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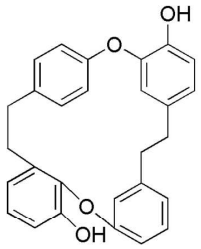
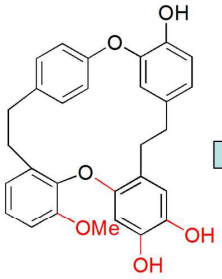


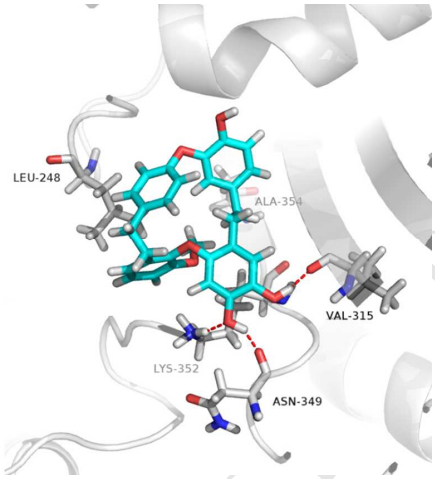
Marchantin C

IC_{50}= 21.22 μM (Hela)
= 12.95 μM (K562)
= 13.36 μM (Hcc1428)
= 12.99 μM (Ht29)



Cpd 47

IC_{50}= 2.61 μM (Hela)
= 1.74 μM (K562)
= 1.51 μM (Hcc1428)
= 1.98 μM (Ht29)



Design, synthesis, biological evaluation and molecular modeling study of novel macrocyclic bisbibenzyl analogues as antitubulin agents

Bin Sun[a,b], Lin Li[b], Qing-wen Hu[b], Hong-bo Zheng[b], Hui Tang[b], Huan-min Niu[c], Hui-qing Yuan[c], and Hong-xiang Lou[a,b] *

[a] *National Glycoengineering Research Center, Shandong University, Jinan 250012, P. R. China*

[b] *Key Laboratory of Natural Products & Chemical Biology, Ministry of Education, Shandong University, Jinan, 250012, P.R. China*

[c] *School of Medicine, Shandong University, Jinan 250012, P.R. China*

ABSTRACT

A series of macrocyclic bisbibenzyls with novel skeletons was designed, synthesized, and evaluated for antiproliferative activity against five anthropic cancer cell lines. Among these novel molecules, compound **47** displayed excellent anticancer activity against HeLa, k562, HCC1428, HT29 and PC-3/Doc cell lines, with IC_{50} values ranging from of 1.51 μM to 5.51 μM, which were more potent than the parent compound, marchantin C. Compounds **44** and **55** with novel bisbibenzyl skeletons also exhibited significantly improved antiproliferative potency. Structure-activity relationship (SAR) analyses of these synthesized compounds were also performed. In addition, compound **47** effectively inhibited tubulin polymerization in HCC1482 cells and induced HCC1482 cell cycle arrest at the G2/M phase in a concentration-dependent manner. The binding mode of compound **47** to tubulin was also investigated utilizing a molecular docking study. In conclusion, the present study discovered several potent antitubulin compounds with novel bisbibenzyl skeletons, and our systematic studies revealed new scaffolds that target tubulin and mitosis and provide progress towards the discovery of novel antitumor drugs discovery.

Keywords: Bisbibenzyls; Tubulin polymerization inhibitors; Anticancer; Molecular modeling

* Corresponding authors: Hongxiang Lou, Ph.D.

Tel: +86-531-88382051; Fax: +86-531-88382019.

E-mail address: louhongxiang@sdu.edu.cn (H. Lou)

1. Introduction

Microtubules are recognized as one of the most important molecular targets for cancer therapies due to their role as one of the major cytoskeletal components in eukaryotic cells and their crucial function in cell shape maintenance, division, protein trafficking and intracellular transport[1-4]. Tubulin–interacting drugs are used widely and successfully in the treatment of a variety of human cancers by interfering with microtubule dynamics, a process that controls the balance between microtubule assembly and microtubule disassembly [5-10]. Three major binding sites for tubulin inhibitors have been identified as the vinca alkaloid-, taxanes-, and colchicine-binding sites. Although antitubulin agents that interact with the vinca alkaloid- or taxanes-binding sites are widely used in clinical cancer therapy, none of the colchicine-binding site drugs are even approved in clinical oncology [11-17]. In fact, most of the colchicine-binding agents have high potency, selective toxicity toward tumor vasculature, and relatively simple structures for optimization, and they show a promising ability to overcome *P*-glycoprotein-mediated multidrug resistance [18-25]. Therefore, agents that interact with the colchicine-binding site show promise for the development of novel and potent anticancer drugs and have attracted great interest from medicinal chemists in recent years.

Macrocyclic bisbibenzyls are a series of phenolic natural products that are mainly found in bryophytes. Each bisbibenzyl skeleton comprises four aromatic rings (arene *A*-*D*) and two ethano bridges, with lunularin as the biosynthetic origin (Fig. 1) [26]. All of these compounds can be divided into several sub-classes that are distinguished by the connectivity between the two lunularin sub-units, which is produced by oxidative coupling to form either biaryl or biaryl ether linkages [27, 28].

Marchantins, isomarchantins, neomarchantins and riccardin II are four main sub-classes of macrocyclic bisbibenzyls that have two diaryl ether sub-units as a common structural feature (Fig. 1) and occupy approximately 25% of all the natural macrocyclic bisbibenzyls discovered to date. These compounds exhibit versatile and excellent biological activities, including antimicrobial, antioxidative, cytotoxic, and multidrug resistance reversal activities [29-36]. The remarkable biological profiles of these natural products make them promising resources for new drug discovery. Among these compounds, marchantin C, a natural macrocyclic bisbibenzyl, was discovered to be a potent tubulin inhibitor that targets the colchicine-binding site and the compound was also found to exhibit multidrug resistance-reversing activity by inhibiting the *P*-glycoprotein [37-39]. In addition, its bisbibenzyl scaffold is similar to the cis-stilbenoid anti-tubulin agents, such as combretastatins. We have recently

reported a series of marchantin C analogues as potent tubulin polymerization inhibitors in which the substitutive groups on the aromatic rings were varied [40]. Continuing our search strategy for novel tubulin inhibitors, we extended our studies to modification of the marchantin C skeleton. In this paper, a panel of novel marchantin C analogues was designed, synthesized and examined as potential tubulin targeting agents. The result of this effort, described below, indicated that these novel marchantin C analogues represent a new class of potent antitubulin agents.

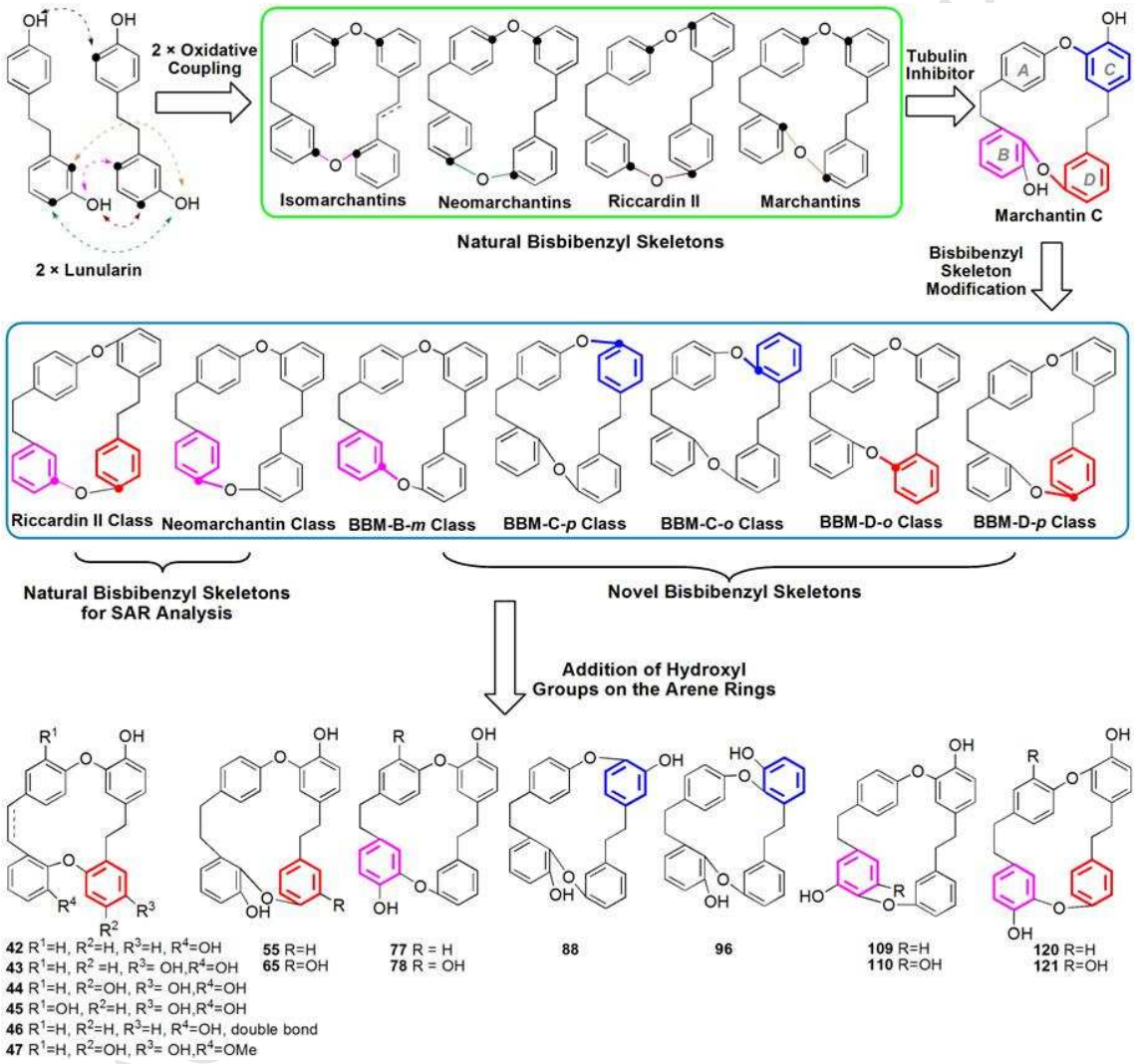


Fig. 1. Modification strategy for macrocyclic bisbibenzyl analogues

[Figure 1 here]

2. Results and Discussion

2.1. Design of marchantin C analogues

In the previous study, marchantin C and its derivatives were found to be potent antimitotic agents that target tubulin, and their macrocyclic bisbibenzyl skeletons were found to fit sterically in the colchicine-binding site. To define the structure-activity relationships (SARs) of bisbibenzyl analogues

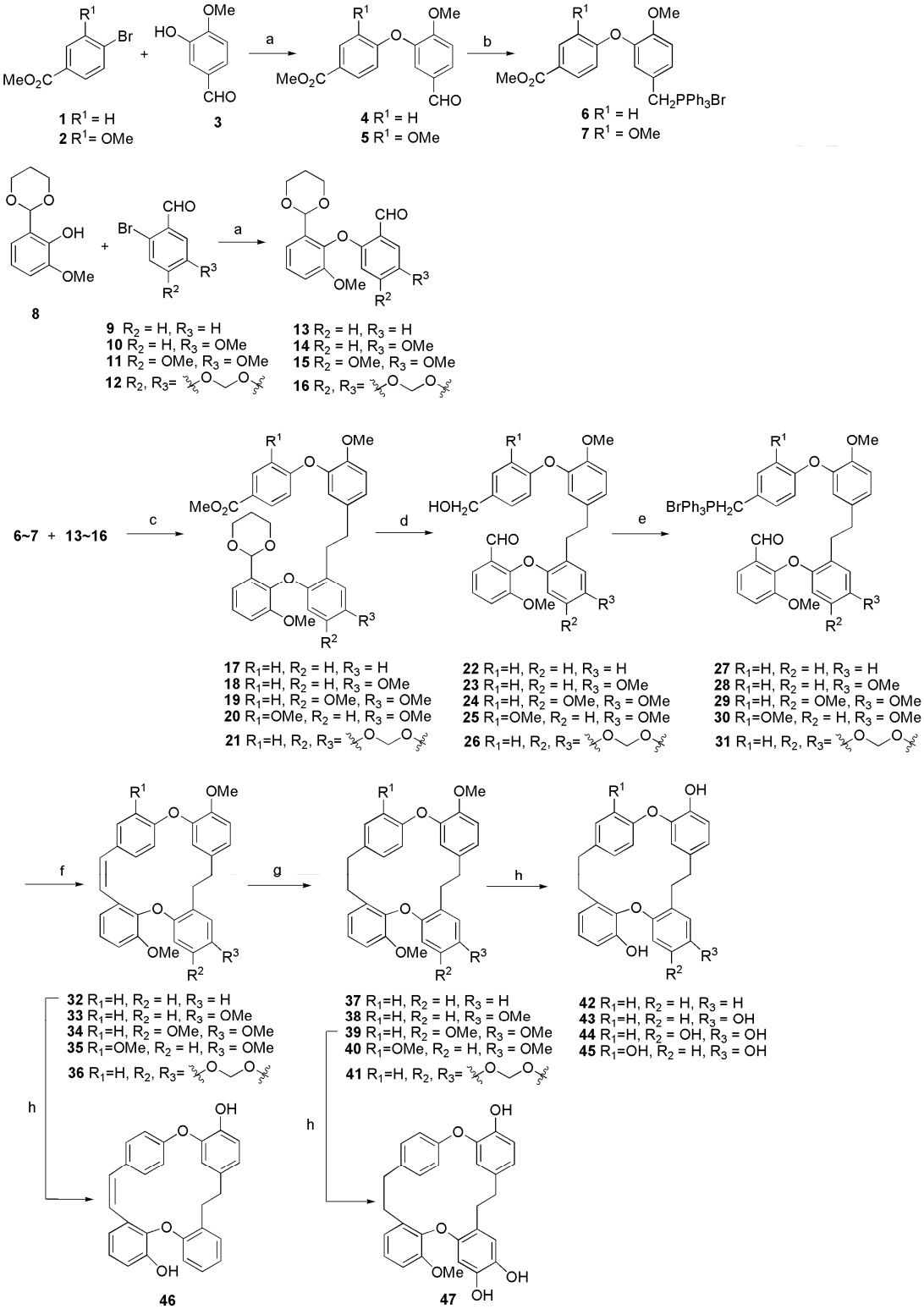
and to develop potential new drug candidates, a series of novel marchantin C analogues were designed. According to the modification strategy shown in Fig. 1, we first systematically varied the substitutive position of the ether bond on the arenes *B*, *C* and *D* of marchantin C, which gave five novel bisbibenzyl skeletons, BBM-B-*m* class, BBM-C-*o* class, BBM-C-*p* class, BBM-D-*o* class and BBM-D-*p* class, as well as two natural bisbibenzyl skeletons, the riccardin II and neomarchantin classes. This modification could change the stereochemical structure of the macrocyclic bisbibenzyls, and we speculated that some of these novel skeletons might be more complementary to the colchicine-binding site (Fig. S1). Second, we changed the ethylene bridge to a double bond and determined the effect of this further stereochemical structural change on the cytotoxic activity. Finally, we focused on modification of the phenyl rings via introduction of hydroxyl groups or methoxyl groups on arenes *A*-*D* to assess the substituent effects on the antiproliferative activity, since those two substituents were mostly founded in the natural bisbibenzyl compounds.

2.2. Chemistry

All of the marchantin C analogues were prepared by eight independent synthetic routes, and the general procedure is outlined in Schemes 1-8. The synthetic route of analogues **53**-**57** began with Ullmann coupling of the appropriately substituted methyl 4-bromobenzoate **1**-**2** with 3-hydroxy-4-methoxybenzaldehyde (**3**), resulting in the formation of diphenyl ethers **4**-**5**. Compounds **4**-**5** were then reduced with sodium borohydride to give the benzyl alcohols, followed by reaction with triphenylphosphonium bromide to afford **6**-**7** in two steps. Compounds **13**-**16** were prepared by Ullmann coupling of the protected 2-hydroxy-3-methoxybenzaldehyde (**8**) with the appropriate 2-bromo-benzaldehydes **9**-**12** in good yield. The building blocks **6**-**7** and **13**-**16** were combined by an intermolecular Wittig reaction in the presence of potassium carbonate and 18-crown-6 followed by hydrogenation over Pd/C to give the bibenzyls **17**-**21**. The carboxylic ester group of **17**-**21** was then reduced with lithium aluminum hydride and subsequently deprotected with HCl/H_2O to give compounds **22**-**26**. The reaction of **22**-**26** with triphenylphosphonium bromide afforded compounds **27**-**31**. The cyclization of **27**-**31** by means of an intramolecular Wittig reaction was achieved with sodium methoxide, leading to key macrocyclic intermediates **32**-**36**. **32**-**36** were then hydrogenated to give compounds **37**-**41**. Finally, **32**, **39** and **37**-**41** were demethylated by boron tribromide to afford compounds **42**-**47** (Scheme 1). The position of the methoxyl group in compound **47** was determined from a NOE spectrum, as shown in Fig. 2. Correlations of H_3-15' with H-4' were determined in

compound **47**.

Compounds **55**, **65**, **77**, **78**, **88**, **96**, **109**, **110**, **120** and **121** were prepared by a protocol similar to that used for compounds **42**-**47**, and the synthetic routes are depicted in Schemes 2-8.



Scheme 1. Synthesis of macrocyclic compounds **32**-**47**. *Reagents and conditions*: (a) CuO, K_2CO_3, Py, reflux, (yields 63%-76%); (b) i. $NaBH_4$, THF, 0 ℃ to r.t.; ii. PPh_3HBr, MeCN, reflux, (yields 78%-89%,

two steps); (c) i. K_2CO_3, 18-crown-6, DCM, reflux; ii. Pd/C (10%), H_2, Et_3N, EtOAc, r.t. (yields 71%-80%, two steps); (d) i. $LiAlH_4$, THF, -40 ℃ to r.t.; ii. HCl/EtOH (1:10), r.t. (yields 80%-86%, two steps); (e) PPh_3HBr, MeCN, reflux, (yields 86%-93%); (f) NaOMe, DCM, r.t. (yields 80%-88%); (g) Pd/C (10%), H_2, EtOAc, r.t. (yields 95%-99%); (h) BBr_3, DCM, -40 ℃ to r.t. (yields 51%-86%).

[Scheme 1 here]

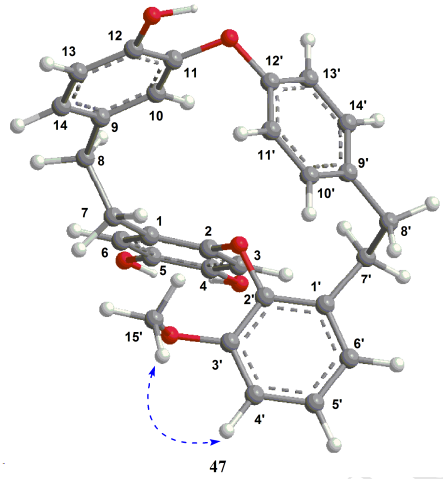
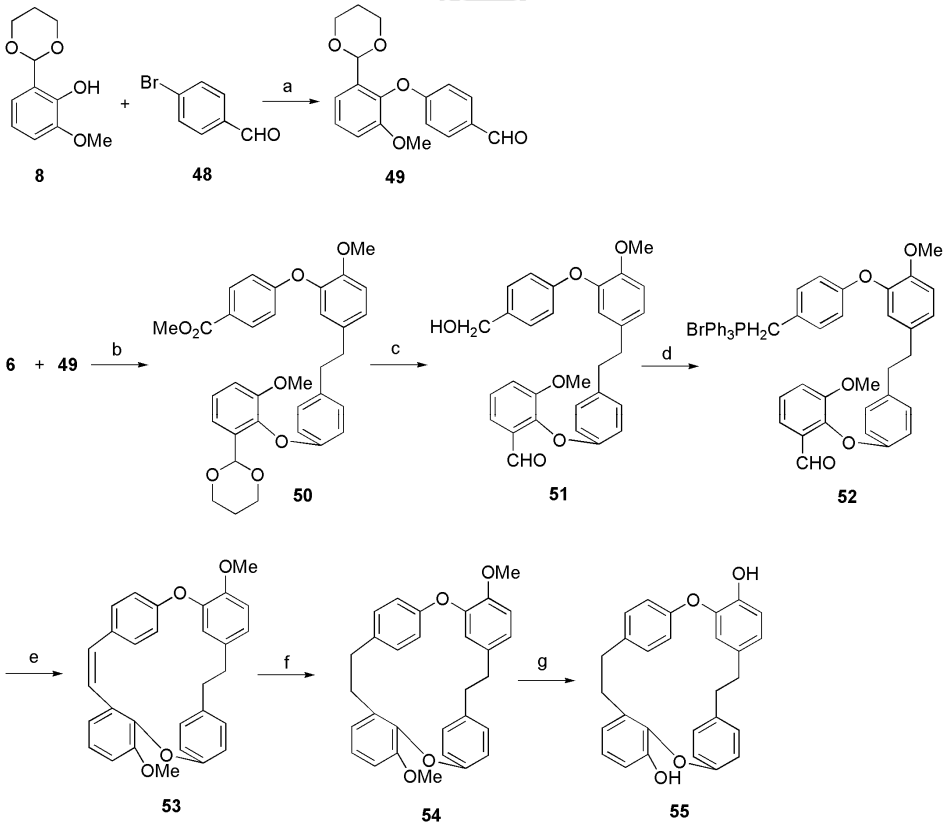


Fig. 2. Key NOESY correlations (dashed blue arrows) for compound **47**.

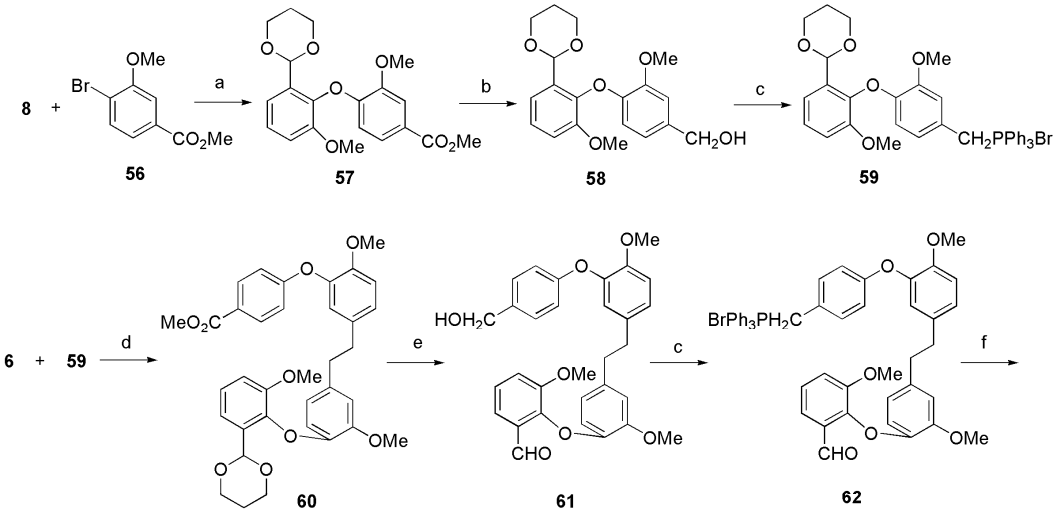
[Figure 2 here]



Scheme 2. Synthesis of macrocyclic compounds **53-55**. *Reagents and conditions*: (a) CuO, K_2CO_3, Py, reflux, (yield 65%); (b) i. K_2CO_3, 18-crown-6, DCM, reflux; ii. Pd/C (10%), H_2, Et_3N, EtOAc, r.t.

