *40*, 2004.
31. Thuaud, F.; Bernard, Y.; Turkeri, G.; Dirr, R.; Aubert, G.; Cresteil, T.; Baguet, A.; Tomasetto, C.; Svitkin, Y.; Sonenberg, N.; Nebigil, C. G.; Désaubry, L. *J. Med. Chem.* **2009**, *52*, 5176.