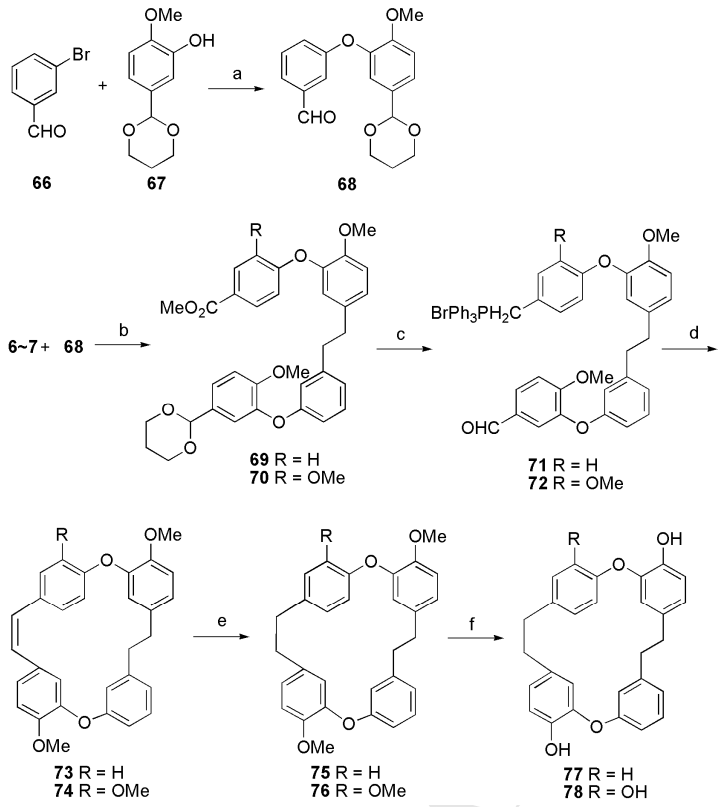
(yield 83%, two steps); (c) i. $LiAlH_4$, THF, -40 ℃ to r.t.; ii. HCl/EtOH (1:10), r.t. (yield 85%, twp steps); (d) PPh_3HBr, MeCN, reflux, (yield 92%); (e) NaOMe, DCM, r.t. (yield 80%); (f) Pd/C (10%), H_2, EtOAc, r.t. (yields 96%); (g) BBr_3, DCM, -40 ℃ to r.t. (yield 86%).

[Scheme 2 here]



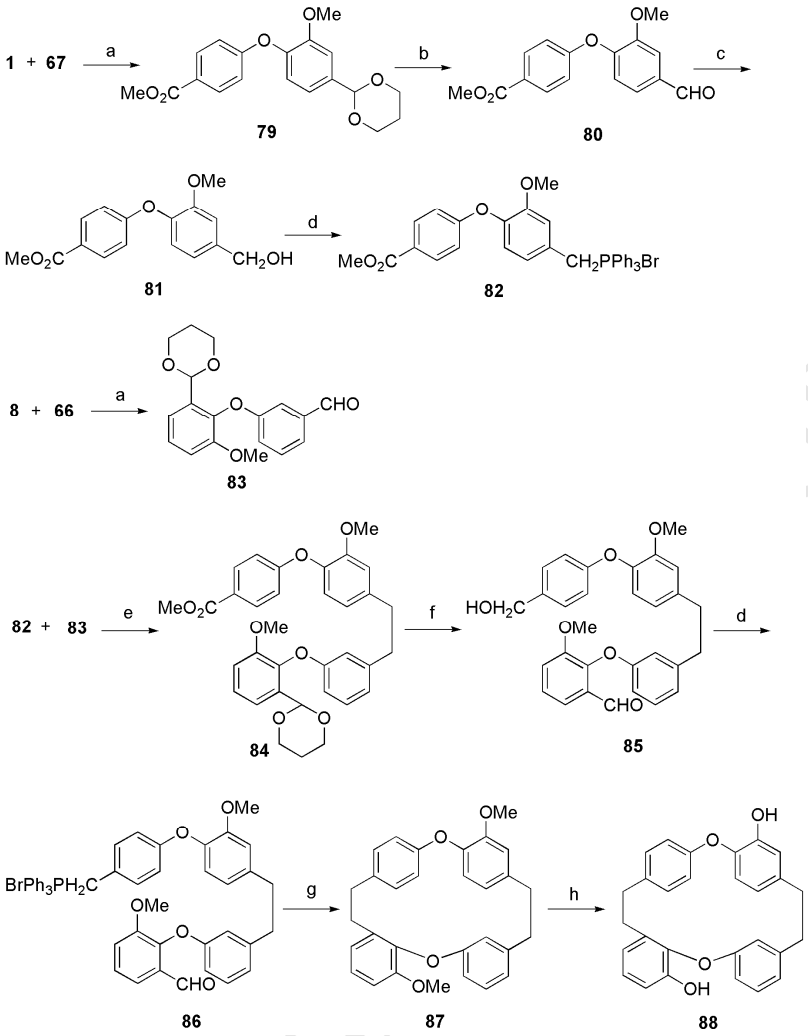
Scheme 3. Synthesis of macrocyclic compounds **63-65**. *Reagents and conditions*: (a) CuO, K_2CO_3, Py, reflux, (yield 61%); (b) $LiAlH_4$, THF, -40 ℃ to r.t. (yield 88%); (c) PPh_3HBr, MeCN, reflux, (yield 90%); (d) i. K_2CO_3, 18-crown-6, DCM, reflux; ii. Pd/C (10%), H_2, Et_3N, EtOAc, r.t. (yield 80%, two steps); (e) i. $LiAlH_4$, THF, -40 ℃ to r.t.; ii. HCl/EtOH (1:10), r.t. (yield 87%, twp steps); (f) NaOMe, DCM, r.t. (yield 73%); (g) Pd/C (10%), H_2, EtOAc, r.t. (yields 92%); (h) BBr_3, DCM, -40 ℃ to r.t. (yield 82%).

[Scheme 3 here]



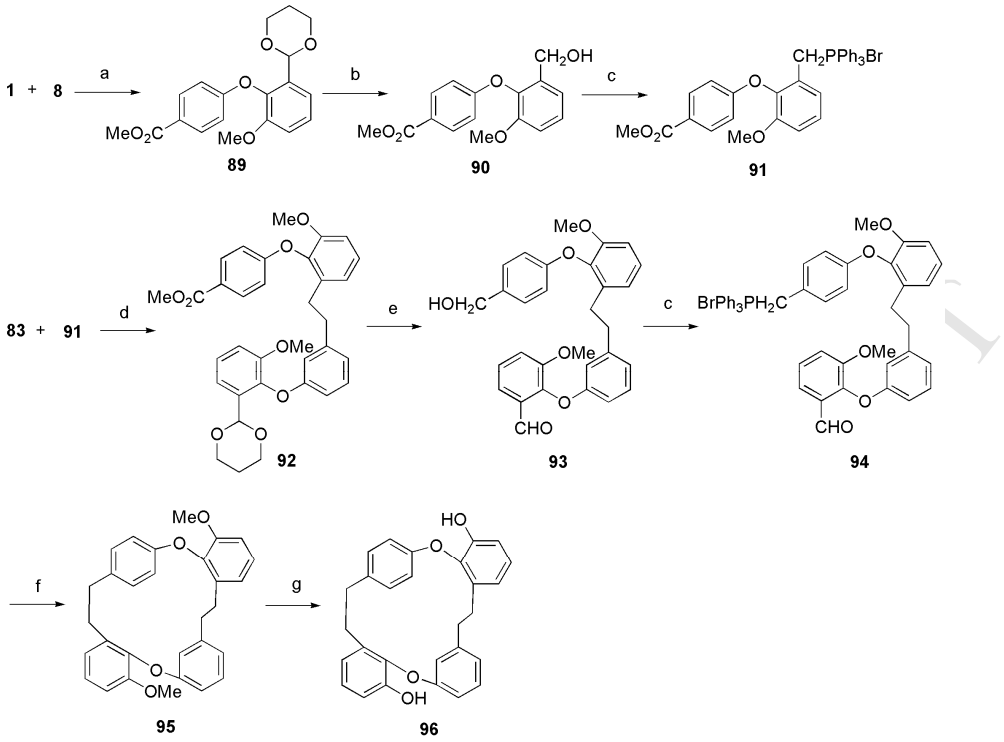
Scheme 4. Synthesis of macrocyclic compounds **73-78**. *Reagents and conditions*: (a) CuO, K_2CO_3, Py, reflux, (yield 70%); (b) i. K_2CO_3, 18-crown-6, DCM, reflux; ii. Pd/C (10%), H_2, Et_3N, EtOAc, r.t. (yield 80-86%); (c) i. $LiAlH_4$, THF, -40 ℃ to r.t.; ii. HCl/EtOH (1:10), r.t.; iii. PPh_3HBr, MeCN, reflux, (yield 70-74%, three steps); (d) NaOMe, DCM, r.t. (yields 71-77%); (e) Pd/C (10%), H_2, EtOAc, r.t. (yields 92-96%); (f) BBr_3, DCM, -40 ℃ to r.t. (yields 79-82%).

[Scheme 4 here]



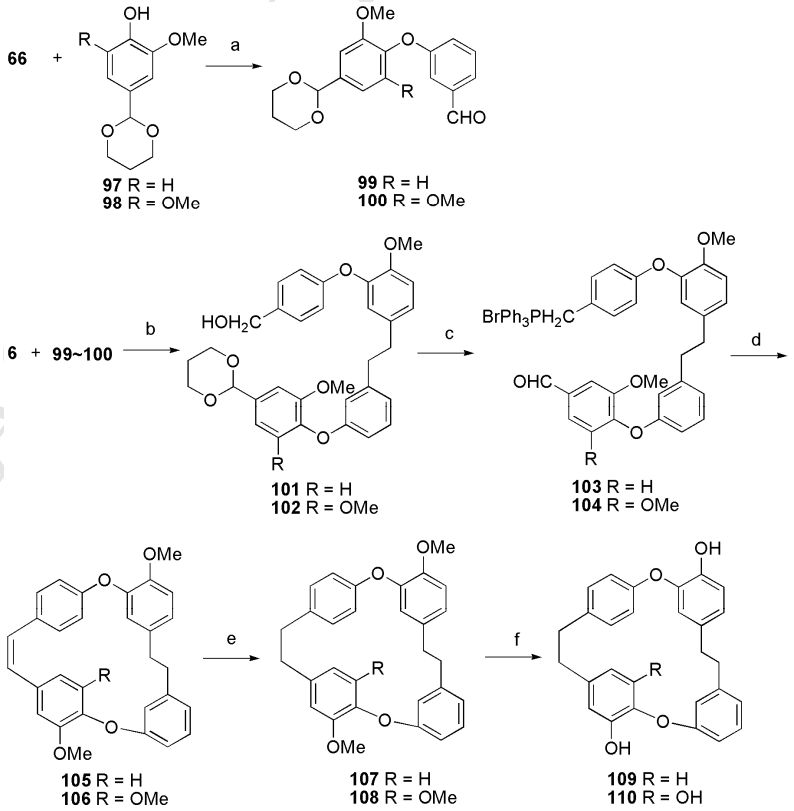
Scheme 5. Synthesis of macrocyclic compounds **87-88**. *Reagents and conditions*: (a) CuO, K_2CO_3, Py, reflux, (yield 75%); (b) HCl/EtOH (1:10), r.t. (yield 79%); (c) $NaBH_4$, THF, 0 ℃ to r.t. (yield 86%); (d) PPh_3HBr, MeCN, reflux, (yield 88%); (e) i. K_2CO_3, 18-crown-6, DCM, reflux; ii. Pd/C (10%), H_2, Et_3N, EtOAc, r.t. (yield 83%, two steps); (f) i. $LiAlH_4$, THF, -40 ℃ to r.t.; ii. HCl/EtOH (1:10), r.t., (yield 73%, two steps); (g) i. NaOMe, DCM, r.t.; ii. Pd/C (10%), H_2, EtOAc, r.t. (yields 75%); (h) BBr_3, DCM, -40 ℃ to r.t. (yields 73%).

[Scheme 5 here]



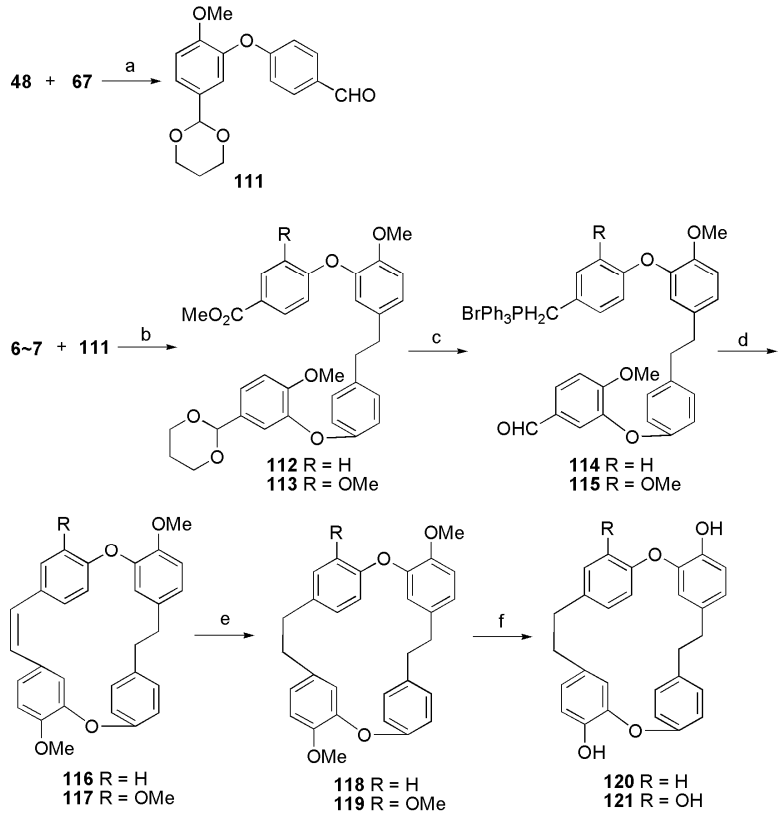
Scheme 6. Synthesis of macrocyclic compounds **95-96**. *Reagents and conditions*: (a) CuO, K_2CO_3, Py, reflux, (yield 76%); (b) i. HCl/EtOH (1:10), r.t.; ii. $NaBH_4$, THF, 0 ℃ to r.t. (yield 61%, two steps); (c) PPh_3HBr, MeCN, reflux, (yield 82%); (d) i. K_2CO_3, 18-crown-6, DCM, reflux; ii. Pd/C (10%), H_2, Et_3N, EtOAc, r.t. (yield 88%); (e) i. $LiAlH_4$, THF, -40 ℃ to r.t.; ii. HCl/EtOH (1:10), r.t., (yield 72%, two steps); (f) i. NaOMe, DCM, r.t.; ii. Pd/C (10%), H_2, EtOAc, r.t. (yields 77%); (g) BBr_3, DCM, -40 ℃ to r.t. (yields 79%).

[Scheme 6 here]



Scheme 7. Synthesis of macrocyclic compounds **105-110**. *Reagents and conditions*: (a) CuO, K_2CO_3, Py, reflux, (yields 54-73%); (b) i. K_2CO_3, 18-crown-6, DCM, reflux; ii. Pd/C (10%), H_2, Et_3N, EtOAc, r.t.; iii. $LiAlH_4$, THF, -40 ℃ to r.t. (yields 64-76%, three steps); (c); i. HCl/EtOH (1:10), r.t.; ii. PPh_3HBr, MeCN, reflux, (yields 74-81%, two steps); (d) NaOMe, DCM, r.t. (yields 81-86%); (e) Pd/C (10%), H_2, EtOAc, r.t. (yields 93-96%); (f) BBr_3, DCM, -40 ℃ to r.t. (yields 73-80%).

[Scheme 7 here]



Scheme 8. Synthesis of macrocyclic compounds **116-121**. *Reagents and conditions*: (a) CuO, K_2CO_3, Py, reflux, (yields 77%); (b) i. K_2CO_3, 18-crown-6, DCM, reflux; ii. Pd/C (10%), H_2, Et_3N, EtOAc, r.t. (yields 66-75%, two steps); (c) i. $LiAlH_4$, THF, -40 ℃ to r.t.; ii. HCl/EtOH (1:10), r.t.; iii. PPh_3HBr, MeCN, reflux, (yields 66-70%, three steps); (d) NaOMe, DCM, r.t. (yields 83-87%); (e) Pd/C (10%), H_2, EtOAc, r.t. (yields 95-96%); (f) BBr_3, DCM, -40 ℃ to r.t. (yields 74-80%).

[Scheme 8 here]

2.3. Biological evaluation

2.3.1. In vitro antiproliferative activity and structure-activity relationship (SAR) analysis

The cytotoxic activity of the synthesized analogues (**42-47**, **55-56**, **77-78**, **88**, **96**, **109-110**, and **120-121**) was evaluated in four human cancer cell lines (HeLa, k562, HCC1428, and HT29) and one paclitaxel-resistant cell line (PC-3/Doc) in parallel with adriamycin (ADR) and marchantin C as positive references. The cells were treated with each compound for 48 h, and the cell viability was assessed using the MTT method. The results are summarized in Table 1.

Among these newly synthesized analogues, compounds **44**, **47** and **55** exhibited excellent cytotoxic activity, with average IC_{50} values ranging from 1.96 μM to 8.95 μM, and they were more potent than the parent marchantin C (average IC_{50} = 15.13 μM). In addition, compound **47** was the most potent cytotoxic agent with an average IC_{50} value of 2.67 μM, which was more potent than that of the reference drug ADR (average IC_{50} = 4.44 μM). Moreover, the antiproliferative activity of compound **47** against the human breast cancer cell line and the paclitaxel-resistant cell line (IC_{50} = 1.51 μM for HCC1428 and IC_{50} = 2.67 μM for PC-3/Doc, respectively) was obviously superior to that of reference ADR (IC_{50} = 1.77 μM for HCC1428 and IC_{50} = 16.89 μM for PC-3/Doc).

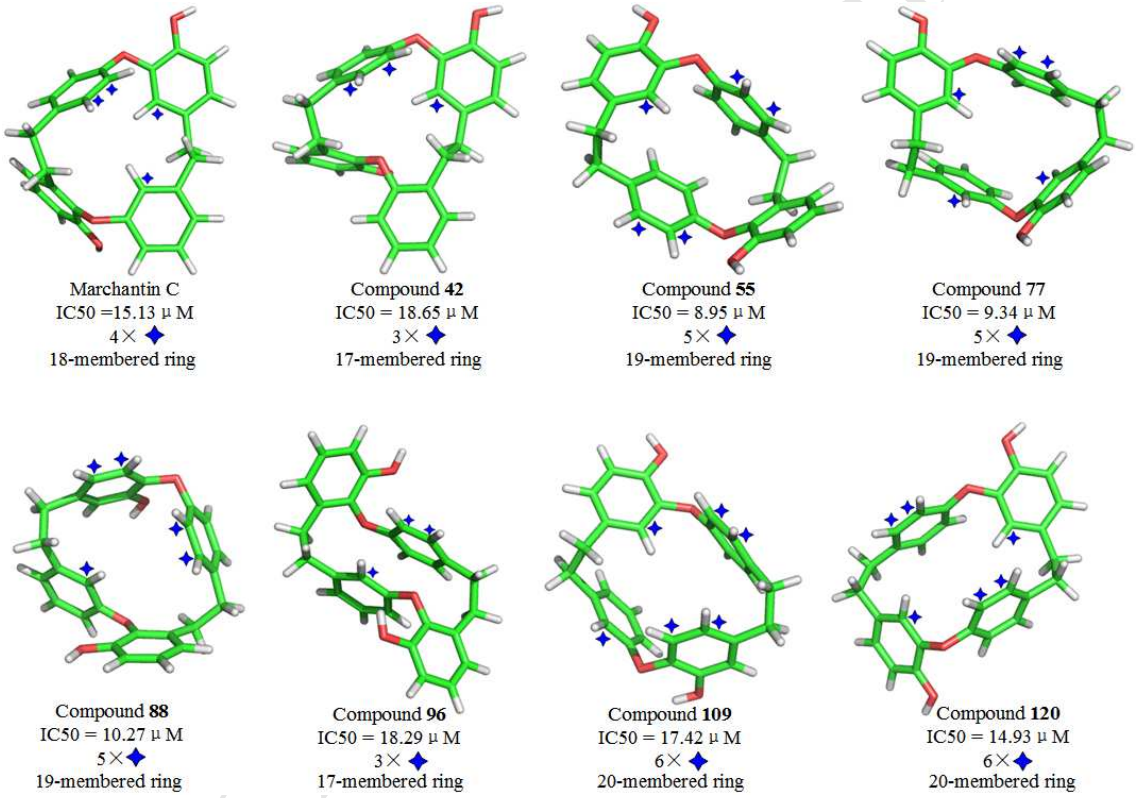


Fig. 3. Three-dimensional structures of compounds **42**, **55**, **77**, **88**, **96**, **109**, **120** and marchantin C; The IC_{50} represents the average IC_{50} value of each compound against four human cancer cell lines (HeLa, k562, HCC1428, and HT29); The aromatic carbons that are included in the macrocyclic ring are indicated by a blue cross symbol.

[Figure 3 here]

The structure-activity relationships of these novel marchantin C analogues were analyzed as follows:

Effects of the bisbibenzyl skeletons: As shown in Fig. 3, for the first step, we systematically modified the marchantin C structure by varying the position of the ether bond on arenes *B*, *C* and *D* while keeping the hydroxyl groups positioned ortho to the ether bond, which was similar to the

substitutive patterns of marchantin C. This gave us seven novel macrocyclic analogues with completely different bisbibenzyl skeletons: **42** (BBM-D-*o* skeleton), **55** (BBM-D-*p* skeleton), **77** (BBM-B-*m* skeleton), **88** (BBM-C-*p* skeleton), **96** (BBM-C-*o* skeleton), **109** (neomarchantin skeleton) and **120** (riccardin II skeleton). The biological activities of these seven compounds are shown in Table 1. The results of the antiproliferative evaluation indicated that all seven analogues consistently exhibited anticancer activity. Interestingly, when the 18-membered macrocyclic ring of marchantin C was converted to a 17-membered bisbibenzyl ring, the resulting analogues **42** and **96** showed decreased anticancer potency, with average IC_{50} values of 18.65 and 18.29 μM, respectively. To our surprise, when the bisbibenzyl ring of marchantin C was expanded to a 19-membered ring, compounds **55**, **77** and **88** displayed enhanced cytotoxicity, with average IC_{50} values of 9.34, 10.16 and 10.27 μM, respectively. Unexpectedly, further expansion of the bisbibenzyl to a 20-membered ring led to compounds **109** and **120** (average IC_{50} = 17.42 and 14.93 μM for **109** and **120**, respectively), which showed a significant decrease in potency compared to compounds **55**, **77** and **88**. In addition, the anticancer activities of compounds **109** and **120** were comparable to or even less potent than that of marchantin C. Based on these data, we find that the trend in anticancer activity for bisbibenzyl skeletons is 19-membered rings > 18-membered rings > 20-membered rings > 17-membered rings. These results suggest that the macrocyclic ring strain and conformational changes may affect molecular antitumor activity to some extent, which is consistent with our prediction mentioned above.

Furthermore, compound **46**, which contains a double bond at C-7' (8'), was also prepared, and this compound displayed moderate anticancer activity with an average IC_{50} value of 16.94 μM, which is comparable to that of compound **42**. This indicated that the introduction of a double bond to the bisbibenzyl skeleton does not significantly impact the anticancer potency.

Effects of the substituents: After confirming the effects of the bisbibenzyl skeleton on the anticancer activity, we then focused on modifying the bisbibenzyls through introduction of a hydroxyl or methoxyl group to the arene rings in order to evaluate the effect of the substituent. As shown in Fig. 1, we started our substituent modification work from compound **55** as a result of its excellent anticancer potency. However, the introduction of a hydroxyl group at the C-5 position on arene *D* decreased the cytotoxicity (average IC_{50} = 22.20 μM for compound **65**). When the hydroxyl group was introduced to another potent compound, **77,** at position C-13' on arene *A*, the anticancer activity was also diminished (compound **78**, average IC_{50} = 15.57 μM). In addition, the introduction of a hydroxyl

group to compounds **109** and **120** also resulted in decreased activity (average IC_{50} = 25.86 μM and 20.00 μM for compounds **110** and **121**, respectively).

Surprisingly, introduction of a hydroxyl group to the less potent compound **42** at the C-5 position of arene *D* resulted in compound **43** (average IC_{50} value of 12.18 μM), which exhibited improved anticancer activity compared to compound **42**. In addition, compound **44** (average IC_{50} =8.13 μM) with two hydroxyl groups at positions C-4 and C-5 of arene *D*, displayed a further increase in potency over compound **43**. When the substituent was changed from a hydroxyl group to a methoxyl group on arene *B*, the most potent compound **47** was obtained, with an average IC_{50} value of 1.96 μM. However, when a hydroxyl group was introduced to the C-13' position on arene *A* to give compound **45**, the anticancer activity was distinctly diminished compared to **43**. This is consistent with the observations made for compounds **78** and **121**. All of these observations suggest that hydrogen bond donors or acceptors are present close to arene *D*, while both arene *A* and arene *B* are located near to the hydrophobic pocket. These findings are consistent with the results of molecular modeling studies discussed below (Fig. 8).

Finally, it is noteworthy that the introduction of a hydroxyl group ortho to the ether bond led to a decrease in activity (**42** vs **45**, **55** vs **65**, **77** vs **78**, **109** vs **110** and **120** vs **121**) and that the anticancer potencies within this series of analogues vary significantly with the substituents on the arene rings.

Table 1. In Vitro cytotoxicity of marchantin C derivatives in four cancer cell lines

Compound	IC_{50} (μM) [a]					
	HeLa	K562	Hcc1428	Ht29	PC-3/Doc	Average
42	21.52±4.10	21.63±3.97	19.04±4.05	12.39±1.87	N/T[b]	18.65
43	15.91±3.77	14.05±3.08	10.78±2.07	7.98±1.16	N/T[b]	12.18
44	10.39±2.98	6.16±1.15	8.46±3.69	7.51±4.17	7.70±1.59	8.04
45	26.81±4.65	25.29±4.44	22.02±3.57	15.94±2.43	N/T[b]	22.52
46	21.86±2.01	19.23±3.08	17.06±2.95	9.60±1.10	N/T[b]	16.94
47	2.61±0.67	1.74±0.55	1.51±0.31	1.98±0.23	5.51±1.41	2.67
55	10.45±2.01	8.52±1.00	9.25±1.23	7.57±1.52	10.92±1.25	9.34
65	27.44±5.89	24.91±5.02	19.49±3.53	16.96±3.70	N/T[b]	22.20
77	11.71±2.22	7.02±1.05	10.65±1.97	7.98±1.96	13.43±2.61	10.16
78	19.52±4.19	10.89±2.30	19.52±2.28	12.36±2.41	N/T[b]	15.57
88	15.75±2.58	6.06±1.46	7.69±1.11	11.59±2.96	N/T[b]	10.27
96	23.56±4.01	11.92±2.55	21.81±3.02	15.86±3.45	N/T[b]	18.29
109	18.89±3.61	15.73±3.90	22.40±2.05	12.65±2.59	N/T[b]	17.42
110	28.30±4.65	29.88±4.97	25.15±3.76	20.11±4.24	N/T[b]	25.86
120	22.70±3.44	10.25±2.28	15.28±3.28	11.49±2.00	N/T[b]	14.93
121	29.45±5.21	15.56±1.99	20.12±4.41	14.85±2.99	N/T[b]	20.00
Marchantin C	21.22±3.55	12.95±2.03	13.36±2.10	12.99±1.95	14.45±2.88	14.99

Adriamycin	1.23±0.15	0.57±0.10	1.77±0.23	1.76±0.14	16.89±2.29	4.44

[a] The IC_{50} values (μM) are the concentrations corresponding to 50% inhibition of each cell line growth; Mean values based on three independent experiments; [b] N/T means not tested.

[Table 1 here]

The antiproliferative activity of the most potent compound **47** in HCC1428 cells was further monitored using the xCELLigence system, and vincristine (VCR) was used as a positive control. As shown in Fig. 4, compound **47** inhibited HCC1428 cell proliferation within 5 h and decreased the number of cells markedly within 20 h, which shows a role similar to VCR. After treatment for approximately 60 h, the effect of **47** was close to that of VCR. The cell growth curve shows that compound **47** inhibited HCC1428 cell proliferation and subsequently induced cell death.

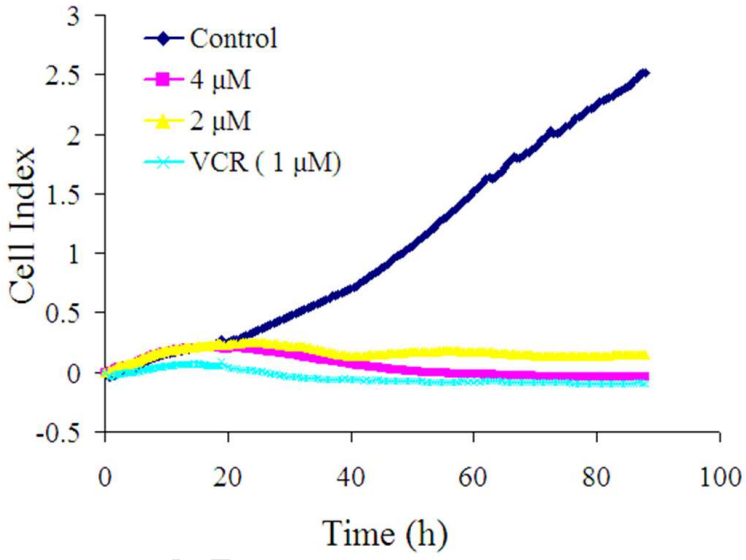


Fig. 4. HCC1428 cells were treated with compound **47** as indicated. Cells were then plated 2000 cells/well into E-plate 16 and analyzed using a xCELLigence RTCA DP instrument. The results are representative of three independent experiments.

[Figure 4 here]

2.3.2. Cell cycle analysis

After the antiproliferative activity evaluation, we extended our work to a mechanistic study. Flow cytometry was used to analyze the effects of the marchantin C analogues on cell growth and division. HCC1428 cells were treated with compound **47** for 24 h. DMSO was used as a vehicle control, and VCR was used as a positive control. As shown in Fig. 5, in the vehicle group, 12.93% of the HCC1428 cells were in the G_2/M phase. Compound **47** increased the proportion of cells in the G_2/M phase to approximately 37.70% and 85.34% when treated for 24 h at concentrations of 3 μM and 6 μM, respectively. These results demonstrate that compound **47** induces cell cycle arrest at the G_2/M phase in

a dose-dependent manner, which is consistent with the results obtained for classical tubulin-targeting drugs.

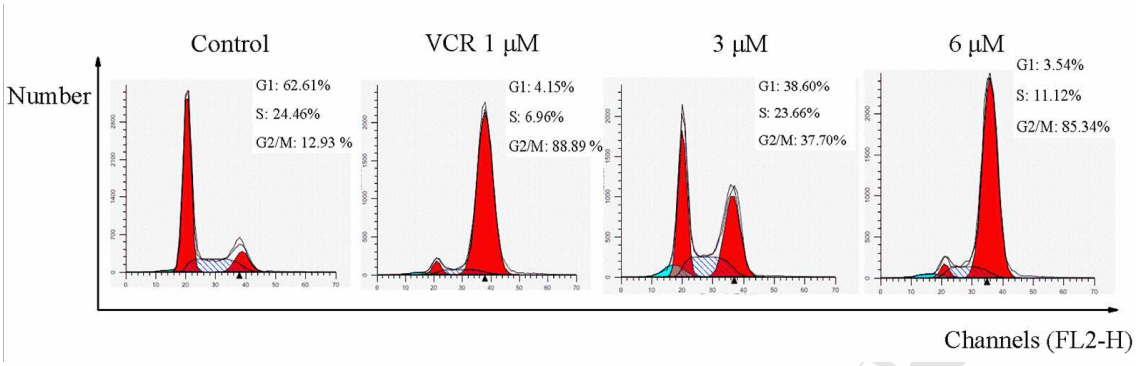


Fig. 5. Compound **47** induced HCC1428 cell cycle arrest at the G_2/M phase. HCC1428 cells were treated with 3 μM and 6 μM concentrations of compound **47** for 24 h, and then trypsinized, fixed and stained with PI to measure the cell cycle profile by flow cytometry. Control cells were treated with DMSO alone. The results are representative of three independent experiments.

[Figure 5 here]

2.3.3. Immunofluorescence staining

The significant cell growth inhibitory properties of the marchantin C analogues and their obvious G_2/M phase arresting properties encouraged us to further investigate the biological mechanism. Given the microtubule-depolymerization activity of marchantin C in culture cells, we next examined the effect of compound **47** on the cytoskeleton network using immunofluorescent staining techniques. The cellular microtubule networks were visualized by confocal microscopy. As shown in Fig. 6, intact microtubule arrays could be observed in untreated cells. However, during treatment with increasing dosages of **47**, the microtubule networks decreased and dispersed in the cytoplasm, which was similar to the result observed for a 1 μM VCR treatment. These results indicate that **47** affects the cellular microtubule dynamics. In addition, effect of the less potent compound **77** on the cytoskeleton network was also tested. As shown in Fig. 6, compound **77** displayed very weak cytoskeleton network disrupting activity at the concentration of 3 μM compared with compound **47**, and as increasing the dosages of **77** to 6 μM and 10 μM, the microtubule networks decreased and dispersed, obviously, which indicated that the antiproliferative activity of these compounds was closely related to the inhibition of tubulin polymerization.

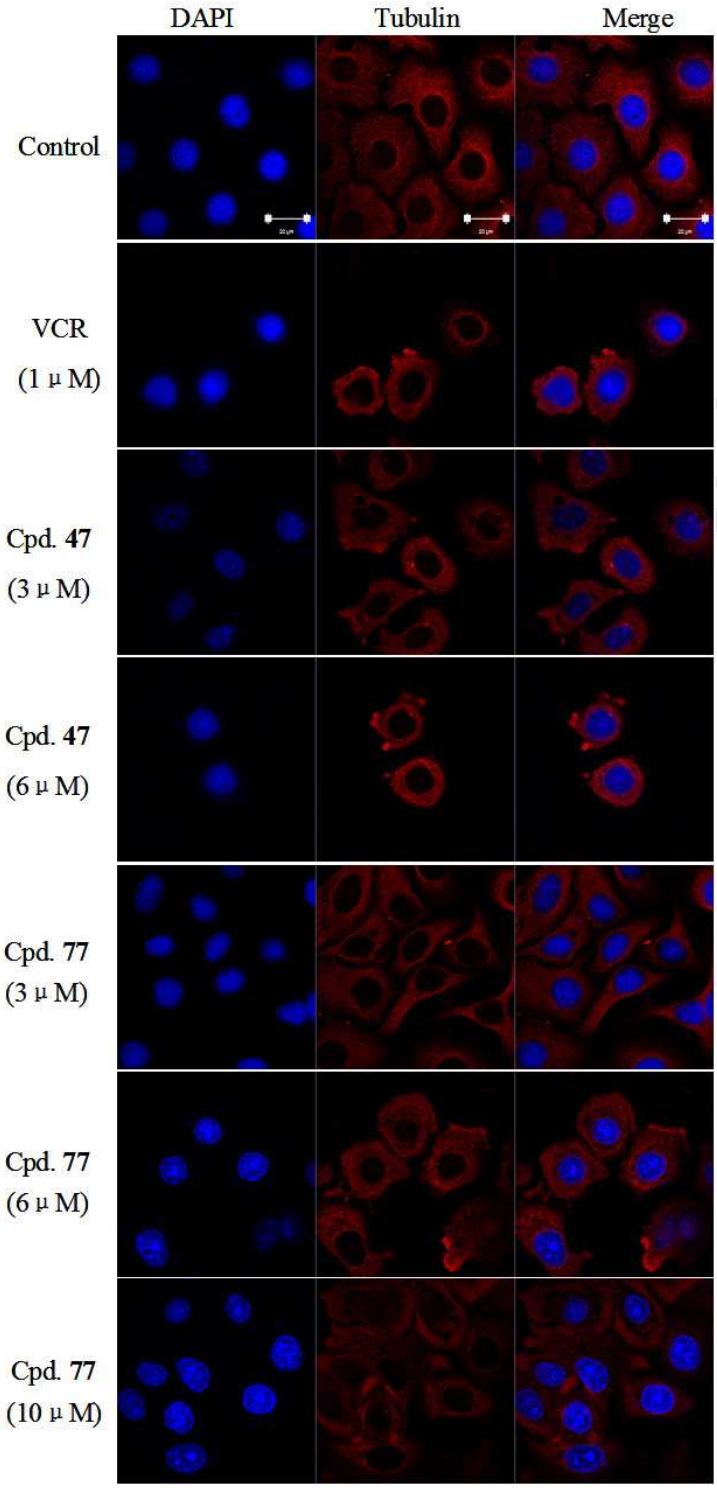


Fig. 6. HCC1428 cells were treated with compound **47** and **77** as indicated for 24 h and then fixed and immunostained with monoclonal anti-α-tubulin antibody (red) and DAPI (blue). One micromolar concentrations of VCR and DMSO were used as controls. The results are representative of three independent experiments. Bar = 10 μm.

[Figure 6 here]

2.3.4. Tubulin polymerization inhibition

We next investigated the inhibition of tubulin polymerization by the selected potent compound **47**

and compared it to the results from a positive control (VCR) and a negative control (taxol). DMSO was used as a blank control. Bovine brain tubulin was incubated with compound **47** at concentrations of 5 and 10 μM. VCR and taxol were both used at a concentration of 5 μM. As shown in Fig. 7, paclitaxel caused an immediate and significant increase in the absorbance, indicating an enhancement of tubulin polymerization. In contrast, VCR and **47** caused a decrease in the absorbance, indicating that the tubulin polymerization was inhibited. Compound **47** showed stronger inhibition than VCR at the two tested concentrations. These results clearly indicate that compound **47** significantly inhibits the polymerization of tubulin *in vitro*.

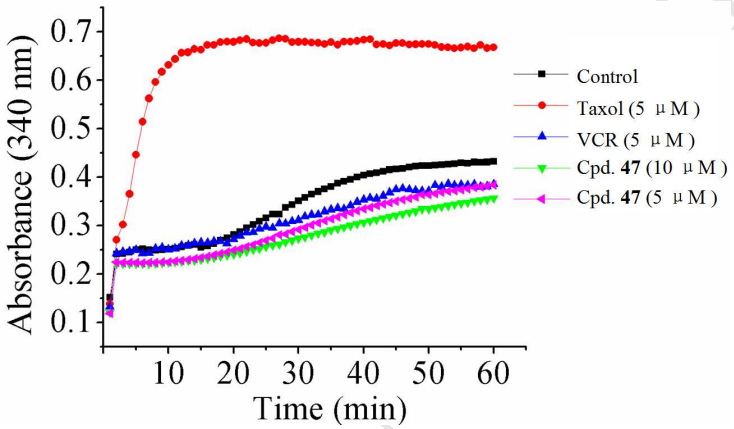


Fig. 7. Effect of compound **47** on tubulin polymerization *in vitro*. Purified bovine brain tubulin was incubated in the presence of taxol, VCR, DMSO (control), and compound **47** under the indicated concentrations at 37℃, and absorbance readings were recorded every minute for 1 h.

[Figure 7 here]

2.4. Molecular modeling

The excellent bioactivity of bisbibenzyl derivatives encouraged us to investigate the possible mechanism of action at the molecular level, and more specifically, the binding mode of active compound **47** to tubulin. In a previous study, a macrocyclic bisbibenzyl compound was found to be a colchicine site binder on tubulin. We anticipated that **47** would also target the colchicine-binding site in tubulin due to its bisbibenzyl skeleton and microtubule-depolymerizing activity. Compound **47** was then docked into the colchicine-binding site on tubulin using the GOLD (Genetic Optimization for Ligand Docking) program. The binding mode of compound **47** was studied further by energy minimization. In the resulting hypothetical structure (Fig. 8A), the hydroxyl group on C-4 of arene *D* may form hydrogen bonds with the residues Lys 352 and Asn 349. In addition, the hydroxyl group on C-5 of arene *D* is involved in a potential hydrogen bond with the carbonyl group of Val 315. It is also possible that arene *B* forms a CH-π interaction with the methyl group of Leu 248. We believe that the

combination of the CH-π interaction and the hydrogen bonds could play a crucial role in the excellent antitubulin activity of derivative **47**. Furthermore, as shown in Fig. 8B, the methoxyl group on arene *B* could fit well into the hydrophobic pocket formed by residues Gln 247, Leu 248, Lys 352 and Ala 354, which might contribute to its enhanced potency compared to compound **44**.

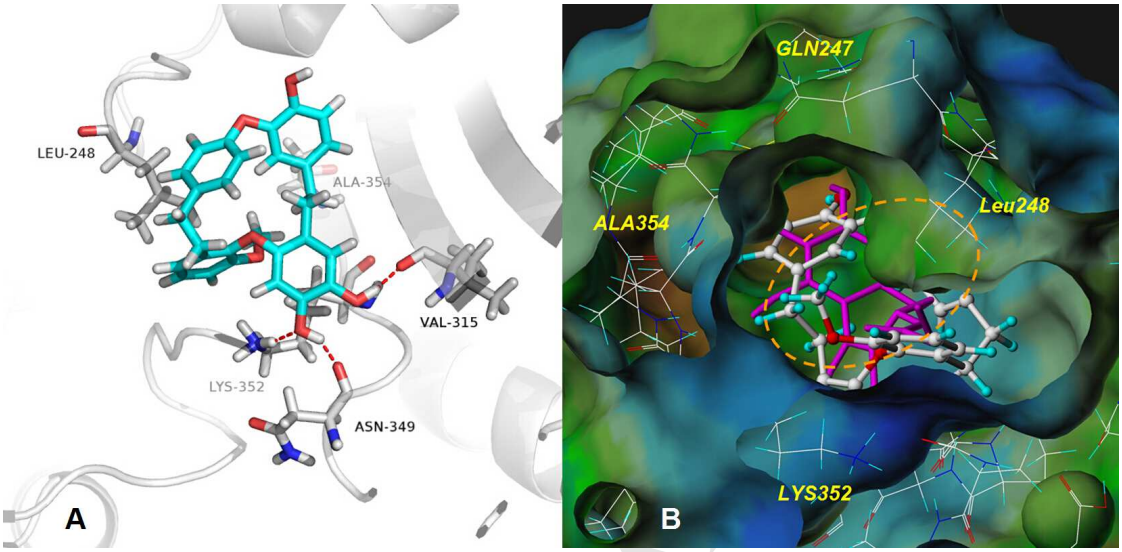


Fig. 8. Proposed binding mode of compound **47** in the colchicine-binding site (PDB code 1SA0). (A) The binding mode of **47** (cyan) in the binding site with hydrogen bonds shown as dotted red where the distance between the ligand and the protein is less than 3 Å. (B) Docking of **47** (grey) into the binding site overlaid with a model of DAMA-colchicine (magenta stick). The methoxyl group could fit well into the hydrophobic pocket formed by residues Gln 247, Leu 248, Lys 352 and Ala 354.

[Figure 8 here]

3. Conclusions

In this report, a series of novel marchantin C analogues was designed, synthesized and evaluated for their antiproliferative activity against five anthropic cancer cell lines, resulting in the discovery of several novel antitumor agents as tubulin polymerization inhibitors. Some of those analogues were also effective against the paclitaxel-resistant cancer cell line. Compound **47** was identified as the most potent compound, with IC_{50} values of 1.51-5.51 μM, which were comparable or superior to the reference drug ADR and much more potent than the parent marchantin C. As a probe in mechanistic studies, compound **47** arrested cancer cells in the G2/M phase in a concentration-dependent manner and disrupted cellular microtubules. Further mechanistic studies confirmed that compound **47** gained its activity by inhibiting tubulin polymerization at the colchicine-binding site. Molecular modeling provided insight into the binding mode of the marchantin C analogue in tubulin. Structure-activity relationships concluded that (1) the macrocyclic bisbibenzyl skeleton is the basic structure for the

antitubulin activity, (2) strain within the macrocyclic ring affects the molecular antitumor activity to some extent, with a 19-membered ring being most active, and (3) the nature and location of the substituents on the arene rings play a critical role in the antiproliferative activity. These marchantin C analogues with novel bisbibenzyl skeletons represent a new class of tubulin inhibitors, and compound **47** could serve as a lead compound for further optimization in the discovery of novel antimitotic agents.

4. Experimental section

4.1. Chemistry

Chemicals were commercially available and used as received without further purification. Solvents (THF, MeCN and DCM) were dried and freshly distilled before use according to procedures reported in the literature. Reactions were monitored by thin-layer chromatography using Merck plates with fluorescent indicator. Column chromatography was carried out on silica gel or alumina (200-300 mesh). The NMR spectra were recorded on a Bruker Spectrospin spectrometer at 600 MHz (^{13}C NMR at 150 MHz) using TMS as an internal standard. The chemical shifts are reported in parts per million (ppm δ) referenced to the residual ^{1}H resonance of the solvent ($CDCl_3$, 7.28 ppm). Abbreviations used in the splitting pattern were as follows: s=singlet, d=doublet, t=triplet, quin=quintet, m=multiplet, and br=broad. Mass spectral analyses were performed at the Shandong University-Chemical Analysis Center. All HRMS spectra (ESI) were obtained on an LTQ Orbitrap mass spectrometer.

General procedure 1 (GP 1) for the Ullmann reaction

A mixture of phenol (0.05 mol) (compounds **3**, **8**, **67**, and **97**-**98**), bromo-benzaldehyde (1.05 equiv.) (compounds **1**-**2**, **9**-**12**, **48**, **56**, and **66**), potassium carbonate (2 equiv.) and cupric oxide (0.3 equiv.) in pyridine (50 mL) was stirred under reflux for 12 h. The pyridine was distilled off in vacuo and the residue was extracted with EtOAc (200 mL). The solution was concentrated and the residue was purified by flash column chromatography (SiO_2 or Al_2O_3), eluting with a hexane-DCM mixture, to yield the pure product as a solid in moderate yield.

General procedure 2 (GP 2) for the preparation of the phosphonium salts

Benzyl alcohol (25 mmol) (compounds **4**-**5**, **22**-**26**, **51**, **58**, **61**, **69**-**70**, **81**, **85**, **90**, **93**, **103**-**104**, and **114**-**115**) and triphenylphosphonium bromide (1.05 quiv.) were dissolved in anhydrous CH_3CN (50 mL), the resulting mixture was then refluxed for 3 h, the solvent was removed in vacuo and the residue was purified by silica gel column chromatography, eluting with 5% methanol in DCM, to yield the pure product as a white solid in satisfactory yield.

General procedure 3 (GP 3) for the intramolecular Wittig reaction

A solution of phosphonium salt (compounds **27**-**31**, **52**, **62**, **71**-**72**, **86**, **94**, **103**-**104**, and **114**-**115**) in anhydrous DCM (150 mL/mmol) was added dropwise (5 h/mmol) to a suspension of MeONa (8 equiv.) in anhydrous DCM (50 mL/mmol). The reaction mixture was stirred for 15 h at room temperature. Insoluble material was filtered off, the solvent was removed in vacuo and the residue was purified by silica gel column chromatography, eluting with DCM, to provide the desired compound in satisfactory yield.

General procedure 4 (GP 4) for the catalytic hydrogenation of stilbenes and benzyl ethers

Palladium on activated carbon (10% Pd, 100 mg/mmol) was added to a solution of stilbene or benzyl ether (compounds **37**-**41**, **54**, **64**, **75**-**76**, **87**, **95**, **107**-**108**, and **118**-**119**) in EtOAc (100-150 mL). The suspension was stirred under H_2 for 24 h at room temperature. The reaction mixture was filtered, and the solution was concentrated to provide the product as a white solid in satisfactory yield.

General procedure 5 (GP 5) for the cleavage of aryl methyl ethers

A solution of boron tribromide (8 equiv.) in anhydrous DCM (10 mL) was added dropwise to a stirred solution of aryl methyl ether (compounds **42**-**45**, **46**-**47**, **55**, **65**, **77**-**78**, **88**, **96**, **109**-**110**, and **120**-**121**) (1 mmol) in anhydrous DCM (10 mL) at -78 ˚C. The reaction mixture was stirred at -78 ˚C for 3 h and then was allowed to warm up to room temperature within 12 h. Ice-cold water was then added, and the reaction mixture was stirred vigorously for 1 h. The solution was then diluted with DCM (50 mL), washed with sat aq NaCl and dried over sodium sulfate. The solution was concentrated, and the residue was purified by silica gel column chromatography, eluting with DCM, to provide a white solid in satisfactory yield.

*Methyl 4-(5-formyl-2-methoxyphenoxy) benzoate (**4**).*

This compound was prepared from methyl 4-bromobenzoate (**1**) and 3-hydroxy-4-methoxy-benzaldehyde (**3**) in 76% yield by following GP 1. Orange solid; mp 118-120 ˚C. ^{1}H NMR ($CDCl_3$) δ 9.87 (s, 1 H), 8.02-7.99 (m, 2 H), 7.76 (dd, *J* = 8.2, 2.1 Hz, 1 H), 7.59 (d, *J* = 2.1 Hz, 1 H), 7.14 (d, *J* = 8.3 Hz, 1 H), 6.94 (d, *J* = 8.7 Hz, 2 H), 3.91 (s, 3 H), 3.90 (s, 3 H); MS (ESI) 287 $(M+H)^+$.

*Methyl 4-(5-formyl-2-methoxyphenoxy)-3-methoxybenzoate (**5**).*

This compound was prepared from 3-hydroxy-4-methoxybenzaldehyde (**3**) and methyl 4-bromo-3-methoxybenzoate (**2**) in 63% yield by following GP 1. Yellow solid; mp 109-110 ˚C. ^{1}H NMR ($CDCl_3$) δ 9.83 (s, 1 H), 7.70 (d, *J* = 1.8 Hz, 1 H), 7.69 (s, 1 H), 7.61 (dd, *J* = 1.8 Hz, 8.4 Hz, 1

H), 7.42 (d, *J* = 1.8 Hz, 1 H), 7.13 (d, *J* = 8.4 Hz, 1 H), 6.81 (d, *J* = 8.4 Hz, 1 H), 3.95 (s, 3 H), 3.94 (s, 3 H), 3.93 (s, 3 H); MS (ESI) 317 $(M+H)^+$.

*(4-Methoxy-3-(4-(methoxycarbonyl)phenoxy)benzyl)triphenylphosphonium Bromide (**6**).*

Sodium borohydride (0.34 g, 9.16 mmol) was added to a solution of **4** (7.21 g, 22.81 mmol) in THF (25 mL) over 15 min at 0 ˚C. The reaction mixture was then stirred at room temperature for 3 h. Water (10 mL) and 1M HCl (10 mL) were added and the THF was evaporated in vacuo. The resulting mixture was extracted with DCM (15 mL), washed with sat aq NaCl, and dried over sodium sulfate. The solution was concentrated to obtain a crude oil. This crude oil and triphenylphosphonium bromide (23 mmol) were then dissolved in anhydrous CH_3CN (50 mL), the resulting mixture was then refluxed for 3 h, the solvent was removed in vacuo and the residue was purified by silica gel column chromatography, eluting with 5% methanol in DCM, to yield the pure product as a white solid, mp 217-219 ˚C. ^{1}H NMR ($CDCl_3$) δ 7.90 (d, *J* = 9.0 Hz, 2 H), 7.80-7.73 (m, 9 H), 7.65-7.58 (m, 6 H), 7.27 (s, 1 H), 6.84 (d, *J* = 8.4 Hz, 1 H), 6.69 (d, *J* = 8.7 Hz, 2 H), 6.51 (s, 1 H), 5.46 (d, *J* = 14 Hz, 2 H), 3.90 (s, 3 H), 3.73 (s, 3 H); MS (ESI) 533 $(M-Br)^+$.

*(4-Methoxy-3-(2-methoxyl-4-(methoxycarbonyl)phenoxy)benzyl)triphenylphosphonium Bromide (**7**).*

This compound was prepared from compound **5** by following the procedure described for **6**, yield 78%, white solid; mp 230-231 ˚C. ^{1}H NMR ($CDCl_3$) δ 7.83-7.70 (m, 9 H), 7.67-7.60 (m, 6 H), 7.57 (d, *J* = 1.8 Hz, 1 H), 7.36 (s, 1 H), 7.03 (d, *J* = 1.8 Hz, 1 H), 6.91 (dd, *J* = 1.8 Hz, 8.4 Hz, 1 H), 6.87 (d, *J* = 8.4 Hz, 1 H), 6.79 (d, *J* = 8.4 Hz, 1 H), 5.40 (d, *J* = 14 Hz, 2 H), 3.92 (s, 3 H), 3.89 (s, 3 H), 3.83 (s, 3 H); MS (ESI) 563 $(M-Br)^+$.

*2-(2-(1,3-Dioxan-2-yl)-6-methoxyphenoxy)benzaldehyde (**13**).*

This compound was prepared from **8** and **9** in 69% yield by following GP 1, yellow oil. ^{1}H NMR ($CDCl_3$) δ 10.78 (s, 1H), 7.92 (dd, J = 7.7, 1.6 Hz, 1H), 7.41-7.38 (m, 1H), 7.36 (d, J = 7.9 Hz, 1H), 7.29 (t, J = 10.9 Hz, 1H), 7.08 (t, J = 7.5 Hz, 1H), 7.01 (d, J = 8.2 Hz, 1H), 6.62 (d, J = 8.4 Hz, 1H), 5.69 (s, 1H), 4.14 (d, J = 7.4 Hz, 2H), 3.83 (t, J = 11.5 Hz, 2H), 3.72 (s, 3H), 2.18 (qd, J = 12.6, 6.3 Hz, 1H), 1.37 (d, J = 13.5 Hz, 1H); MS (ESI) 315 $(M+H)^+$.

*2-(2-(1,3-Dioxan-2-yl)-6-methoxyphenoxy)-5-methoxybenzaldehyde (**14**).*

This compound was prepared from **8** and **10** in 67% yield by following GP 1, colorless oil. ^{1}H NMR ($CDCl_3$) δ 10.76 (s, 1 H), 7.39 (d, *J* = 3.0 Hz, 1 H), 7.36 (d, *J* = 7.8 Hz, 1 H), 7.28 (dd, *J* = 3.0 Hz,

7.8 Hz, 1 H), 7.00 (d, *J* = 7.2 Hz, 2 H), 6.61 (d, *J* = 9.0 Hz, 1 H), 5.73 (s, 1 H), 4.18 (dd, *J* = 4.8 Hz, 10.8 Hz, 2 H), 3.88 (t, *J* = 10.8 Hz, 2 H), 3.84 (s, 3 H), 3.72 (s, 3 H), 2.25-2.16 (m, 1 H), 1.39 (d, *J* = 13.2 Hz, 1 H); MS (ESI) 345 $(M+H)^+$.

*2-(2-(1,3-Dioxan-2-yl)-6-methoxyphenoxy)-4,5-dimethoxybenzaldehyde (**15**).*

This compound was prepared from **8** and **11** in 76% yield by following GP 1, colorless oil. ^{1}H NMR ($CDCl_3$) δ 10.62 (s, 1H), 7.37 (s, 1H), 7.35 (dd, *J* = 8.2, 1.1 Hz, 1H), 7.28 (t, *J* = 8.0 Hz, 1H), 6.99 (dd, *J* = 8.1, 1.1 Hz, 1H), 6.24 (s, 1H), 5.76 (s, 1H), 4.18 (dd, *J* = 10.7, 3.5 Hz, 2H), 3.91 (s, 3H), 3.87 (t, *J* = 11.5 Hz, 2H), 3.72 (s, 3H), 3.68 (s, 3H), 2.36-2.11 (m, 1H), 1.40 (d, *J* = 13.5 Hz, 1H) ; MS (ESI) 375 $(M+H)^+$.

*6-(2-(1,3-Dioxan-2-yl)-6-methoxyphenoxy)benzo[d][1,3]dioxole-5-carbaldehyde (**16**).*

This compound was prepared from **8** and **12** in 76% yield by following GP 1, colorless oil. ^{1}H NMR ($CDCl_3$) δ 10.58 (s, 1H), 7.35 (d, *J* = 7.0 Hz, 1H), 7.32 (s, 1H), 7.29 (t, *J* = 7.9 Hz, 1H), 7.00 (d, *J* = 7.3 Hz, 1H), 6.16 (s, 1H), 5.98 (s, 2H), 5.69 (s, 1H), 4.18 (d, *J* = 7.2 Hz, 2H), 3.87 (t, *J* = 11.4 Hz, 2H), 3.75 (s, 3H), 2.26-2.13 (m, 1H), 1.39 (d, *J* = 13.5 Hz, 1H) ; MS (ESI) 359 $(M+H)^+$.

*Methyl 4-(5-(2-(2-(1,3-dioxan-2-yl)-6-methoxyphenoxy)phenethyl)-2-methoxyphenoxy)-benzoate (**17**).*

Potassium carbonate (4.45 g, 32.22 mmol) and a trace of 18-crown-6 were added to a solution of **6** (10.34 g, 16.11 mmol) and **13** (5.06 g, 16.06 mmol) in anhydrous DCM, the resulting mixture was stirred under reflux for 24 h. The insoluble material was then filtered off and the filtrate was concentrated to provide the orange oil that was purified by flash column chromatography (Al_2O_3), eluting with a 3:1 solution of hexane-dichloromethane to afford a mixture of *Z/E* isomers as a yellow oil. Pd/C 10% (0.7 g) and triethylamine (16 mL) were then added to the solution of isomers in ethyl acetate (100 mL). The suspension was stirred under H_2 for 24 h at room temperature. The mixture was filtered, and concentrated to afford **17** (6.87 g, 75%) as colorless oil. ^{1}H NMR ($CDCl_3$) δ 8.02-7.92 (m, 2H), 7.37 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.26 (t, *J* = 8.0 Hz, 1H), 7.12 (dd, *J* = 8.3, 2.1 Hz, 1H), 7.06 (dd, *J* = 7.4, 1.6 Hz, 1H), 7.04-7.00 (m, 1H), 6.98 (dd, *J* = 8.2, 1.4 Hz, 1H), 6.97 (d, *J* = 8.4 Hz, 1H), 6.95 (d, *J* = 2.1 Hz, 1H), 6.91-6.86 (m, 3H), 6.43 (d, *J* = 8.2 Hz, 1H), 5.67 (s, 1H), 4.15 (dd, *J* = 10.7, 3.5 Hz, 2H), 3.91 (s, 3H), 3.79 (s, 3H), 3.66 (s, 3H), 2.26-2.15 (m, 1H), 1.37-1.31 (m, 1H); MS (ESI) 571 $(M+H)^+$.

Methyl 4-(5-(2-(2-(1,3-dioxan-2-yl)-6-methoxyphenoxy)-5-methoxyphenethyl)-2-methoxyphenoxy)

*benzoate (**18**).*

This compound was prepared from **6** and **14** by following the procedure described for **17**, yield 71%, colorless oil. ^{1}H NMR ($CDCl_3$) δ 7.97 (d, *J* = 8.2 Hz, 2H), 7.36 (d, *J* = 7.4 Hz, 1H), 7.24 (t, *J* = 7.7 Hz, 1H), 7.12 (d, *J* = 7.5 Hz, 1H), 6.97 (d, *J* = 7.6 Hz, 3H), 6.89 (d, *J* = 8.2 Hz, 2H), 6.64 (s, 1H), 6.54 (d, *J* = 8.3 Hz, 1H), 6.36 (d, *J* = 8.7 Hz, 1H), 5.68 (s, 1H), 4.16 (d, *J* = 9.1 Hz, 2H), 3.91 (s, 3H), 3.84 (t, *J* = 10.8 Hz, 2H), 3.79 (s, 3H), 3.73 (s, 3H), 3.66 (s, 3H), 3.09-2.96 (m, 4H), 2.27-2.13 (m, 1H), 1.35 (d, *J* = 13.7 Hz, 1H); MS (ESI) 601 $(M+H)^+$.

*Methyl 4-(5-(2-(2-(1,3-dioxan-2-yl)-6-methoxyphenoxy)-4,5-dimethoxyphenethyl)-2-methoxy-phenoxy) benzoate (**19**).*

This compound was prepared from **6** and **15** by following the procedure described for **17**, yield 79%, colorless oil. ^{1}H NMR ($CDCl_3$) δ 8.01-7.91 (m, 2H), 7.36 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.25 (t, *J* = 8.0 Hz, 1H), 7.09 (dd, *J* = 8.4, 2.1 Hz, 1H), 6.99-6.94 (m, 3H), 6.91-6.84 (m, 2H), 6.56 (s, 1H), 6.15 (s, 1H), 5.71 (s, 1H), 4.17 (dd, *J* = 11.4, 4.6 Hz, 2H), 3.90 (s, 3H), 3.89-3.82 (m, 2H), 3.79 (s, 3H), 3.79 (s, 3H), 3.66 (s, 3H), 3.60 (s, 3H), 3.10-2.96 (m, 4H), 2.24-2.20 (m, 1H), 1.40-1.33 (m, 1H); MS (ESI) 631 $(M+H)^+$.

*Methyl 4-(5-(2-(2-(1,3-dioxan-2-yl)-6-methoxyphenoxy)-5-methoxyphenethyl)-2-methoxy- phenoxy) -3-methoxybenzoate (**20**)*

This compound was prepared from **7** and **14** by following the procedure described for **17**, yield 80%, colorless oil. ^{1}H NMR ($CDCl_3$) δ 7.64 (s, 1H), 7.54 (d, *J* = 7.9 Hz, 1H), 7.35 (d, *J* = 7.0 Hz, 1H), 7.24 (t, *J* = 7.0 Hz, 1H), 7.08 (d, *J* = 7.5 Hz, 1H), 7.02-6.90 (m, 3H), 6.64 (s, 1H), 6.61 (d, *J* = 8.1 Hz, 1H), 6.53 (d, *J* = 8.3 Hz, 1H), 6.36 (d, *J* = 8.6 Hz, 1H), 5.68 (s, 1H), 4.16 (d, *J* = 8.8 Hz, 2H), 3.98 (s, 3H), 3.91 (s, 3H), 3.86-3.84 (m, 2H), 3.78 (s, 3H), 3.72 (s, 3H), 3.67 (s, 3H), 3.17-2.96 (m, 4H), 2.29-2.14 (m, 1H), 1.36-1.34 (m, 1H); MS (ESI) 631 $(M+H)^+$.

*Methyl 4-(5-(2-(5-(2-(1,3-dioxan-2-yl)-6-methoxyphenoxy)benzo[d][1,3]dioxol-6-yl) ethyl)-2-methoxyphenoxy)benzoate (**21**)*

This compound was prepared from **6** and **16** by following by following the procedure described for **17**, yield 74%, colorless oil. ^{1}H NMR ($CDCl_3$) δ 7.32 (dd, J = 7.6, 1.4 Hz, 1H), 7.20 (t, J = 8.0 Hz, 1H), 7.15 (s, 1H), 7.10 (d, J = 8.1 Hz, 2H), 6.88 (dd, J = 8.0, 2.1 Hz, 1H), 6.80-6.76 (m, 2H), 6.70 (d, J = 8.4 Hz, 2H), 6.62 (d, J = 1.9 Hz, 1H), 6.43 (s, 1H), 5.98 (s, 1H), 5.79 (s, 2H), 5.65 (s, 1H), 4.16 (d, J

= 7.3 Hz, 2H), 3.83-3.76 (m, 2H), 3.70 (s, 3H), 3.66 (s, 3H), 3.59 (s, 3H), 2.97-2.91 (m, 2H), 2.86-2.80 (m, 2H), 2.20-2.14 (m, 1H), 1.34 (d, J = 13.6 Hz, 1H); MS (ESI) 615 $(M+H)^+$.

*2-(2-(3-(4-(Hydroxymethyl)phenoxy)-4-methoxyphenethyl)phenoxy)-3-methoxybenzaldehyde (**22**).*

A solution of **17** (13.11 g, 23.72 mmol) in THF (25 mL) was added dropwise to a stirred suspension of lithium aluminum hydride (1.75 g, 46.07 mmol) in anhydrous THF (30 mL). The resulting mixture was stirred at room temperature for 2.5 h and carefully hydrolysed with sat aq NH_4Cl (10 mL). THF was removed in vacuo and the resulting mixture was diluted with DCM (70 mL), washed with saturated aqueous NaCl and dried over sodium sulfate. The solvent was removed in vacuo to yield crude oil. The crude oil was then dissolved in a solution of ethanol (100 mL) and 10 % aq HCl (20 mL). The resulting mixture was then stirred at room temperature for 12 h. Sat aq sodium bicarbonate was added and the ethanol was removed in vacuo. The resulting mixture was extracted with DCM, washed with saturated aqueous NaCl and dried over sodium sulfate. The solution was concentrated to yield **22** (9.20 g, 80%) as colorless oil. ^{1}H NMR ($CDCl_3$) δ 10.19 (s, 1H), 7.57 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.32 (td, *J* = 8.0, 0.7 Hz, 1H), 7.28-7.26 (m, 2H), 7.25 (dd, *J* = 8.2, 1.5 Hz, 1H), 7.10 (dd, *J* = 7.5, 1.6 Hz, 1H), 7.06-7.01 (m, 2H), 6.95 (d, *J* = 8.4 Hz, 1H), 6.93 (td, *J* = 7.6, 1.6 Hz, 1H), 6.90-6.86 (m, 2H), 6.84 (d, *J* = 2.0 Hz, 1H), 6.40 (dd, *J* = 8.2, 0.7 Hz, 1H), 4.64 (s, 2H), 3.83 (s, 3H), 3.71 (s, 3H), 3.13-2.99 (m, 4H); MS (ESI) 485 $(M+H)^+$.

*2-(2-(3-(4-(Hydroxymethyl)phenoxy)-4-methoxyphenethyl)-4-methoxyphenoxy)-3-methoxybenzald ehyde (**23**).*

This compound was prepared from compound **18** by following the procedure described for **22**, yield 78%, colorless oil. ^{1}H NMR ($CDCl_3$) δ 10.20 (s, 1H), 7.92 (d, *J* = 8.4 Hz, 2H), 7.32 (d, *J* = 8.0 Hz, 1H), 7.21 (t, *J* = 8.0 Hz, 1H), 7.15 (d, *J* = 7.6 Hz, 1H), 6.97-6.90 (m, 3H), 6.86 (d, *J* = 8.0 Hz, 2H), 6.60 (s, 1H), 6.56 (d, *J* = 8.0 Hz, 1H), 6.30 (d, *J* = 8.6 Hz, 1H), 4.59 (s, 2H), 3.79 (s, 3H), 3.73 (s, 3H), 3.66 (s, 3H), 3.07-2.98 (m, 4H); MS (ESI) 515 $(M+H)^+$.

*2-(2-(3-(4-(Hydroxymethyl)phenoxy)-4-methoxyphenethyl)-4,5-dimethoxyphenoxy)-3-methoxybenz aldehyde (**24**).*

This compound was prepared from compound **19** by following the procedure described for **22**, yield 71%, colorless oil. ^{1}H NMR ($CDCl_3$) δ 10.19 (s, 1H), 7.56 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.30 (td, *J* = 8.0, 0.8 Hz, 1H), 7.28-7.24 (m, 2H), 7.23 (dd, *J* = 8.2, 1.5 Hz, 1H), 6.98 (dd, *J* = 8.3, 2.1 Hz, 1H), 6.93 (d, *J* = 8.4 Hz, 1H), 6.89-6.85 (m, 2H), 6.78 (d, *J* = 2.1 Hz, 1H), 6.57 (s, 1H), 6.00 (s, 1H), 4.62 (s, 2H),

3.83 (s, 3H), 3.77 (s, 3H), 3.70 (s, 3H), 3.60 (s, 3H), 3.05-2.93 (m, 4H); MS (ESI) 545 $(M+H)^+$.

*2-(2-(3-(4-(Hydroxymethyl)-2-methoxyphenoxy)-4-methoxyphenethyl)-4-methoxyphenoxy)-3-methoxybenzaldehyde (**25**).*

This compound was prepared from compound **20** by following by following the procedure described for **22**, yield 71%, colorless oil. ^{1}H NMR ($CDCl_3$) δ 10.19 (s, 1H), 7.69 (s, 1H), 7.56 (d, *J* = 8.0 Hz, 1H), 7.30 (d, *J* = 7.4 Hz, 1H), 7.21 (t, *J* = 7.6 Hz, 1H), 7.04 (d, *J* = 7.6 Hz, 1H), 7.00-6.85 (m, 3H), 6.61 (s, 1H), 6.60 (d, *J* = 8.0 Hz, 1H), 6.55 (d, *J* = 8.0 Hz, 1H), 6.37 (d, *J* = 8.0 Hz, 1H), 4.68 (s, 2H), 3.88 (s, 3H), 3.74 (s, 3H), 3.70 (s, 3H), 3.66 (s, 3H), 3.17-2.96 (m, 4H); MS (ESI) 545 $(M+H)^+$.

*2-(5-(3-(4-(Hydroxymethyl)phenoxy)-4-methoxyphenethyl)benzo[d][1,3]dioxol-6-yloxy)-3-methoxybenzaldehyde (**26**).*

This compound was prepared from compound **21** by following by following the procedure described for **22**, yield 76%, colorless oil. ^{1}H NMR ($CDCl_3$) δ 10.06 (s, 1H), 7.46 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.21 (t, *J* = 8.1 Hz, 1H), 7.17 (s, 1H), 7.14 (d, *J* = 8.1 Hz, 2H), 6.90 (dd, *J* = 8.3, 1.9 Hz, 1H), 6.87-6.82 (m, 2H), 6.80 (d, *J* = 8.4 Hz, 2H), 6.70 (d, *J* = 1.9 Hz, 1H), 6.47 (s, 1H), 5.91 (s, 1H), 5.77 (s, 2H), 4.55 (s, 2H), 3.75 (s, 3H), 3.64 (s, 3H), 2.95-2.89 (m, 2H), 2.87-2.82 (m, 2H); MS (ESI) 529 $(M+H)^+$.

*2-(2-(3-(4-((Bromotriphenylphosphoranyl)methyl)phenoxy)-4-methoxyphenethyl)phenoxy)-3-methoxybenzaldehyde (**27**).*

This compound was prepared from **22** in 88% yield by following GP 2, white solid; mp 167-168 ˚C. ^{1}H NMR ($CDCl_3$) δ 10.19 (s, 1H), 7.80-7.72 (m, 9H), 7.68-7.65 (m, 6H), 7.49 (td, *J* = 7.6, 2.9 Hz, 2H), 7.33 (t, *J* = 7.9 Hz, 1H), 7.09 (d, *J* = 6.9 Hz, 1H), 6.99 (dd, *J* = 8.2, 1.7 Hz, 4H), 6.92-6.88 (m, 2H), 6.78 (d, *J* = 2.0 Hz, 1H), 6.67 (d, *J* = 7.8 Hz, 2H), 6.37 (d, *J* = 8.0 Hz, 1H), 5.34 (d, *J* = 13.6 Hz, 2H), 3.80 (s, 3H), 3.70 (s, 3H), 3.10-2.97 (m, 4H); MS (ESI) 729 $(M-Br)^+$.

*2-(2-(3-(4-((Bromotriphenylphosphoranyl)methyl)phenoxy)-4-methoxyphenethyl)-4-methoxyphenoxy)-3-methoxybenzaldehyde (**28**).*

This compound was prepared from **23** in 90% yield by following GP 2, white solid; mp 155-156 ˚C. ^{1}H NMR ($CDCl_3$) δ 10.20 (s, 1H), 7.86 (d, *J* = 8.0 Hz, 2H), 7.82-7.76 (m, 9H), 7.67-7.66 (m, 6H), 7.36 (d, *J* = 8.0 Hz, 1H), 7.24 (t, *J* = 8.0 Hz, 1H), 7.17 (d, *J* = 8.0 Hz, 1H), 6.99-6.93 (m, 3H), 6.87 (d, *J* = 8.6 Hz, 2H), 6.62 (s, 1H), 6.59 (d, *J* = 8.0 Hz, 1H), 6.33 (d, *J* = 8.0 Hz, 1H), 5.35 (d, *J* = 13.4 Hz, 2H), 3.81 (s, 3H), 3.74 (s, 3H), 3.68 (s, 3H), 3.04-2.95 (m, 4H); MS (ESI) 759 $(M-Br)^+$.

*2-(2-(3-(4-((Bromotriphenylphosphoranyl)methyl)phenoxy)-4-methoxyphenethyl)-4,5-dimethoxyphenoxy)-3-methoxybenzaldehyde (**29**).*

This compound was prepared from **24** in 90% yield by following GP 2, white solid; mp 174-175 ˚C. ^{1}H NMR ($CDCl_3$) δ 10.24 (s, 1H), 7.80-7.72 (m, 9H), 7.69-7.65 (m, 6H), 7.31 (d, *J* = 7.8 Hz, 1H), 7.30 (d, *J* = 1.5 Hz, 1H), 7.02 (d, *J* = 8.4 Hz, 2H), 6.96 (dd, *J* = 8.3, 2.0 Hz, 2H), 6.90 (d, *J* = 7.8 Hz, 1H), 6.78 (d, *J* = 2.0 Hz, 1H), 6.70 (d, *J* = 8.1 Hz, 2H), 6.60 (s, 1H), 6.01 (s, 1H), 5.38 (d, *J* = 13.6 Hz, 2H), 3.81 (s, 3H), 3.78 (s, 3H), 3.71 (s, 3H), 3.59 (s, 3H), 3.02-2.99 (m, 2H), 2.94-2.90 (m, 2H); MS (ESI) 789 $(M\text{-}Br)^+$.

*2-(2-(3-(4-((Bromotriphenylphosphoranyl)methyl)-2-methoxyphenoxy)-4-methoxyphenethyl)-4-methoxyphenoxy)-3-methoxybenzaldehyde (**30**).*

This compound was prepared from **25** in 87% yield by following GP 2, white solid; mp 156-157 ˚C. ^{1}H NMR ($CDCl_3$) δ 10.20 (s, 1H), 7.86-7.75 (m, 9H), 7.72-7.65 (m, 6H), 7.67 (s, 1H), 7.55 (d, *J* = 8.0 Hz, 1H), 7.32 (d, *J* = 8.0 Hz, 1H), 7.20 (t, *J* = 8.4 Hz, 1H), 7.06 (d, *J* = 8.0 Hz, 1H), 7.05-6.92 (m, 3H), 6.64 (s, 1H), 6.61 (d, *J* = 8.0 Hz, 1H), 6.57 (d, *J* = 8.0 Hz, 1H), 6.32 (d, *J* = 8.0 Hz, 1H), 5.36 (d, *J* = 13.6 Hz, 2H), 3.87 (s, 3H), 3.73 (s, 3H), 3.68 (s, 3H), 3.65 (s, 3H), 3.12-2.90 (m, 4H); MS (ESI) 789 $(M\text{-}Br)^+$.

*Macrocycle (stilbene bridge) (**32**).*

This compound was prepared from **27** in 83% yield by following GP 3, white solid; mp 162-163 ˚C. ^{1}H NMR ($CDCl_3$) δ 7.27 (d, *J* = 6.0 Hz, 1H), 7.23 (d, *J* = 8.0 Hz, 1H), 7.13 (dd, *J* = 1.2 Hz, *J* = 7.6 Hz, 1H), 7.01 (dd, *J* = 1.2 Hz, *J* = 8.4 Hz, 1H), 6.97-6.96 (m, 1H), 6.92 (d, *J* = 8.0 Hz, 1H), 6.90-6.87 (m, 2H), 6.77-6.72 (m, 3H), 6.26 (d, *J* = 8.0 Hz, 1H), 6.12 (d, *J* = 16.0 Hz, 1H), 5.21 (d, *J* = 2.0 Hz, 1H), 4.00 (s, 3H), 3.88 (s, 3H), 3.01-2.71 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 165.5, 165.4, 153.3,151.7, 146.2, 142.1, 140.2, 134.3, 133.2, 131.6, 128.1, 127.7, 125.8, 123.4, 123.3, 121.7, 121.2, 118.4, 113.8, 112.9, 112.0, 119.9, 56.3, 56.2, 29.0, 24.0. MS (ESI) 451 $(M+H)^+$.

*Macrocycle (stilbene bridge) (**33**).*

This compound was prepared from **28** in 83% yield by following GP 3, white solid; mp 186-187 ˚C. ^{1}H NMR ($CDCl_3$) δ 7.31 (s, 1 H), 7.24 (t, *J* = 7.8 Hz, 1 H), 7.13 (d, *J* = 7.8 Hz, 2 H), 7.00 (d, *J* = 8.4 Hz, 2 H), 6.93-6.86 (m, 3 H), 6.88 (d, *J* = 15.6 Hz, 1 H), 6.49 (d, *J* = 8.4 Hz, 1 H), 6.38 (s, 1 H), 6.20 (d, *J* = 8.4 Hz, 1 H), 6.11 (d, *J* = 15.6 Hz, 1 H), 5.24 (s, 1 H), 4.00 (s, 3 H), 3.89 (s, 3 H), 3.58 (s, 3 H), 3.06 (s, 4 H); ^{13}C NMR ($CDCl_3$) δ 156.6, 154.0, 153.3, 151.7, 150.8, 146.1, 142.4, 140.3, 134.4,

132.9, 132.4, 131.4, 129.4, 125.6, 121.8, 118.4, 114.5, 113.8, 113.4, 111.9, 111.8, 110.2, 56.2, 55.6, 29.1, 24.2; MS (ESI) 503 $(M+Na)^+$.

*Macrocycle (stilbene bridge) (**34**).*

This compound was prepared from **29** in 80% yield by following GP 3, white solid; mp 173-174 ˚C. ^{1}H NMR ($CDCl_3$) δ 7.28-7.27 (m, 2 H), 7.23 (t, *J* = 8.4 Hz, 1 H), 7.12 (d, *J* = 7.8 Hz, 2 H), 7.01 (d, *J* = 7.8 Hz, 2 H), 6.91 (d, *J* = 2.4 Hz, 1 H), 6.89 (d, *J* = 4.8 Hz, 1 H), 6.86 (dd, *J* = 1.2 Hz, *J* = 8.4 Hz, 1 H), 6.33 (s, 1 H), 6.08 (d, *J* = 9.6 Hz, 1 H), 5.91 (s, 1 H), 5.24 (d, *J* = 1.2 Hz, 1 H), 3.99 (s, 3 H), 3.89 (s, 3 H), 3.62 (s, 3 H), 3.52 (s, 3 H), 2.95-2.57 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 156.0, 152.5, 151.1, 149.8, 147.7, 146.7, 145.6, 142.7, 141.7, 139.6, 133.8, 131.9, 130.9, 125.1, 121.1, 119.1, 117.9, 113.5, 111.9, 111.4, 111.3, 98.8, 55.9, 55.7, 55.6, 55.5, 28.8, 23.0; MS (ESI) 511 $(M+H)^+$.

*Macrocycle (stilbene bridge) (**35**).*

This compound was prepared from **30** in 87% yield by following GP 3, white solid; mp 183-184 ˚C. ^{1}H NMR ($CDCl_3$) δ 7.22 (d, *J* = 8.4 Hz, 1 H), 6.97 (d, *J* = 7.2 Hz, 1 H), 6.94 (d, *J* = 7.2 Hz, 1 H), 6.91 (s, 1 H), 6.87 (d, *J* = 16.2 Hz, 1 H), 6.85 (d, *J* = 7.8 Hz, 1 H), 6.83 (d, *J* = 16.2 Hz, 1 H), 6.80 (d, *J* = 8.4 Hz, 1 H), 6.79-6.65 (m, 4 H), 6.55-6.51 (m, 1 H), 5.54 (s, 1 H), 3.98 (s, 3 H), 3.91 (s, 3 H), 3.86 (s, 3 H), 3.71 (s, 3 H), 2.85-2.69 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 157.3, 152.8, 152.1, 149.4, 146.7, 144.0, 141.4, 137.3, 135.0, 134.5, 131.6, 130.4, 128.8, 128.7, 125.4, 123.7, 122.0, 119.4, 117.4, 115.6, 113.7, 111.9, 111.4, 108.9, 55.9, 55.6, 55.2, 54.3, 34.6, 33.0; MS (ESI) 511 $(M+H)^+$.

*Macrocycle (stilbene bridge) (**36**).*

This compound was prepared from **31** in 88% yield by following GP 3, white solid; mp 195-196 ˚C. ^{1}H NMR ($CDCl_3$) δ 7.16 (s, 1 H), 7.12 (d, *J* = 8.4 Hz, 1 H), 7.03 (d, *J* = 8.4 Hz, 2 H), 6.89 (d, *J* = 8.4 Hz, 1 H), 6.86 (d, *J* = 15.6 Hz, 1 H), 6.80 (d, *J* = 8.4 Hz, 2 H), 6.75 (dd, *J* = 1.8 Hz, *J* = 8.4 Hz, 2 H), 6.20 (s, 1 H), 6.00 (d, *J* = 15.6 Hz, 1 H), 5.85 (s, 1 H), 5.71 (s, 2 H), 5.11 (d, *J* = 1.8 Hz, 1 H), 3.90 (s, 3 H), 3.78 (s, 3 H), 2.96-2.43 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 156.7, 153.2, 151.8, 151.1, 146.2, 145.4, 142.1, 141.4, 140.3, 134.3, 132.8, 132.4, 131.5, 125.9, 121.8, 120.6, 118.4, 113.7, 112.0, 111.8, 107.7, 100.8, 96.3, 56.2, 56.1, 29.3, 23.8. MS (ESI) 495 $(M+H)^+$.

*Macrocyclic derivative (**37**).*

This compound was prepared from **32** in 96% yield by following GP 4, white solid; mp 200-201 ˚C. ^{1}H NMR ($CDCl_3$) δ 7.27 (dd, *J* = 2.0 Hz, *J* = 8.4 Hz, 1 H), 7.22 (t, *J* = 8.0 Hz, 1 H), 7.13-7.10 (m, 2 H), 6.99 (dd, *J* = 2.4 Hz, *J* = 8.0 Hz, 1 H), 6.93 (td, *J* = 1.6 Hz, *J* = 7.6 Hz, 1 H), 6.82 (t, *J* = 8.8 Hz, 1

H), 6.80-6.72 (m, 4 H), 6.36 (dd, *J* = 2.0 Hz, *J* = 8.0 Hz, 1 H), 6.24 (d, *J* = 8.0 Hz, 1 H), 6.07 (s, 1 H), 3.95 (s, 3 H), 3.46 (s, 3 H), 3.15-2.99 (m, 2 H), 2.89-2.72 (m, 4 H), 2.63-2.43 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 157.5, 154.9, 151.9, 151.6, 146.5, 143.0, 138.2, 136.7, 135.5, 130.6, 129.9, 129.8, 126.9, 125.0, 123.6, 122.0, 121.1, 119.8, 117.5, 112.9, 110.8, 110.4, 56.2, 55.6, 37.3, 35.5, 35.0, 30.7. MS (ESI) 453 $(M+H)^+$.

*Macrocyclic derivative (**38**).*

This compound was prepared from **33** in 95% yield by following GP 4.white solid; mp 192-193 ˚C. ^{1}H NMR ($CDCl_3$) δ 7.29 (s, 1 H), 7.22 (t, *J* = 7.8 Hz, 1 H), 7.11 (d, *J* = 7.8 Hz, 1 H), 7.01 (d, *J* = 6.6 Hz, 1 H), 6.80 (d, *J* = 7.8 Hz, 2 H), 6.75 (t, *J* = 7.8 Hz, 2 H), 6.72 (s, 1 H), 6.47 (d, *J* = 7.8 Hz, 1 H), 6.36 (d, *J* = 7.8 Hz, 1 H), 6.17 (d, *J* = 8.4 Hz, 1 H), 6.08 (s, 1 H), 3.97 (s, 3 H), 3.74 (s, 3 H), 3.48 (s, 3 H), 3.16 (d, *J* = 9.6 Hz, 1 H), 3.05 (t, *J* = 12.0 Hz, 1 H), 2.94-2.86 (m, 3 H), 2.75 (t, *J* = 12.0 Hz, 1 H), 2.60-2.47 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 154.8, 153.6, 152.0, 151.6, 151.4, 146.4, 143.3, 138.3, 136.5, 135.5, 131.3, 130.6, 129.8, 124.8, 123.5, 122.1, 122.0, 119.7, 117.4, 115.7, 113.4, 111.0, 110.6, 110.4, 56.1, 55.6, 55.5, 37.3, 35.7, 34.9, 30.7; MS (ESI) 505 $(M+Na)^+$.

*Macrocyclic derivative (**39**).*

This compound was prepared from **34** in 97% yield by following GP 4. white solid; mp 198-199 ˚C. ^{1}H NMR ($CDCl_3$) δ 7.30 (dd, *J* = 8.3, 2.2 Hz, 1H), 7.22 (t, *J* = 7.9 Hz, 1H), 7.11 (dd, *J* = 7.8, 1.1 Hz, 1H), 7.01 (dd, *J* = 8.3, 2.5 Hz, 1H), 6.80 (dd, *J* = 8.1, 2.6 Hz, 2H), 6.76 (dd, *J* = 8.1, 1.3 Hz, 1H), 6.73 (dd, *J* = 8.0, 1.8 Hz, 1H), 6.68 (s, 1H), 6.36 (dd, *J* = 8.2, 2.2 Hz, 1H), 6.07 (d, *J* = 1.9 Hz, 1H), 5.89 (s, 1H), 3.97 (s, 3H), 3.84 (s, 3H), 3.57 (s, 3H), 3.48 (s, 3H), 3.17 (dt, *J* = 6.7, 3.1 Hz, 1H), 3.02-2.85 (m, 4H), 2.76-2.68 (m, 1H), 2.58-2.45 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 154.8, 152.0, 151.4, 151.2, 147.4, 146.5, 143.1, 143.0, 138.2, 136.6, 135.3, 130.6, 129.8, 124.9, 123.5, 122.1, 122.0, 121.7, 119.7, 117.4, 113.5, 110.6, 110.4, 99.0, 56.4, 56.2, 56.1, 55.6, 37.3, 35.2, 35.0, 30.6; MS (ESI) 513 $(M+H)^+$.

*Macrocyclic derivative (**40**).*

This compound was prepared from **35** in 99% yield by following GP 4, white solid; mp 156-157 ˚C. ^{1}H NMR ($CDCl_3$) δ 7.26 (d, *J* = 7.8 Hz, 1 H), 7.21 (d, *J* = 7.2 Hz, 1 H), 6.89-6.85 (m, 2 H), 6.79 (d, *J* = 7.8 Hz, 1 H), 6.71 (d, *J* = 7.8 Hz, 1 H), 6.68 (d, *J* = 7.8 Hz, 1 H), 6.51 (s, 1 H), 6.46-6.44 (m, 3 H), 5.83 (s, 1 H), 3.92 (s, 3 H), 3.68 (s, 3 H), 3.61 (s, 3 H), 3.52 (s, 3 H), 3.06 (s, 4 H), 2.75-2.77 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 155.7, 152.6, 151.2, 147.3, 147.1, 141.8, 141.3, 139.3, 136.1, 134.5, 133.8, 129.4, 125.3, 122.4, 122.1, 121.7, 120.9, 116.4, 114.0, 113.2, 111.8, 110.0, 56.1, 55.8, 55.6, 54.9, 37.0, 36.9,

35.4, 29.2; MS (ESI) 513 $(M+H)^+$.

*Macrocyclic derivative (**41**).*

This compound was prepared from **36** in 97% yield by following GP 4, white solid; mp 129-130 ˚C. ^{1}H NMR ($CDCl_3$) δ 7.19 (t, *J* = 7.8 Hz, 1H), 7.07 (d, *J* = 7.8 Hz, 1H), 6.97 (d, *J* = 8.2 Hz, 1H), 6.77-6.76 (m, 3H), 6.73 (d, *J* = 8.1 Hz, 1H), 6.70 (d, *J* = 8.1 Hz, 1H), 6.60 (s, 1H), 6.32 (d, *J* = 8.1 Hz, 1H), 6.01 (s, 1H), 5.87 (s, 1H), 5.80 (d, *J* = 13.0 Hz, 2H), 3.94 (s, 3H), 3.48 (s, 3H), 2.91-2.85 (m, 4H), 2.69-2.62 (m, 1H), 2.52-2.39 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 154.9, 152.1, 151.9, 151.5, 146.5, 145.9, 143.1, 141.1, 138.2, 136.5, 135.4, 130.6, 129.8, 125.1, 123.5, 122.1, 122.0, 119.8, 117.4, 110.7, 110.3, 109.7, 100.8, 96.2, 56.1, 55.6, 37.3, 35.3, 35.2, 30.6; MS (ESI) 497 $(M+H)^+$.

*Macrocyclic derivative (**42**).*

This compound was prepared from **37** in 80% yield by following GP 5, white solid; mp 249-250 ˚C. ^{1}H NMR ($CDCl_3$) δ 7.20 (t, *J* = 8.0 Hz, 1 H, Ar-H), 7.16 (dd, *J* = 2.0 Hz, *J* = 7.2 Hz, 1 H, Ar-H), 7.10 (dd, *J* = 1.2 Hz, *J* = 8.0 Hz, 1 H, Ar-H), 7.00 (td, *J* = 2.0 Hz, *J* = 8.0 Hz, 1 H, Ar-H), 6.95 (dd, *J* = 2.4 Hz, *J* = 8.4 Hz, 1 H, Ar-H), 6.91 (td, *J* = 1.2 Hz, *J* = 7.2 Hz, 1 H, Ar-H), 6.82 (dd, *J* = 2.8 Hz, *J* = 8.0 Hz, 1 H, Ar-H), 6.80 (d, *J* = 8.0 Hz, 2 H, Ar-H), 6.66 (dd, *J* = 2.0 Hz, *J* = 8.0 Hz, 1 H, Ar-H), 6.40 (dd, *J* = 2.0 Hz, *J* = 8.0 Hz, 1 H, Ar-H), 6.33 (dd, *J* = 0.8 Hz, *J* = 8.0 Hz, 1 H, Ar-H), 5.98 (d, *J* = 2.0 Hz, 1 H, Ar-H), 5.52 (s, 1 H, -OH), 4.48 (s, 1 H, -OH), 3.15-3.10 (m, 1 H, $-CH_2-$), 2.94-2.88 (m, 2 H, $-CH_2-$), 2.79-2.59 (m, 5 H, $-CH_2-$); ^{13}C NMR ($CDCl_3$) δ 155.6, 154.8, 149.6, 148.0, 143.1, 138.9, 135.6, 134.8, 130.8, 130.7, 130.3, 129.7, 127.6, 125.9, 123.5, 122.3, 120.7, 116.6, 114.7, 114.1, 112.8, 37.4, 36.4, 34.9, 30.9; MS (ESI) 425 $(M+H)^+$; HRMS calcd for $C_{28}H_{24}O_4Na$ 447.1567, found: 447.1554 $(M+Na)^+$.

*Macrocyclic derivative (**43**).*

This compound was prepared from **38** in 72% yield by following GP 5, white solid; mp 226-227 ˚C. ^{1}H NMR ($CDCl_3$) δ 7.31-7.30 (m, 1 H, Ar-H), 7.21 (t, *J* = 7.8 Hz, 1 H, Ar-H), 7.11 (d, *J* = 7.8 Hz, 1 H, Ar-H), 6.97 (d, *J* = 6.6 Hz, 1 H, Ar-H), 6.85-6.81 (m, 3 H, Ar-H), 6.69 (d, *J* = 1.8 Hz, 2 H, Ar-H), 6.47 (dd, *J* = 2.4 Hz, 9.0 Hz, 1 H, Ar-H), 6.40 (d, *J* = 7.2 Hz, 1 H, Ar-H), 6.23 (d, *J* = 8.4 Hz, 1 H, Ar-H), 5.99 (s, 1 H, Ar-H), 5.54 (s, 1 H, -OH), 4.49 (s, 1 H, -OH), 4.45 (s, 1 H, -OH), 3.17-3.15 (m, 1 H, $-CH_2-$), 2.95-2.91 (m, 2 H, $-CH_2-$), 2.81-2.72 (m, 2 H, $-CH_2-$), 2.65-2.60 (m, 3H, $-CH_2-$); ^{13}C NMR ($CDCl_3$) δ 154.5, 150.3, 149.5, 149.4, 147.9, 143.0, 141.0, 138.9, 135.5, 134.6, 131.5, 130.8, 129.7, 125.8, 123.5, 122.4, 122.2, 120.6, 117.6, 116.5, 114.7, 114.1, 113.6, 113.5, 37.4, 36.3, 34.9, 30.9; MS

(ESI) 441 $(M+H)^+$; HRMS calcd for $C_{28}H_{24}O_5Na$ 463.1516, found: 463.1512 $(M+Na)^+$.

*Macrocyclic derivative (**44**).*

This compound was prepared from **41** in 76% yield by following GP 5, white solid; mp 136-137 ˚C. ^{1}H NMR (Acetone) δ 7.73 (s, 1H, Ar-H), 7.19 (s, 1H, Ar-H), 6.89 (d, *J* = 6.9 Hz, 2H, Ar-H), 6.82 (s, 1H, Ar-H), 6.77 (d, *J* = 7.4 Hz, 2H, Ar-H), 6.68 (d, *J* = 7.1 Hz, 1H, Ar-H), 6.61 (t, *J* = 7.4 Hz, 1H, Ar-H), 6.48 (s, 1H, Ar-H), 6.20 (s, 1H, Ar-H), 6.17 (d, *J* = 7.7 Hz, 1H, Ar-H), 2.87-2.83 (m, 4H, -CH_2-), 2.57-2.51 (m, 2H, -CH_2-), 2.36-2.30 (m, 2H, -CH_2-); ^{13}C NMR (Acetone) δ 153.7, 148.0, 146.6, 146.5, 144.6, 144.3, 144.0, 142.3, 137.2, 133.9, 130.6, 127.3, 126.0, 122.6, 121.4, 120.5, 118.4, 116.3, 115.4, 109.8, 109.0, 37.5, 36.3, 34.0; MS (ESI) 457 $(M+H)^+$; HRMS (ESI) calcd for $C_{28}H_{25}O_6$ 457.1646; found 457.1642 $(M+H)^+$.

*Macrocyclic derivative (**45**).*

This compound was prepared from **40** in 68% yield by following GP 5, white solid; mp 140-141 ˚C. ^{1}H NMR ($CDCl_3$) δ 7.03 (t, *J* = 7.2 Hz, 2 H, Ar-H), 7.01 (d, *J* = 7.8 Hz, 1 H, Ar-H), 6.96 (d, *J* = 7.8 Hz, 1 H, Ar-H), 6.94 (t, *J* = 7.2 Hz, 2 H, Ar-H), 6.78 (s, 1 H, Ar-H), 6.47 (d, *J* = 7.8 Hz, 1 H, Ar-H), 6.30 (d, *J* = 7.8 Hz, 1 H, Ar-H), 6.26-6.23 (m, 2 H, Ar-H), 6.12 (s, 1 H, Ar-H), 5.76 (s, 1 H, Ar-H), 2.86-2.77 (m, 8 H, -CH_2-); ^{13}C NMR ($CDCl_3$) δ 151.4, 150.3, 149.6, 149.5, 148.8, 144.1, 143.8, 142.3, 141.2, 139.8, 135.7, 134.6, 131.0, 124.9, 123.3, 120.6, 120.2, 118.1, 117.1, 115.3, 114.7, 113.5, 113.0, 37.5, 35.8, 34.9, 30.8; MS (ESI) 457 $(M+H)^+$; HRMS (ESI) calcd for $C_{28}H_{25}O_6$ 457.1646; found 457.1642 $(M+H)^+$.

*Macrocyclic derivative (**46**).*

This compound was prepared from **32** in 69% yield by following GP 5, white solid; mp 190-191 ˚C. ^{1}H NMR ($CDCl_3$) δ 7.28 (dd, *J* = 2.0 Hz, *J* = 8.4 Hz, 1 H, Ar-H), 7.19 (t, *J* = 7.9 Hz, 1H, Ar-H), 7.15 (d, *J* = 7.4 Hz, 1H, Ar-H), 7.05-6.98 (m, 3H, Ar-H), 6.96 (dd, *J* = 2.0 Hz, *J* = 8.3 Hz, 1H, Ar-H), 6.93-6.91 (m, 2H, Ar-H), 6.87 (d, *J* = 8.0 Hz, 1H, Ar-H), 6.78 (d, *J* = 7.9 Hz, 1H, Ar-H), 6.75 (d, *J* = 11.9 Hz, 1H, -CH=), 6.65 (d, *J* = 7.9 Hz, 1H, Ar-H), 6.61 (d, *J* = 11.9 Hz, 1H, -CH=), 6.48 (d, *J* = 8.2 Hz, 1H, Ar-H), 5.68 (s, 1H, Ar-H), 5.48 (s, 1H, -OH), 4.57 (s, 1H, -OH), 2.72-2.57 (m, 4H, -CH_2-); ^{13}C NMR ($CDCl_3$) δ 156.5, 155.6, 150.0, 148.7, 142.8, 139.2, 135.6, 134.6, 133.2, 132.3, 131.4, 130.7, 128.8, 127.6, 126.1, 125.4, 123.7, 123.4, 122.7, 120.8, 117.4, 116.4, 114.3, 114.2, 35.6, 33.4; MS (ESI) 423 $(M+H)^+$; HRMS calcd for $C_{28}H_{23}O_4$ 423.1591, found: 423.1591 $(M+H)^+$.

*Macrocyclic derivative (**47**).*

A solution of boron tribromide (3 equiv.) in anhydrous DCM (10 mL) was added dropwise to a stirred solution of **39** (1 equiv) in anhydrous DCM (10 mL) at -78 ˚C. The reaction mixture was stirred at -78 ˚C for 1 h, and then was allowed to warm up to room temperature within 6 h. The ice-cold water was added, and the reaction mixture was stirred vigorously for 0.5 h. The solution was then diluted with DCM, washed with sat aq NaCl and dried over sodium sulfate. The solution was concentrated, and the residue was purified by silica gel column chromatography, eluating with DCM, to provide a white solid in 51% yield; mp 181-182 ˚C. ^{1}H NMR ($CDCl_3$) δ 7.30 (d, *J* = 8.3 Hz, 1H, Ar-H), 7.22 (t, *J* = 7.9 Hz, 1H), 7.10 (d, *J* = 7.8 Hz, 1H, Ar-H), 6.96 (dd, *J* = 8.3, 2.0 Hz, 1H, Ar-H), 6.81 (d, *J* = 7.9 Hz, 1H, Ar-H), 6.77-6.75 (m, 2H, Ar-H), 6.67 (d, *J* = 7.9 Hz, 1H, Ar-H), 6.64 (s, 1H, Ar-H), 6.36 (d, *J* = 8.1 Hz, 1H, Ar-H), 6.01 (s, 1H, Ar-H), 5.87 (s, 1H, Ar-H), 5.56 (s, 1H, -OH), 5.01 (s, 1H, -OH), 4.82 (s, 1H, -OH), 3.49 (s, 3H, $-CH_3$), 3.18-3.15 (m, 1H, $-CH_2$-), 3.00-2.82 (m, 4H, $-CH_2$-), 2.64-2.60 (m, 1H, $-CH_2$-), 2.50-2.41 (m, 2H, $-CH_2$-); ^{13}C NMR ($CDCl_3$) δ 154.4, 152.0, 151.7, 149.4, 143.2, 142.7, 138.6, 136.6, 136.3, 135.3, 130.8, 129.8, 125.0, 123.3, 122.0, 120.4, 116.9, 116.7, 113.8, 110.4, 101.7, 55.6, 37.2, 35.2, 35.0, 30.6; MS (ESI) 471 $(M+H)^+$; HRMS calcd for $C_{29}H_{26}O_6Na$ 493.1622, found: 493.1612 $(M+Na)^+$.

*4-(2-(1,3-Dioxan-2-yl)-6-methoxyphenoxy)benzaldehyde (**49**).*

This compound was prepared from **8** and **48** in 65% yield by following GP 1, yellow oil. ^{1}H NMR ($CDCl_3$) δ 9.91 (s, 1 H), 7.37 (s, 1 H), 7.31 (dd, *J* = 7.8 Hz, 11.4 Hz, 1 H), 7.03 (s, 1 H), 6.98 (d, *J* = 8.4 Hz, 2 H), 5.66 (s, 1 H), 4.15-4.13 (m, 2 H), 3.84 (t, *J* = 9.6 Hz, 2 H), 3.74 (s, 3 H), 2.20-2.17 (m, 1 H), 1.37 (d, *J* = 12.6 Hz, 1 H); MS (ESI) 315 $(M+H)^+$.

*Methyl 4-(5-(4-(2-(1,3-dioxan-2-yl)-6-methoxyphenoxy)phenethyl)-2-methoxyphenoxy)benzoate (**50**).*

This compound was prepared from **6** and **49** by following the procedure described for **17**, yield 83%, colorless oil. ^{1}H NMR ($CDCl_3$) δ 8.00 (d, *J* = 6.9 Hz, 2H), 7.35 (d, *J* = 6.8 Hz, 1H), 7.32-7.21 (m, 1H), 7.08-7.03 (m, 3H), 6.98 (d, *J* = 8.6 Hz, 2H), 6.95 (d, *J* = 8.6 Hz, 2H), 6.91-6.87 (m, 3H), 6.78 (d, *J* = 6.3 Hz, 2H), 5.68 (s, 1H), 4.15 (d, *J* = 6.9 Hz, 2H), 3.91 (s, 3H), 3.85-3.82 (m, 2H), 3.78 (s, 3H), 3.72 (s, 3H), 2.85 (s, 4H), 1.35 (d, *J* = 13.1 Hz, 1H), 1.28 (s, 1H); MS (ESI) 571 $(M+H)^+$.

*2-(4-(3-(4-(Hydroxymethyl)phenoxy)-4-methoxyphenethyl)phenoxy)-3-methoxybenzaldehyde (**51**).*

This compound was prepared from **50** by following the procedure described for **22**, yield 86%, colorless oil. ^{1}H NMR ($CDCl_3$) δ 8.00 (d, *J* = 6.9 Hz, 2H), 7.35 (d, *J* = 6.8 Hz, 1H), 7.32-7.21 (m, 1H),

7.08-7.03 (m, 3H), 6.98 (d, *J* = 8.6 Hz, 2H), 6.95 (d, *J* = 8.6 Hz, 2H), 6.91-6.87 (m, 3H), 6.78 (d, *J* = 6.3 Hz, 2H), 5.68 (s, 1H), 4.15 (d, *J* = 6.9 Hz, 2H), 3.91 (s, 3H), 3.85-3.82 (m, 2H), 3.78 (s, 3H), 3.72 (s, 3H), 2.85 (s, 4H), 1.35 (d, *J* = 13.1 Hz, 1H), 1.28 (s, 1H); MS (ESI) 571 $(M+H)^+$.

*Macrocycle (stilbene bridge) (**53**).*

This compound was prepared from **52** in 80% yield by following GP 3, white solid; mp 242-243 ˚C. ^{1}H NMR ($CDCl_3$) δ 7.24 (d, *J* = 8.4 Hz, 2 H), 7.22-7.19 (m, 2 H), 6.97 (d, *J* = 7.2 Hz, 1 H), 6.92 (d, *J* = 8.4 Hz, 2 H), 6.89 (d, *J* = 8.4 Hz, 1 H), 6.84 (d, *J* = 8.4 Hz, 2 H), 6.80 (d, *J* = 8.4 Hz, 1 H), 6.76 (d, *J* = 16.2 Hz, 1 H), 6.69 (d, *J* = 16.2 Hz, 1 H), 6.65 (d, *J* = 8.4 Hz, 2 H), 5.52 (s, 1 H), 3.98 (s, 3 H), 3.91 (s, 3 H), 2.90-2.88 (m, 2 H), 2.78-2.77 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 157.2, 155.6, 152.8, 150.3, 146.8, 141.5, 136.2, 135.1, 134.2, 131.8, 130.3, 129.2, 128.6, 126.8, 125.4, 122.8, 122.1, 117.4, 115.7, 115.3, 111.8, 115.3, 111.8, 111.4, 56.2, 56.2, 34.1, 32.6; MS (ESI) 473 $(M+Na)^+$.

*Macrocyclic derivative (**54**).*

This compound was prepared from **53** in 96% yield by following GP 4, white solid; mp 210-211 ˚C. ^{1}H NMR ($CDCl_3$) δ 7.26 (t, *J* = 7.8 Hz, 1 H), 7.19 (d, *J* = 7.8 Hz, 1 H), 6.90 (d, *J* = 7.8 Hz, 1 H), 6.88-6.83 (m, 4 H), 6.73 (d, *J* = 7.8 Hz, 2 H), 6.68 (d, *J* = 7.8 Hz, 2 H), 6.47 (d, *J* = 7.8 Hz, 2 H), 6.00 (s, 1 H), 3.91 (s, 3 H), 3.68 (s, 3 H), 3.08-3.05 (m, 4 H), 2.78-2.73 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 155.7, 154.0, 152.5, 147.9, 147.0, 141.2, 137.5, 136.1, 134.7, 133.5, 129.5, 129.3, 125.3, 122.7, 121.8, 120.3, 118.1, 114.2, 112.0, 110.0, 56.1, 55.8, 36.8, 36.6, 34.9, 29.1; MS (ESI) 475 $(M+Na)^+$.

*Macrocyclic derivative (**55**).*

This compound was prepared from **54** in 86% yield by following GP 5, white solid; mp 217-218 ˚C. ^{1}H NMR ($CDCl_3$) δ 7.22 (t, *J* = 7.8 Hz, 1 H, Ar-H), 7.15 (d, *J* = 7.8 Hz, 1 H, Ar-H), 6.93 (t, *J* = 8.4 Hz, 2 H, Ar-H), 6.91 (t, *J* = 7.8 Hz, 2 H, Ar-H), 6.80 (d, *J* = 7.8 Hz, 1 H, Ar-H), 6.75 (d, *J* = 8.4 Hz, 2 H, Ar-H), 6.70 (d, *J* = 8.4 Hz, 2 H, Ar-H), 6.55 (d, *J* = 8.4 Hz, 2 H, Ar-H), 5.68 (s, 1 H, Ar-H), 5.59 (s, 1 H, -OH), 4.74 (s, 1 H, -OH), 3.08-3.02 (m, 4 H, $-CH_2-$), 2.77-2.73 (m, 4 H, $-CH_2-$); ^{13}C NMR ($CDCl_3$) δ 154.3, 153.7, 148.7, 144.8, 144.4, 139.5, 138.4, 135.6, 135.0, 133.7, 130.2, 129.7, 126.0, 123.4, 121.6, 120.4, 117.2, 115.2, 114.3, 114.2, 36.8, 36.5, 34.6, 29.5; MS (ESI) 423 $(M-H)^-$; HRMS calcd for $C_{28}H_{24}O_4Na$ 447.1567, found: 447.1560 $(M+Na)^+$.

*Methyl 4-(2-(1,3-dioxan-2-yl)-6-methoxyphenoxy)-3-methoxybenzoate (**57**).*

This compound was prepared from **8** and **56** in 61% yield by following GP 1, colorless oil. ^{1}H NMR ($CDCl_3$) δ 7.66 (d, *J* = 1.7 Hz, 1H), 7.49 (dd, *J* = 8.5, 1.8 Hz, 1H), 7.35 (d, *J* = 7.8 Hz, 1H), 7.27

(t, *J* = 8.4 Hz, 1H), 6.98 (d, *J* = 8.1 Hz, 1H), 6.50 (d, *J* = 8.5 Hz, 1H), 5.71 (s, 1H), 4.11 (dd, *J* = 11.2, 4.6 Hz, 2H), 4.04 (s, 3H), 3.89 (s, 3H), 3.83 (t, *J* = 11.2 Hz, 2H), 3.71 (s, 3H), 2.25-2.12 (m, 1H), 1.35 (d, *J* = 13.5 Hz, 1H); MS (ESI) 375 $(M+H)^+$.

*(4-(2-(1,3-Dioxan-2-yl)-6-methoxyphenoxy)-3-methoxyphenyl)methanol (**58**).*

A solution of **57** (6.92 g, 20.00 mmol) in THF (15 mL) was added dropwise to a stirred suspension of lithium aluminum hydride (1.52 g, 40 mmol) in anhydrous THF (20 mL). The resulting mixture was stirred at room temperature for 2 h and carefully hydrolysed with sat aq NH_4Cl (10 mL). THF was removed in vacuo and the resulting mixture was diluted with DCM (50 mL), washed with saturated aqueous NaCl and dried over sodium sulfate. The solvent was removed in vacuo, and the residue was purified by silica gel column chromatography, eluating with DCM, to provide a colorless oil in 88% yield. ^{1}H NMR ($CDCl_3$) δ 7.35 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.25 (t, *J* = 8.0 Hz, 1H), 7.04 (d, *J* = 1.9 Hz, 1H), 6.98 (dd, *J* = 8.2, 1.5 Hz, 1H), 6.73 (dd, *J* = 8.2, 2.0 Hz, 1H), 6.48 (d, *J* = 8.2 Hz, 1H), 5.76 (s, 1H), 4.64 (d, *J* = 5.5 Hz, 2H), 4.20-4.11 (m, 2H), 4.01 (s, 3H), 3.86 (td, *J* = 12.4, 2.5 Hz, 2H), 3.72 (s, 3H), 2.27-2.15 (m, 1H), 1.38-1.35 (m, 1H) ; MS (ESI) 347$(M+H)^+$.

*(4-(2-(1,3-Dioxan-2-yl)-6-methoxyphenoxy)-3-methoxybenzyl)bromotriphenylphosphorane (**59**).*

This compound was prepared from **58** in 80% yield by following GP 2, white solid; mp 170-171 ˚C. ^{1}H NMR ($CDCl_3$) δ 7.32 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.24 (t, *J* = 8.0 Hz, 1H), 7.00 (d, *J* = 2.0 Hz, 1H), 6.97 (dd, *J* = 8.0, 1.6 Hz, 1H), 6.70 (dd, *J* = 8.2, 2.0 Hz, 1H), 6.46 (d, *J* = 8.0 Hz, 1H), 5.74 (s, 1H), 5.39 (d, *J* = 13.9 Hz, 2H), 4.22-4.18 (m, 2H), 3.99 (s, 3H), 3.84 (t, *J* = 12.4 Hz, 2H), 3.70 (s, 3H), 2.25-2.16 (m, 1H), 1.36-1.30 (m, 1H) ; MS (ESI) 591$(M-Br)^+$.

*Methyl 4-(5-(4-(2-(1,3-dioxan-2-yl)-6-methoxyphenoxy)-3-methoxyphenethyl)-2-methoxy-phenoxy) benzoate (**60**).*

This compound was prepared from **6** and **59** by following the procedure described for **17**, yield 80%, colorless oil. ^{1}H NMR ($CDCl_3$) δ 8.03-7.95 (m, 2H), 7.33 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.23 (t, *J* = 8.0 Hz, 1H), 7.02 (dd, *J* = 8.3, 2.1 Hz, 1H), 6.98-6.93 (m, 2H), 6.92-6.88 (m, 3H), 6.73 (d, *J* = 2.0 Hz, 1H), 6.55 (dd, *J* = 8.2, 2.0 Hz, 1H), 6.42 (d, *J* = 8.2 Hz, 1H), 5.75 (s, 1H), 4.15-4.10 (m, 2H), 3.95 (s, 3H), 3.91 (s, 3H), 3.83 (td, *J* = 12.4, 2.5 Hz, 2H), 3.78 (s, 3H), 3.70 (s, 3H), 2.88-2.82 (m, 4H), 2.24-2.14 (m, 1H), 1.37-1.31 (m, 1H) ; MS (ESI) 601 $(M+H)^+$.

*2-(4-(3-(4-(Hydroxymethyl)phenoxy)-4-methoxyphenethyl)-2-methoxyphenoxy)-3-methoxybenzald ehyde (**61**).*

This compound was prepared from **60** by following the procedure described for **22**, yield 78%, colorless oil. ^{1}H NMR ($CDCl_3$) δ 10.23 (s, 1H), 7.95-7.89 (m, 2H), 7.30 (dd, *J* = 8.4, 2.4 Hz, 1H), 7.20 (t, *J* = 8.4 Hz, 1H), 6.99 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.97-6.90 (m, 2H), 6.89-6.85 (m, 3H), 6.70 (d, *J* = 2.4 Hz, 1H), 6.51 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.40 (d, *J* = 8.2 Hz, 1H), 4.65 (s, 2H), 4.12-4.08 (m, 2H), 3.90 (s, 3H), 3.88 (s, 3H), 3.76 (s, 3H) , 2.86-2.80 (m, 4H); MS (ESI) 515 $(M+H)^+$.

*3-Methoxy-2-(2-methoxy-4-(4-methoxy-3-(4-((triphenyl-4-phosphanyl)methyl)phenoxy)phenethyl) phenoxy)benzaldehyde (**62**)*

This compound was prepared from **61** in 88% yield by following GP 2, white solid; mp 165-166 ˚C. ^{1}H NMR ($CDCl_3$) δ 10.25 (s, 1H), 7.78-7.70 (m, 9H), 7.64-7.62 (m, 6H), 7.51 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.27 (t, *J* = 8.0 Hz, 1H), 7.22 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.02 (dd, *J* = 8.7, 2.5 Hz, 2H), 6.91-6.84 (m, 2H), 6.73-6.67 (m, 4H), 6.51 (dd, *J* = 8.2, 1.8 Hz, 1H), 6.36 (d, *J* = 8.2 Hz, 1H), 5.35 (d, *J* = 13.8 Hz, 2H), 3.88 (s, 3H), 3.79 (s, 3H), 3.74 (s, 3H), 2.78 (s, 4H); MS (ESI) 759$(M-Br)^+$.

*Macrocycle (stilbene bridge) (**63**).*

This compound was prepared from **61** in 69% yield by following GP 2 and GP 3, white solid; mp 198-199 ˚C. ^{1}H NMR ($CDCl_3$) δ 7.42 (s, 1 H), 7.18-7.13 (m, 3 H), 6.92 (dd, *J* = 2.4 Hz, *J* =7.2 Hz, 2 H), 6.89 (s, 1 H), 6.85 (d, *J* = 12.4 Hz, 1 H), 6.80 (s, 1 H), 6.77 (dd, *J* = 2.0 Hz, *J* = 8.4 Hz, 1 H), 6.65 (d, *J* = 13.6 Hz, 1 H), 6.42-6.40 (m, 2 H), 6.30 (d, *J* = 8.8 Hz, 1 H), 5.48 (d, *J* = 2.0 Hz, 1 H), 3.96 (s, 3 H), 3.88 (s, 3 H), 3.86 (s, 3 H), 2.92-2.58 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 155.3, 153.1, 150.5, 148.1, 146.8, 146.5, 142.8, 136.4, 135.6, 135.2, 131.4, 130.0, 128.7, 125.1, 122.0, 120.3, 117.5, 116.2, 115.3, 112.0, 111.8, 111.4, 56.2, 55.8, 53.4, 34.8, 33.3; MS (ESI) 481 $(M+H)^+$.

*Macrocyclic derivative (**64**).*

This compound was prepared from **63** in 92% yield by following GP 4, white solid; mp 138-139 ˚C. ^{1}H NMR ($CDCl_3$) δ 7.24 (t, *J* = 8.0 Hz, 1H), 7.17 (dd, *J* = 7.9, 1.4 Hz, 1H), 6.94-6.86 (m, 3H), 6.82 (dd, *J* = 8.2, 1.7 Hz, 2H), 6.72-6.67 (m, 2H), 6.66 (d, *J* = 1.9 Hz, 1H), 6.05 (dd, *J* = 8.2, 1.9 Hz, 1H), 6.02 (d, *J* = 2.0 Hz, 1H), 5.94 (d, *J* = 8.2 Hz, 1H), 3.92 (s, 3H), 3.91 (s, 3H), 3.66 (s, 3H), 3.18-2.98 (m, 4H), 2.86-2.65 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 154.0, 152.4, 148.0, 147.9, 147.1, 145.3, 141.3, 137.7, 136.2, 134.7, 133.9, 129.6, 125.3, 122.6, 121.7, 120.8, 120.3, 118.0, 112.8, 112.4, 112.0, 110.0, 56.1, 56.0, 55.8, 37.3, 36.4, 34.9, 29.3; MS (ESI) 483 $(M+H)^+$.

*Macrocyclic derivative (**65**).*

This compound was prepared from **64** in 82% yield by following GP 5, white solid; mp 230-231

°C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.22 (t, *J* = 7.9 Hz, 1H, Ar-H), 7.14 (d, *J* = 6.8 Hz, 1H, Ar-H), 6.93-6.83 (m, 4H, Ar-H), 6.78-6.72 (m, 2H, Ar-H), 6.67 (d, *J* = 8.4 Hz, 2H, Ar-H), 6.04 (d, *J* = 8.2 Hz, 1H, Ar-H), 5.97 (dd, *J* = 8.2, 1.9 Hz, 1H, Ar-H), 5.86 (d, *J* = 1.9 Hz, 1H, Ar-H), 5.64 (s, 1H, -OH), 5.56 (s, 1H, -OH), 4.79 (s, 1H, -OH), 3.12-3.04 (m, 2H, $-CH_2-$), 3.01-2.94 (m, 2H, $-CH_2-$), 2.78-2.71 (m, 2H, $-CH_2-$), 2.70-2.62 (m, 2H, $-CH_2-$); ^{13}C NMR ($CDCl_3$) δ 153.8, 148.4, 144.7, 144.5, 144.4, 141.2, 138.9, 138.0, 136.3, 135.6, 133.7, 129.6, 126.5, 123.4, 121.8, 121.2, 120.4, 117.3, 115.8, 115.1, 114.7, 111.7, 37.1, 36.4, 34.7, 29.4; MS (ESI) 441 $(M+H)^+$; HRMS calcd for $C_{28}H_{24}O_5Na$ 463.1516, found: 463.1512 $(M+Na)^+$.

*3-(5-(1,3-Dioxan-2-yl)-2-methoxyphenoxy)benzaldehyde (**68**).*

This compound was prepared from 3-bromobenzaldehyde (**66**) and 5-(1, 3-dioxan-2-yl)-2-methoxyphenol (**67**) in 68% yield by following GP 1, yellow oil. ^{1}H NMR ($CDCl_3$) δ 9.94 (s, 1 H), 7.56 (d, *J* = 7.2 Hz, 1 H), 7.46 (t, *J* = 7.8 Hz, 1 H), 7.37 (s, 1 H), 7.35 (d, *J* = 8.4 Hz, 1 H), 7.22 (s, 2 H), 7.03 (d, *J* = 8.4 Hz, 1 H), 5.46 (s, 1 H), 4.25 (dd, *J* = 4.2 Hz, 10.8 Hz, 2 H), 3.98 (t, *J* = 12.0 Hz, 2 H), 3.82 (s, 3 H), 2.24-2.16 (m, 1 H), 1.44 (d, *J* = 13.8 Hz, 1 H); MS (ESI) 315 $(M+H)^+$.

*Methyl 4-(5-(3-(5-(1,3-dioxan-2-yl)-2-methoxyphenoxy)phenethyl)-2-methoxyphenoxy) benzoate (**69**).*

This compound was prepared from **6** and **68** by following the procedure described for **17**, yield 86%, colorless oil. ^{1}H NMR ($CDCl_3$) δ 7.96 (d, *J* = 6.9 Hz, 2H), 7.16 (d, *J* = 6.8 Hz, 1H), 7.10 (s, 1H), 6.99-6.96 (m, 2H), 6.92 (s, 1H), 6.89-6.76 (m, 3H), 6.79 (d, *J* = 8.6 Hz, 2H), 6.75 (s, 1H), 5.40 (s, 1H), 4.20 (s, 2H), 3.93 (s, 2H), 3.88 (s, 3H), 3.81 (s, 3H), 3.76 (s, 3H), 2.83 (s, 4H), 1.41-1.39 (m, 1H), 1.36-1.26 (m, 1H) ; MS (ESI) 571 $(M+H)^+$.

*Methyl 4-(5-(3-(5-(1,3-dioxan-2-yl)-2-methoxyphenoxy)phenethyl)-2-methoxyphenoxy)-3-methoxy-benzoate (**70**).*

This compound was prepared from **7** and **68** by following the procedure described for **17**, yield 80%, colorless oil. ^{1}H NMR ($CDCl_3$) δ 7.66 (s, 1H), 7.56 (d, *J* = 8.1 Hz, 1H), 7.28 (d, *J* = 7.9 Hz, 1H), 7.17 (d, *J* = 7.0 Hz, 1H), 7.12 (s, 1H), 7.00 (d, *J* = 8.2 Hz, 1H), 6.96 (d, *J* = 7.1 Hz, 1H), 6.92 (d, *J* = 8.1 Hz, 1H), 6.86 (s, 1H), 6.81 (s, 2H), 6.76 (d, *J* = 7.6 Hz, 1H), 6.62 (d, *J* = 8.2 Hz, 1H), 5.42 (s, 1H), 4.23 (d, *J* = 10.6 Hz, 2H), 3.99 (s, 3H), 3.97-3.95 (m, 2H), 3.92 (s, 3H), 3.84 (s, 3H), 3.78 (s, 3H), 2.83 (s, 4H), 2.19-2.17 (m, 1H), 1.43 (d, *J* = 13.5 Hz, 1H); MS (ESI) 601 $(M+H)^+$.

*Macrocycle (stilbene bridge) (**73**).*

This compound was prepared from **69** in 71% yield by following GP 2 and GP 3, white solid; mp 161-162 ˚C. ^{1}H NMR ($CDCl_3$) δ 7.19 (d, *J* = 8.4 Hz, 2 H), 7.11-7.07 (m, 3 H), 6.99 (d, *J* = 8.4 Hz, 1 H), 6.96 (d, *J* = 8.4 Hz, 1 H), 6.75 (d, *J* = 7.8 Hz, 2 H), 6.64 (d, *J* = 7.8 Hz, 2 H), 6.55 (d, *J* = 8.4 Hz, 2 H), 6.47 (d, *J* = 16.0 Hz, 1 H), 6.44 (d, *J* = 16.0 Hz, 1 H), 6.13 (s, 1 H), 3.82 (s, 3 H), 3.81 (s, 3 H), 2.87-2.77 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 157.6, 156.7, 151.3, 150.2, 142.5, 142.2, 134.6, 133.7, 130.4, 130.2, 130.0, 129.9, 128.7, 127.7, 127.2, 125.7, 124.5, 123.1, 115.4, 114.8, 112.9, 112.4, 56.0, 55.9, 37.9, 37.4; MS (ESI) 473 $(M+Na)^+$.

*Macrocycle (stilbene bridge) (**74**).*

This compound was prepared from **70** in 74% yield by following GP 2 and GP 3, white solid; mp 96-97 ˚C. ^{1}H NMR ($CDCl_3$) δ 7.11-7.05 (m, 2 H), 7.00 (s, 1 H), 6.98 (d, *J* = 14.4 Hz, 1 H), 6.96 (d, *J* = 14.4 Hz, 1 H), 6.93 (d, *J* = 7.8 Hz, 1 H), 6.87 (d, *J* = 7.8 Hz, 2 H), 6.75 (s, 1 H), 6.43 (s, 3 H), 6.10 (d, *J* = 7.2 Hz, 1 H), 5.57 (s, 1 H), 3.94 (s, 3 H), 3.92 (s, 3 H), 3.71 (s, 3 H), 2.78 (s, 4 H); ^{13}C NMR ($CDCl_3$) δ 159.0, 151.7, 151.6, 147.2, 146.6, 144.8, 142.6, 142.2, 134.3, 133.4, 129.9, 128.5, 128.3, 128.2, 127.4, 124.4, 122.3, 121.9, 121.4, 120.5, 118.3, 116.3, 113.3, 113.1, 112.2, 111.9, 56.1, 56.0, 55.7, 38.4, 37.6; MS (ESI) 503 $(M+Na)^+$.

*Macrocyclic derivative (**75**).*

This compound was prepared from **73** in 92% yield by following GP 4, white solid; mp 175-176 ˚C. ^{1}H NMR ($CDCl_3$) δ 7.04-6.95 (m, 6 H), 6.84 (d, *J* = 7.8 Hz, 2 H), 6.60 (d, *J* = 7.8 Hz, 2 H), 6.40 (d, *J* = 8.4 Hz, 1 H), 6.24 (d, *J* = 7.2 Hz, 1 H), 6.18 (s, 1 H), 5.92 (s, 1 H), 3.90 (s, 3 H), 3.89 (s, 3 H), 2.87-2.81 (m, 8 H); ^{13}C NMR ($CDCl_3$) δ 158.7, 154.5, 150.4, 148.3, 145.6, 144.3, 142.5, 136.1, 134.8, 133.8, 130.4, 128.4, 125.3, 123.9, 123.1, 122.9, 119.3, 118.9, 118.0, 113.8, 112.5, 112.4, 56.1, 38.1, 37.2, 37.1, 37.0; MS (ESI) 475 $(M+Na)^+$.

*Macrocyclic derivative (**76**).*

This compound was prepared from **74** in 96% yield by following GP 4, white solid; mp 207-208 ˚C. ^{1}H NMR ($CDCl_3$) δ 7.02 (d, *J* = 8.4 Hz, 1 H), 7.00-6.97 (m, 2 H), 6.93-6.97 (m, 3 H), 6.68 (s, 1 H), 6.44 (d, *J* = 7.8 Hz, 1 H), 6.39 (d, *J* = 7.8 Hz, 1 H), 6.27 (d, *J* = 7.8 Hz, 1 H), 6.24 (d, *J* = 7.2 Hz, 1 H), 6.22 (s, 1 H), 5.74 (s, 1 H), 3.91 (s, 3 H), 3.89 (s, 3 H), 3.75 (s, 3 H), 2.91-2.79 (m, 8 H); ^{13}C NMR ($CDCl_3$) δ 158.4, 151.2, 150.2, 147.8, 146.1, 144.8, 142.7, 142.4, 137.6, 134.7, 133.7, 128.4, 124.9, 124.1, 122.6, 122.3, 121.9, 120.3, 118.2, 117.5, 114.4, 112.7, 112.5, 112.1, 56.1, 56.0, 55.8, 38.3, 37.5, 37.4, 36.6; MS (ESI) 505 $(M+Na)^+$.

*Macrocyclic derivative (**77**).*

This compound was prepared from **75** in 79% yield by following GP 5, white solid; mp 162-163 ˚C. ^{1}H NMR ($CDCl_3$) δ 7.05-6.99 (m, 4 H, Ar-H), 6.96 (d, *J* = 7.8 Hz, 1 H, Ar-H), 6.90 (d, *J* = 7.8 Hz, 1 H, Ar-H), 6.87 (d, *J* = 7.8 Hz, 2 H, Ar-H), 6.61 (d, *J* = 8.4 Hz, 2 H, Ar-H), 6.47 (d, *J* = 7.8 Hz, 1 H, Ar-H), 6.28 (d, *J* = 7.2 Hz, 1 H, Ar-H), 6.11 (s, 1 H, Ar-H), 5.79 (s, 1 H, Ar-H), 5.52 (s, 1 H, -OH), 5.50 (s, 1 H, -OH), 2.85 (s, 4 H, -CH_2-), 2.81 (s, 4 H, -CH_2-); ^{13}C NMR ($CDCl_3$) δ 158.0, 153.7, 146.6, 144.6, 143.6, 143.0, 142.6, 137.1, 134.2, 133.0, 130.6, 128.6, 125.8, 125.0, 123.4, 121.2, 119.1, 118.5, 117.6, 115.7, 115.5, 114.2, 38.1, 37.4, 37.1; MS (ESI) 423 $(M-H)^-$; HRMS calcd for $C_{28}H_{24}O_4Na$ 447.1567, found: 447.1560 $(M+Na)^+$.

*Macrocyclic derivative (**78**).*

This compound was prepared from **76** in 82% yield by following GP 5, white solid; mp 212-213 ˚C. ^{1}H NMR ($CDCl_3$) δ 7.03 (t, *J* = 7.2 Hz, 2 H, Ar-H), 7.01 (d, *J* = 7.8 Hz, 1 H, Ar-H), 6.96 (d, *J* = 7.8 Hz, 1 H, Ar-H), 6.94 (t, *J* = 7.2 Hz, 2 H, Ar-H), 6.78 (s, 1 H, Ar-H), 6.47 (d, *J* = 7.8 Hz, 1 H, Ar-H), 6.30 (d, *J* = 7.8 Hz, 1 H, Ar-H), 6.26-6.23 (m, 2 H, Ar-H), 6.12 (s, 1 H, Ar-H), 5.76 (s, 1 H, Ar-H), 5.50 (s, 2 H, -OH), 5.31 (s, 1 H, -OH), 2.86-2.77 (m, 8 H, -CH_2-); ^{13}C NMR ($CDCl_3$) δ 157.9, 147.3, 146.5, 144.5, 142.9, 142.8, 142.6, 140.2, 139.0, 134.2, 133.4, 128.6, 125.7, 124.9, 124.2, 122.0, 120.9, 118.7, 118.5, 117.2, 116.5, 116.0, 115.6, 114.4, 38.1, 37.5, 37.3, 36.7; MS (EI) 439 $(M-H)^-$; HRMS calcd for $C_{28}H_{24}O_5Na$ 463.1516, found: 463.1508 $(M+Na)^+$.

*Methyl 4-(4-(1,3-dioxan-2-yl)-2-methoxyphenoxy)benzoate (**79**).*

This compound was prepared from **1** and **67** in 75% yield by following GP 1, colorless oil. ^{1}H NMR ($CDCl_3$) δ 7.96 (d, *J* = 7.3 Hz, 2H), 7.23 (s, 1H), 7.09 (d, *J* = 11.3 Hz, 2H), 6.90 (d, *J* = 7.6 Hz, 2H), 5.54 (s, 1H), 4.39-4.26 (m, 2H), 4.03 (t, *J* = 11.5 Hz, 2H), 3.89 (s, 3H), 3.83 (s, 3H), 2.23-2.23 (m, 1H), 1.49 (d, *J* = 13.4 Hz, 1H); MS (ESI) 345 $(M+H)^+$.

*Methyl 4-(4-formyl-2-methoxyphenoxy)benzoate (**80**).*

Compound **79** (10 g, 29 mmol) was added into a solution of ethanol (100 mL) and 10 % aq HCl (10 mL). The resulting mixture was then stirred at room temperature for 2 h. Sat aq sodium bicarbonate was added and the ethanol was removed in vacuo. The resulting mixture was extracted with DCM, washed with saturated aqueous NaCl and dried over sodium sulfate. The solution was concentrated, and the residue was purified by silica gel column chromatography, eluating with dichloromethane, to provide a colorless oil in 79% yield. ^{1}H NMR ($CDCl_3$) δ 9.96 (s, 1H), 8.11-7.96 (m, 2H), 7.57 (d, *J* =

1.8 Hz, 1H), 7.48 (dd, *J* = 8.1, 1.9 Hz, 1H), 7.13 (d, *J* = 8.1 Hz, 1H), 7.04-6.98 (m, 2H), 3.92 (s, 3H), 3.92 (s, 3H); MS (ESI) 287$(M+H)^+$.

*Methyl 4-(4-((bromotriphenylphosphoranyl)methyl)-2-methoxyphenoxy)benzoate (**82**).*

This compound was prepared from **80** by following the procedure described for **6**, yield 76%, white solid; mp 196-197 ˚C. ^{1}H NMR ($CDCl_3$) δ 7.93 (d, *J* = 8.7 Hz, 2H), 7.80-7.69 (m, 6 H), 7.70-7.61 (m, 9H), 7.06 (s, 1H), 6.82 (s, 1 H), 6.81 (d, *J* = 8.7 Hz, 2H), 6.67 (d, *J* = 6.9 Hz, 1H), 5.37 (d, *J* = 13.8 Hz, 2H), 3.86 (s, 3H), 3.44 (s, 3H) ; MS (ESI) 533 $(M-Br)^+$.

*3-(2-(1,3-Dioxan-2-yl)-6-methoxyphenoxy)benzaldehyde (**83**).*

This compound was prepared from 2-(1,3-dioxan-2-yl)-6-methoxy-phenol (**66**) and 3-bromo-benzaldehyde (**8**) in 79% yield by following GP 1, yellow solid; mp 105-106 ˚C. ^{1}H NMR ($CDCl_3$) δ 9.95 (s, 1 H), 7.55 (d, *J* = 7.2 Hz, 1 H), 7.43 (t, *J* = 7.8 Hz, 1 H), 7.37 (d, *J* = 8.4 Hz, 2 H), 7.30 (t, *J* = 7.8 Hz, 1 H), 7.15 (d, *J* = 5.4 Hz, 1 H), 7.02 (d, *J* = 7.8 Hz, 1 H), 5.69 (s, 1 H), 4.14 (d, *J* = 7.8 Hz, 2 H), 3.85 (t, *J* = 12.0 Hz, 2 H), 3.74 (s, 3 H), 2.21-2.16 (m, 1 H), 1.37 (d, *J* = 13.2 Hz, 1 H); MS (ESI) 315 $(M+H)^+$.

*Methyl 4-(4-(3-(2-(1,3-dioxan-2-yl)-6-methoxyphenoxy)phenethyl)-2-methoxyphenoxy)benzoate (**84**).*

This compound was prepared from **82** and **83** by following the procedure described for **17**, yield 83%, colorless oil. ^{1}H NMR ($CDCl_3$) δ 8.02-7.95 (m, 2H), 7.36 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.26 (t, *J* = 8.0 Hz, 1H), 7.15 (t, *J* = 7.8 Hz, 1H), 7.02 (dd, *J* = 8.3, 2.1 Hz, 1H), 6.99 (dd, *J* = 8.2, 1.5 Hz, 1H), 6.94 (d, *J* = 8.4 Hz, 1H), 6.91-6.87 (m, 2H), 6.86 (d, *J* = 2.1 Hz, 1H), 6.77 (d, *J* = 7.6 Hz, 1H), 6.76-6.72 (m, 1H), 6.69 (dd, *J* = 8.1, 2.5 Hz, 1H), 5.68 (s, 1H), 4.20-4.11 (m, 2H), 3.91 (s, 3H), 3.83 (td, *J* = 12.4, 2.5 Hz, 2H), 3.78 (s, 3H), 3.70 (s, 3H), 2.85 (s, 4H), 2.24-2.16 (m, 1H), 1.36-1.34 (m, 1H) ; MS (ESI) 571 $(M+H)^+$.

*2-(3-(4-(4-((Bromotriphenylphosphoranyl)methyl)phenoxy)-3-methoxyphenethyl)phenoxy)-3-methoxybenzaldehyde (**86**).*

This compound was prepared from **85** in 88% yield by following GP 2, white solid; mp 199-200 ˚C. ^{1}H NMR ($CDCl_3$) δ 10.22 (s, 1H), 7.79-7.74 (m, 9H), 7.66-7.63 (m, 6H), 7.53 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.32 (td, *J* = 8.0, 0.7 Hz, 1H), 7.28 (dd, *J* = 8.1, 1.7 Hz, 1H), 7.17 – 7.10 (m, 1H), 7.04 (dd, *J* = 8.8, 2.6 Hz, 2H), 6.86 (d, *J* = 1.5 Hz, 1H), 6.81 (d, *J* = 7.6 Hz, 1H), 6.71 (s, 1H), 6.68 (d, *J* = 8.1 Hz, 2H), 6.64-6.60 (m, 2H), 5.40 (d, *J* = 13.9 Hz, 2H), 3.80 (s, 3H), 3.77 (s, 3H), 2.83-2.75 (m, 4H); MS (ESI)

729 $(M\text{-}Br)^+$.

*Macrocyclic derivative (**87**).*

This compound was prepared from **86** in 75% yield by following GP 3 and GP 4, white solid; mp 143-144 ˚C. ^{1}H NMR ($CDCl_3$) δ 7.23 (t, *J* = 8.0 Hz, 1H), 7.11 (dd, *J* = 7.9, 1.4 Hz, 1H), 6.95 (d, *J* = 8.5 Hz, 2H), 6.92 (t, *J* = 8.0 Hz, 1H), 6.88-6.85 (m, 2H), 6.80 (dd, *J* = 8.2, 2.0 Hz, 1H), 6.67-6.64 (m, 1H), 6.63 (d, *J* = 8.4 Hz, 2H), 6.45 (dd, *J* = 8.2, 2.0 Hz, 1H), 6.26 (d, *J* = 7.5 Hz, 1H), 5.51 (d, *J* = 2.0 Hz, 1H), 3.93 (s, 3H), 3.69 (s, 3H), 3.10-3.02 (m, 4H), 2.88-2.82 (m, 2H), 2.81-2.74 (m, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 158.0, 152.9, 152.4, 148.2, 146.8, 141.9, 141.1, 138.7, 136.7, 133.5, 129.5, 127.9, 125.3, 122.5, 122.4, 121.7, 121.4, 116.3, 115.3, 112.0, 111.6, 110.1, 56.0, 55.7, 36.5, 35.9, 34.8, 30.1; MS (ESI) 453 $(M+H)^+$.

*Macrocyclic derivative (**88**).*

This compound was prepared from **87** in 73% yield by following GP 5, white solid; mp 156-157 ˚C. ^{1}H NMR ($CDCl_3$) δ 7.18 (t, *J* = 7.9 Hz, 1H, Ar-H), 7.05 (dd, *J* = 7.8, 1.5 Hz, 1H, Ar-H), 7.01 (t, *J* = 7.9 Hz, 1H, Ar-H), 6.97 (d, *J* = 8.5 Hz, 2H, Ar-H), 6.91 (d, *J* = 7.8 Hz, 1H, Ar-H), 6.90 (dd, *J* = 7.5, 2.1 Hz, 1H, Ar-H), 6.77 (dd, *J* = 8.1, 2.0 Hz, 1H, Ar-H), 6.68-6.64 (m, 1H, Ar-H), 6.63 (d, *J* = 8.3 Hz, 2H, Ar-H), 6.57 (dd, *J* = 8.2, 2.0 Hz, 1H, Ar-H), 6.41 (d, *J* = 7.5 Hz, 1H, Ar-H), 5.55 (d, *J* = 2.0 Hz, 1H, Ar-H), 5.52 (s, 1H, -OH), 4.87 (s, 1H, -OH), 3.08-3.00 (m, 4H, $-CH_2-$), 2.89-2.79 (m, 4H, $-CH_2-$); ^{13}C NMR (151 MHz, $CDCl_3$) δ 156.7, 152.8, 148.7, 146.1, 143.4, 143.1, 139.6, 139.1, 136.1, 132.7, 129.7, 128.9, 126.1, 123.4, 122.4, 122.0, 121.3, 115.6, 115.5, 114.9, 114.3, 112.0, 35.8, 35.3, 34.0, 30.3; MS (ESI) 425 $(M+H)^+$; HRMS calcd for $C_{28}H_{24}O_4Na$ 447.1567, found: 447.1560 $(M+Na)^+$.

*Methyl 4-(2-(1,3-dioxan-2-yl)-6-methoxyphenoxy)benzoate (**89**).*

This compound was prepared from **1** and **8** in 76% yield by following GP 1, colorless oil. ^{1}H NMR ($CDCl_3$) δ 7.97 (d, *J* = 8.9 Hz, 2H), 7.36 (d, *J* = 7.9 Hz, 1H), 7.30 (d, *J* = 8.1 Hz, 1H), 7.01 (d, *J* = 8.2 Hz, 1H), 6.88 (d, *J* = 8.9 Hz, 2H), 5.65 (s, 1H), 4.15 (d, *J* = 4.2 Hz, 1H), 4.13 (d, *J* = 4.8 Hz, 1H), 3.90 (s, 3H), 3.83 (t, *J* = 11.5 Hz, 2H), 3.73 (s, 3H), 2.26-2.14 (m, 1H), 1.36 (d, *J* = 13.6 Hz, 1H); MS (ESI) 345 $(M+H)^+$.

*Methyl 4-(2-(hydroxymethyl)-6-methoxyphenoxy)benzoate (**90**).*

Compound **89** (10 g, 29 mmol) was added into a solution of ethanol (100 mL) and 10 % aq HCl (10 mL). The resulting mixture was then stirred at room temperature for 2 h. Sat aq sodium bicarbonate was added and the ethanol was removed in vacuo. The resulting mixture was extracted with DCM,

washed with saturated aqueous NaCl and dried over sodium sulfate. The solution was concentrated to yield the crude oil. This oil was dissolved in THF, and sodium borohydride (0.45 g, 12.05 mmol) was added to the reaction mixture over 15 min at 0 ˚C. The reaction mixture was then stirred at room temperature for 3 h. The THF was evaporated in vacuo, and the resulting mixture was extracted with DCM (15 mL), washed with sat aq NaCl, and dried over sodium sulfate. The solution was concentrated, and the residue was purified by silica gel column chromatography, eluating with DCM, to provide a colorless oil in 61% yield. ^{1}H NMR ($CDCl_3$) δ 7.98 (d, *J* = 8.9 Hz, 2H), 7.27 (t, *J* = 7.8 Hz, 1H), 7.15 (d, *J* = 7.6 Hz, 1H), 7.00 (d, *J* = 8.0 Hz, 1H), 6.87 (d, *J* = 8.9 Hz, 2H), 4.64 (d, *J* = 6.3 Hz, 2H), 3.90 (s, 3H), 3.76 (s, 3H); MS (ESI) 289 $(M+H)^+$.

*Methyl 4-(2-((bromotriphenylphosphoranyl)methyl)-6-methoxyphenoxy)benzoate (**91**).*

This compound was prepared from **90** by following the GP 2, yield 79%, white solid; mp 156-157 ˚C. ^{1}H NMR ($CDCl_3$) δ 7.81 (d, J = 8.9 Hz, 2H), 7.75-7.71 (m, 3H), 7.61-7.54 (m, 12H), 7.02 (t, J = 8.0 Hz, 1H), 6.98 (d, J = 8.1 Hz, 1H), 6.88 (d, J = 8.1 Hz, 1H), 6.43 (d, J = 8.9 Hz, 2H), 4.95 (d, J = 14.3 Hz, 2H), 3.80 (s, 3H), 3.53 (s, 3H); MS (ESI) 533 (M-Br)+.

*(4-(2-(3-(2-(1,3-Dioxan-2-yl)-6-methoxyphenoxy)phenethyl)-6-methoxyphenoxy)phenyl)methanol (**92**).*

This compound was prepared from **83** and **91** by following the procedure described for **17**, yield 88%, colorless oil. ^{1}H NMR ($CDCl_3$) δ 7.37 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.28 (t, *J* = 8.0 Hz, 1H), 7.25-7.20 (m, 2H), 7.15 (t, *J* = 7.9 Hz, 1H), 7.11 (t, *J* = 7.8 Hz, 1H), 7.00 (dd, *J* = 8.2, 1.5 Hz, 1H), 6.89 (dd, *J* = 8.3, 1.3 Hz, 1H), 6.87 (dd, *J* = 7.7, 1.3 Hz, 1H), 6.81-6.78 (m, 2H), 6.74 (d, *J* = 7.6 Hz, 1H), 6.65 (ddd, *J* = 8.2, 2.5, 0.7 Hz, 1H), 6.63-6.60 (m, 1H), 5.66 (s, 1H), 4.61 (s, 2H), 4.16-4.13 (m, 2H), 3.86-3.80 (m, 2H), 3.78 (s, 3H), 3.70 (s, 3H), 2.82-2.72 (m, 4H), 2.26-2.14 (m, 1H), 1.39-1.32 (m, 1H); MS (ESI) 543 $(M+H)^+$.

*2-(3-(2-(4-(Hydroxymethyl)phenoxy)-3-methoxyphenethyl)phenoxy)-3-methoxybenzaldehyde (**93**).*

This compound was prepared from **92** by following the procedure described for **22**, yield 72%, colorless oil. ^{1}H NMR ($CDCl_3$) δ 10.21 (s, 1H), 7.58 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.34 (td, *J* = 8.0, 0.8 Hz, 1H), 7.28-7.21 (m, 3H), 7.15 (d, *J* = 8.0 Hz, 1H), 7.13 (d, *J* = 8.1 Hz, 1H), 6.89 (dd, *J* = 8.3, 1.3 Hz, 1H), 6.82 (dd, *J* = 7.7, 1.4 Hz, 1H), 6.79 (d, *J* = 7.6 Hz, 1H), 6.78-6.76 (m, 2H), 6.65 (ddd, *J* = 8.2, 2.6, 0.8 Hz, 1H), 6.60-6.56 (m, 1H), 4.64 (s, 2H), 3.77 (s, 3H), 3.77 (s, 3H), 2.77 (s, 4H); MS (ESI) 485 $(M+H)^+$.

*2-(3-(2-(4-((bromotriphenylphosphoranyl)methyl)phenoxy)-3-methoxyphenethyl)phenoxy)-3-meth oxybenzaldehyde (**94**).*

This compound was prepared from **93** in 82% yield by following GP 2, white solid; mp 143-144 ˚C. ^{1}H NMR ($CDCl_3$) δ 10.17 (s, 1H), 7.78-7.68 (m, 9H), 7.66-7.56 (m, 6H), 7.52 (dd, *J* = 7.5, 1.8 Hz, 1H), 7.34-7.32 (m, 2H), 7.14 (t, *J* = 7.9 Hz, 1H), 7.10 (t, *J* = 7.6 Hz, 1H),7.10 (t, *J* = 8.0 Hz, 1H), 6.99 (d, *J* = 6.3 Hz, 2H), 6.85 (dd, *J* = 8.3, 1.2 Hz, 1H), 6.78-6.75 (m, 2H), 6.64 (dd, *J* = 7.8, 2.4 Hz, 1H), 6.60-6.56 (m, 3H), 5.32 (d, *J* = 13.6 Hz, 2H), 3.75 (s, 3H), 3.74 (s, 3H), 2.73 (s, 4H); MS (ESI) 729 $(M\text{-}Br)^{+}$.

*Macrocyclic derivative (**95**).*

This compound was prepared from **94** in 77% yield by following GP 3 and GP 4, white solid; mp 102-103 ˚C.^{1}H NMR ($CDCl_3$) δ 7.17 (td, *J* = 7.9, 3.4 Hz, 2H), 7.13 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.08 (t, *J* = 8.6 Hz, 1H), 7.01 (dd, *J* = 7.8, 1.3 Hz, 1H), 6.87 (dd, *J* = 8.0, 1.5 Hz, 1H), 6.85 (dd, *J* = 8.0, 1.5 Hz, 1H), 6.75 (dd, *J* = 8.0, 1.5 Hz, 1H), 6.73 (d, *J* = 8.6 Hz, 2H), 6.62 (d, *J* = 7.5 Hz, 1H), 6.38-6.32 (m, 2H), 5.44-5.36 (m, 1H), 3.79 (s, 3H), 3.61 (s, 3H), 3.06-3.03 (m, 2H), 3.02-2.94 (m, 2H), 2.80 (t, *J* = 7.5 Hz, 2H), 2.62 (t, *J* = 7.5 Hz, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 158.2, 156.3, 153.3, 152.3, 142.4, 142.0, 141.4, 136.1, 135.3, 134.1, 129.6, 128.3, 125.3, 124.8, 121.8, 121.5, 120.9, 114.5, 114.1, 113.8, 110.2, 109.8, 55.9, 55.8, 35.2, 34.6, 29.3, 29.2; MS (ESI) 475 $(M+Na)^{+}$.

*Macrocyclic derivative (**96**).*

This compound was prepared from **95** in 79% yield by following GP 5, white solid; mp 190-191 ˚C. ^{1}H NMR ($CDCl_3$) δ 7.15 (dd, *J* = 16.2, 8.2 Hz, 2H, Ar-H), 7.12-7.09 (m, 2H, Ar-H), 6.96 (dd, *J* = 8.1, 1.9 Hz, 1H, Ar-H), 6.91 (d, *J* = 8.0 Hz, 2H, Ar-H), 6.82 (dd, *J* = 7.9, 1.6 Hz, 1H, Ar-H), 6.80-6.74 (m, 2H, Ar-H), 6.70 (d, *J* = 7.6 Hz, 1H, Ar-H), 6.50-6.42 (m, 2H, Ar-H), 5.52 (s, 1H, Ar-H), 3.01 (s, 4H, $-CH_2-$), 2.70 (t, *J* = 7.6 Hz, 2H, $-CH_2-$), 2.60 (t, *J* = 7.6 Hz, 2H, $-CH_2-$); ^{13}C NMR (151 MHz, $CDCl_3$) δ 156.9, 155.7, 149.5, 148.7, 143.6, 140.3, 139.9, 135.5, 134.7, 134.5, 129.9, 129.3, 125.8, 125.7, 122.3, 121.3, 120.9, 115.2, 114.3, 114.1, 113.5, 113.4, 34.9, 33.9, 29.3, 29.2; MS (ESI) 425 $(M+H)^{+}$; HRMS calcd for $C_{28}H_{24}O_4Na$ 447.1567, found: 447.1560 $(M+Na)^{+}$.

*3-(4-(1,3-Dioxan-2-yl)-2-methoxyphenoxy)benzaldehyde (**99**).*

This compound was prepared from **66** and **97** in 73% yield by following GP 1, colorless oil. ^{1}H NMR ($CDCl_3$) δ 9.93 (s, 1H), 7.56 (d, *J* = 7.5 Hz, 1H), 7.45 (t, *J* = 7.8 Hz, 1H), 7.35 (s, 1H), 7.23 (s, 1H), 7.21 (dd, *J* = 8.2, 1.7 Hz, 1H), 7.10 (dd, *J* = 8.1, 1.3 Hz, 1H), 7.05 (d, *J* = 8.1 Hz, 1H), 5.54 (s, 1H),

4.32 (dd, *J* = 10.8, 4.9 Hz, 2H), 4.04 (t, *J* = 11.1 Hz, 2H), 3.85 (s, 3H), 2.31-2.23 (m, 1H), 1.50 (d, *J* = 13.6 Hz, 1H); MS (ESI) 315 $(M+H)^+$.

*3-(4-(1,3-Dioxan-2-yl)-2,6-dimethoxyphenoxy)benzaldehyde (**100**).*

This compound was prepared from **66** and **98** in 54% yield by following GP 1, colorless oil. ^{1}H NMR ($CDCl_3$) δ 9.90 (s, 1H), 7.50 (d, *J* = 7.6 Hz, 1H), 7.40 (t, *J* = 7.8 Hz, 1H), 7.19 (dd, *J* = 8.2, 1.8 Hz, 1H), 6.85 (s, 2H), 5.52 (s, 1H), 4.31 (dd, *J* = 11.0, 4.8 Hz, 2H), 4.03 (t, *J* = 11.2 Hz, 2H), 3.80 (s, 6H), 2.27 (dt, *J* = 17.7, 10.1 Hz, 1H), 1.49 (d, *J* = 13.6 Hz, 1H); MS (ESI) 345 $(M+H)^+$.

*(4-(5-(3-(4-(1,3-Dioxan-2-yl)-2-methoxyphenoxy)phenethyl)-2-methoxyphenoxy)phenyl)methanol (**101**).*

This compound was prepared from **6** and **99** by following the procedure described for **22**, yield 67%, colorless oil. ^{1}H NMR ($CDCl_3$) δ 7.28 (d, *J* = 8.1 Hz, 2H), 7.18 (s, 1H), 7.16 (t, *J* = 8.1 Hz, 1H), 7.00 (dd, *J* = 8.1, 1.4 Hz, 1H), 6.91 (s, 2H), 6.90-6.85 (m, 3H), 6.80 (d, *J* = 7.6 Hz, 1H), 6.77 (d, *J* = 8.0 Hz, 1H), 6.74 (s, 2H), 5.51 (s, 1H), 4.64 (d, *J* = 5.8 Hz, 2H), 4.31 (dd, *J* = 11.1, 4.5 Hz, 2H), 4.02 (t, *J* = 12.2 Hz, 2H), 3.86 (s, 3H), 3.82 (s, 3H), 2.80 (s, 4H), 2.37-2.19 (m, 1H), 1.50 (s, 1H); MS (ESI) 543 $(M+H)^+$.

*(4-(5-(3-(4-(1,3-Dioxan-2-yl)-2,6-dimethoxyphenoxy)phenethyl)-2-methoxyphenoxy)phenyl)methanol (**102**).*

This compound was prepared from **6** and **100** by following the procedure described for **22**, yield 59%, colorless oil. ^{1}H NMR ($CDCl_3$) δ7.28 (d, *J* = 8.1 Hz, 2H), 7.10 (t, *J* = 7.8 Hz, 1H), 6.93 (dd, *J* = 16.1, 8.4 Hz, 2H), 6.89 (d, *J* = 8.5 Hz, 2H), 6.83 (s, 2H), 6.77-6.71 (m, 3H), 6.67 (d, *J* = 6.6 Hz, 1H), 5.52 (s, 1H), 4.64 (s, 2H), 4.33 (dd, *J* = 11.0, 4.6 Hz, 2H), 4.04 (t, *J* = 11.3 Hz, 2H), 3.82 (s, 3H), 3.78 (s, 6H), 2.79 (s, 4H), 2.36-2.23 (m, 1H), 1.50 (d, *J* = 13.5 Hz, 1H) ; MS (ESI) 573 $(M+H)^+$.

*4-(3-(3-(4-((Bromotriphenylphosphoranyl)methyl)phenoxy)-4-methoxyphenethyl)phenoxy)-3-methoxybenzaldehyde (**103**).*

This compound was prepared from **101** in 86% yield by following GP 2, white solid; mp 186-187 ˚C. ^{1}H NMR ($CDCl_3$) δ 9.90 (s, 1H), 7.77-7.67 (m, 6H), 7.66-7.63 (m, 9H), 7.55 (t, *J* = 7.6, 1H), 7.51 (s, 1H), 7.48-7.46 (m, 2H), 7.37 (d, *J* = 8.4 Hz, 1H), 7.25 (t, *J* = 7.6 Hz, 1H), 6.95 (d, *J* = 8.4 Hz, 1H), 6.89-6.84 (m, 3H), 6.80 (d, *J* = 8.4 Hz, 2H), 6.68-6.66 (m, 2H), 5.27 (d, *J* = 13.8 Hz, 2H), 3.95 (s, 3H), 3.77 (s, 3H), 2.85-2.80 (m, 4H); MS (ESI) 729 $(M-Br)^+$.

4-(3-(3-(4-((Bromotriphenylphosphoranyl)methyl)phenoxy)-4-methoxyphenethyl)phenoxy)-3,5-di

*methoxybenzaldehyde (**104**).*

This compound was prepared from **102** in 89% yield by following GP 2, white solid; mp 178-179 ˚C. ^{1}H NMR ($CDCl_3$) δ 9.98 (s, 1H), 7.88-7.72 (m, 9H), 7.67-7.65 (m, 6H), 7.24 (s, 2H), 7.12 (t, *J* = 7.6 Hz, 1H), 7.04 (dd, *J* = 8.4, 2.1 Hz, 2H), 6.92 (dd, *J* = 8.3, 2.0 Hz, 1H), 6.88 (d, *J* = 8.4 Hz, 1H), 6.80 (d, *J* = 7.6 Hz, 1H), 6.75-6.66 (m, 4H), 6.63 (dd, *J* = 7.9, 2.2 Hz, 1H), 5.42 (d, *J* = 13.8 Hz, 2H), 3.85 (s, 6H), 3.79 (s, 3H), 2.85-2.77 (m, 4H); MS (ESI) 759 $(M\text{-}Br)^{+}$.

*Macrocycle (stilbene bridge) (**105**).*

This compound was prepared from **103** in 81% yield by following GP 3, white solid; mp 163-164 ˚C. ^{1}H NMR ($CDCl_3$) δ 7.15 (d, *J* = 8.4 Hz, 2 H), 7.08-7.05 (m, 3 H), 6.99 (d, *J* = 8.4 Hz, 1 H), 6.92 (d, *J* = 7.8 Hz, 1 H), 6.87-6.83 (m, 4 H), 6.75-6.74 (m, 2 H), 6.64 (d, *J* = 2.4 Hz, 1 H), 6.36-6.35 (m, 1 H), 3.94 (s, 3 H), 3.66 (s, 3 H), 2.62-2.56 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 157.7, 153.9, 150.6, 147.3, 146.6, 143.5, 141.4, 135.1, 134.8, 133.1, 130.8, 130.0, 129.2, 121.6, 121.3, 120.8, 120.3, 119.3, 116.0, 114.5, 113.4, 111.9, 55.6, 55.1, 40.7, 39.4; MS (ESI) 451 $(M+H)^{+}$.

*Macrocycle (stilbene bridge) (**106**).*

This compound was prepared from **104** in 86% yield by following GP 3, white solid; mp 137-138 ˚C. ^{1}H NMR ($CDCl_3$) δ 7.27 (d, *J* = 7.8 Hz, 1H), 7.16 (d, *J* = 8.6 Hz, 2H), 7.11 (dd, *J* = 8.2, 2.5 Hz, 1H), 7.09 (d, *J* = 8.7 Hz, 2H), 6.91 (d, *J* = 8.2 Hz, 1H), 6.89-6.80 (m, 4H), 6.66 (d, *J* = 1.9 Hz, 1H), 6.43 (s, 2H), 6.23 (dd, *J* = 2.2, 1.4 Hz, 1H), 3.94 (s, 3H), 3.65 (s, 6H), 2.57 (s, 4H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 157.2, 153.9, 152.1, 147.3, 146.4, 143.3, 135.1, 134.7, 133.1, 131.2, 131.0, 129.9, 129.4, 128.9, 120.9, 119.9, 119.1, 116.1, 113.7, 112.0, 111.9, 106.0, 55.6, 55.4, 41.0, 39.6; MS (ESI) 481 $(M+H)^{+}$.

*Macrocyclic derivative (**107**).*

This compound was prepared from **105** in 96% yield by following GP 4, white solid; mp 150-151 ˚C. ^{1}H NMR ($CDCl_3$) δ 7.23 (t, *J* = 8.1 Hz, 1H), 7.18-7.12 (m, 2H), 7.03 (dd, *J* = 8.2, 2.6 Hz, 1H), 7.02-6.98 (m, 2H), 6.94 (d, *J* = 8.0 Hz, 1H), 6.86 (d, *J* = 8.1 Hz, 1H), 6.79 (d, *J* = 7.4 Hz, 1H), 6.78 (dd, *J* = 8.2, 2.1 Hz, 1H), 6.76 (d, *J* = 2.0 Hz, 1H), 6.73 (dd, *J* = 8.0, 1.9 Hz, 1H), 6.23 (d, *J* = 2.0 Hz, 1H), 6.08 (dd, *J* = 2.3, 1.6 Hz, 1H), 3.95 (s, 3H), 3.74 (s, 3H), 3.14 (s, 4H), 2.52-2.47 (m, 4H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 159.1, 153.3, 151.6, 148.8, 147.3, 144.0, 141.3, 138.2, 136.5, 135.4, 130.0, 129.5, 122.5, 121.5, 121.1, 120.8, 120.7, 115.8, 114.8, 113.6, 113.5, 111.8, 56.2, 55.9, 41.1, 40.0, 35.8, 35.2; MS (ESI) 453 $(M+H)^{+}$.

*Macrocyclic derivative (**108**).*

This compound was prepared from **106** in 93% yield by following GP 4, white solid; mp 183-184 ˚C. ^{1}H NMR ($CDCl_3$) δ 7.23 (t, *J* = 7.8 Hz, 1H), 7.17 (d, *J* = 8.4 Hz, 2H), 7.09 (dd, *J* = 8.1, 2.4 Hz, 1H), 7.02 (d, *J* = 8.4 Hz, 2H), 6.86 (d, *J* = 8.1 Hz, 1H), 6.80-6.74 (m, 2H), 6.43 (s, 2H), 6.24 (d, *J* = 1.9 Hz, 1H), 6.02 (s, 1H), 3.95 (s, 3H), 3.72 (s, 6H), 3.14 (s, 4H), 2.54-2.42 (m, 4H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 158.5, 153.4, 152.8, 148.9, 147.3, 143.8, 138.0, 136.5, 135.4, 130.0, 129.6, 129.4, 121.1, 120.8, 120.6, 115.8, 114.3, 112.4, 111.8, 106.0, 56.2, 56.1, 41.3, 40.1, 36.3, 35.1; MS (ESI) 483 $(M+H)^+$.

*Macrocyclic derivative (**109**).*

This compound was prepared from **107** in 73% yield by following GP 5, white solid; mp 210-211 ˚C. ^{1}H NMR ($CDCl_3$) δ 7.27 (t, *J* = 8.4 Hz, 1H, Ar-H), 7.16 (d, *J* = 8.5 Hz, 2H, Ar-H), 7.04 (dd, *J* = 8.2, 2.6 Hz, 1H, Ar-H), 7.01-6.96 (m, 2H, Ar-H), 6.95 (d, *J* = 2.0 Hz, 1H, Ar-H), 6.90 (d, *J* = 8.2 Hz, 1H, Ar-H), 6.86 (d, *J* = 7.5 Hz, 1H, Ar-H), 6.82 (d, *J* = 8.2 Hz, 1H, Ar-H), 6.72 (dd, *J* = 8.0, 1.9 Hz, 1H, Ar-H), 6.52 (dd, *J* = 8.2, 2.0 Hz, 1H, Ar-H), 6.27-6.22 (m, 1H, Ar-H), 6.19 (d, *J* = 2.0 Hz, 1H, Ar-H), 5.58 (s, 1H, -OH), 5.35 (s, 1 H, -OH), 3.14-3.07 (m, 4H, $-CH_2-$), 2.57-2.46 (m, 4H, $-CH_2-$); ^{13}C NMR (151 MHz, $CDCl_3$) δ 158.4, 152.8, 148.0, 146.5, 144.8, 143.8, 139.6, 138.3, 137.0, 134.9, 130.3, 129.9, 121.9, 121.6, 121.4, 120.8, 120.7, 116.3, 115.0, 114.9, 114.1, 40.9, 39.7, 35.6, 35.1; MS (ESI) 425 $(M+H)^+$; HRMS calcd for $C_{28}H_{24}O_4Na$ 447.1567, found: 447.1554 $(M+Na)^+$.

*Macrocyclic derivative (**110**).*

This compound was prepared from **108** in 80% yield by following GP 5, white solid; mp 231-232 ˚C. ^{1}H NMR ($CDCl_3$) δ 7.29 (t, *J* = 8.4 Hz, 1H, Ar-H), 7.21 (d, *J* = 8.4 Hz, 2H, Ar-H), 7.10 (dd, *J* = 8.2, 2.1 Hz, 1H, Ar-H), 6.99 (d, *J* = 8.5 Hz, 2H, Ar-H), 6.89 (dd, *J* = 7.6, 2.5 Hz, 2H, Ar-H), 6.71 (dd, *J* = 8.0, 1.9 Hz, 1H, Ar-H), 6.43 (s, 2H, Ar-H), 6.17 (t, *J* = 2.8 Hz, 2H, Ar-H), 5.62 (s, 1H, -OH), 5.11 (s, 2H, -OH), 3.15-3.10 (m, 2H, $-CH_2-$), 3.09-3.04 (m, 2H, $-CH_2-$), 2.54- 2.50 (m, 2H, $-CH_2-$), 2.50-2.44 (m, 2H, $-CH_2-$); ^{13}C NMR (151 MHz, $CDCl_3$) δ 156.7, 152.8, 148.5, 146.7, 145.2, 143.7, 139.1, 137.0, 134.7, 130.2, 130.1, 126.3, 122.6, 121.4, 120.9, 114.9, 114.8, 114.4, 112.3, 108.7, 41.2, 39.7, 35.4, 34.4; MS (ESI) 441 $(M+H)^+$; HRMS calcd for $C_{28}H_{24}O_5Na$ 463.1516, found: 463.1512 $(M+Na)^+$.

*4-(5-(1,3-Dioxan-2-yl)-2-methoxyphenoxy)benzaldehyde (**111**).*

This compound was prepared from methyl 4-bromobenzaldehyde (**48**) and 5-(1,3-dioxan-2-yl)-2-methoxyphenol (**67**) in 71% yield by following GP 1, yellow oil. ^{1}H NMR

($CDCl_3$) δ 9.90 (s, 1 H), 7.80 (d, *J* = 9.0 Hz, 2 H), 7.36 (dd, *J* = 1.8 Hz, 8.4 Hz, 1 H), 7.26 (d, *J* = 1.8 Hz, 1 H), 7.02 (d, *J* = 8.4 Hz, 1 H), 6.98 (d, *J* = 9.0 Hz, 2 H), 5.46 (s, 1 H), 4.25 (dd, *J* = 4.8 Hz, 10.8 Hz, 2 H), 3.97 (t, *J* = 10.8 Hz, 2 H), 3.79 (s, 3 H), 2.24-2.16 (m, 1 H), 1.44 (d, *J* = 13.8 Hz, 1 H); MS (ESI) 315 $(M+H)^+$.

*Methyl 4-(5-(4-(5-(1,3-dioxan-2-yl)-2-methoxyphenoxy)phenethyl)-2-methoxyphenoxy)benzoate (**112**).*

This compound was prepared from **6** and **111** by following the procedure described for **17**, yield 75%, colorless oil. ^1H NMR ($CDCl_3$) δ 8.00 (d, *J* = 8.0 Hz, 2H), 7.28 (d, *J* = 9.8 Hz, 1H), 7.12 (s, 1H), 7.06 (d, *J* = 7.5 Hz, 2H), 7.00 (d, *J* = 8.2 Hz, 2H), 6.94 (d, *J* = 8.8 Hz, 1H), 6.91 (d, *J* = 7.1 Hz, 3H), 6.87 (d, *J* = 7.7 Hz, 2H), 5.42 (s, 1H), 4.24 (d, *J* = 10.7 Hz, 2H), 3.95 (t, *J* = 11.6 Hz, 2H), 3.90 (s, 3H), 3.84 (s, 3H), 3.79 (s, 3H), 2.86 (s, 4H), 2.20-2.16 (m, 1H), 1.43 (d, *J* = 13.4 Hz, 1H); MS (ESI) 571 $(M+H)^+$.

*Methyl 4-(5-(4-(5-(1,3-dioxan-2-yl)-2-methoxyphenoxy)phenethyl)-2-methoxyphenoxy)-3-methoxybenzoate (**113**).*

This compound was prepared from **7** and **111** by following the procedure described for **17**, yield 70%, colorless oil. ^1H NMR ($CDCl_3$) δ 8.02 (dd, *J* = 1.8 Hz, 8.0 Hz, 1H), 7.29 (d, *J* = 8.6 Hz, 1H), 7.21(d, *J* = 8.6 Hz, 1H), 7.07 (dd, *J* = 1.8 Hz, 7.5 Hz, 2H), 7.02 (d, *J* = 8.2 Hz, 2H), 6.94 (d, *J* = 8.8 Hz, 1H), 6.93-6.91 (m, 3H), 6.87 (d, *J* = 8.4 Hz, 2H), 5.40 (s, 1H), 4.23 (d, *J* = 10.6 Hz, 2H), 3.91 (t, *J* = 11.2 Hz, 2H), 3.96 (s, 3H), 3.88 (s, 3H), 3.80 (s, 3H), 3.78 (s, 3H), 2.81 (s, 4H), 2.25-2.22 (m, 1H), 1.46-1.40 (m, 1H); MS (ESI) 601 $(M+H)^+$.

*Macrocycle (stilbene bridge) (**116**).*

This compound was prepared from **112** in 70% yield by following the procedure described for **22**, white solid; mp 240-241 ˚C. ^1H NMR ($CDCl_3$) δ 7.19 (d, *J* = 8.4 Hz, 2 H), 7.10-7.07 (m, 4 H), 6.99 (d, *J* = 8.4 Hz, 1 H), 6.96 (d, *J* = 8.4 Hz, 1 H), 6.75 (d, *J* = 7.8 Hz, 2 H), 6.64 (d, *J* = 7.8 Hz, 2 H), 6.55 (d, *J* = 8.4 Hz, 2 H), 6.46 (d, *J* = 5.4 Hz, 1 H), 6.13 (s, 1 H), 3.81 (s, 6 H), 2.82 (s, 4 H); ^{13}C NMR ($CDCl_3$) δ 157.6, 156.7, 151.3, 150.2, 142.5, 142.2, 134.6, 133.7, 130.4, 130.2, 130.0, 129.9, 128.7, 127.7, 127.2, 125.7, 124.5, 123.1, 115.4, 114.8, 112.9, 112.4, 56.0, 55.9, 37.9, 37.4; MS (ESI) 473 $(M+Na)^+$.

*Macrocycle (stilbene bridge) (**117**).*

This compound was prepared from **113** in 73% yield by following the procedure described for **22**, white solid; mp 188-189 ˚C. ^1H NMR ($CDCl_3$) δ 7.08 (s, 1 H), 7.05 (d, *J* = 8.4 Hz, 2 H), 6.96 (t, *J* = 8.4

Hz, 2 H), 6.82-6.79 (m, 2 H), 6.75 (d, *J* = 8.4 Hz, 2 H), 6.66 (d, *J* = 7.2 Hz, 2 H), 6.45 (s, 2 H), 6.14 (d, *J* = 8.4 Hz, 1 H), 6.08 (s, 1 H), 3.87 (s, 3 H), 3.82 (s, 3 H), 3.81 (s, 3 H), 2.80 (s, 4 H); ^{13}C NMR ($CDCl_3$) δ 156.1, 151.0, 149.7, 149.0, 146.2, 143.0, 142.8, 134.3, 134.2, 131.1, 130.1, 128.7, 128.2, 126.9, 125.1, 123.4, 123.2, 121.9, 120.8, 115.5, 115.4, 112.7, 112.6, 112.2, 56.0, 55.9, 55.8, 37.9, 37.3; MS (ESI) 503 $(M+Na)^+$.

*Macrocyclic derivative (**118**).*

This compound was prepared from **116** in 96% yield by following GP 4, white solid; mp 256-257 ˚C. ^{1}H NMR ($CDCl_3$) δ 7.08 (d, *J* = 7.8 Hz, 1 H), 6.97 (d, *J* = 7.8 Hz, 1 H), 6.71 (d, *J* = 7.8 Hz, 2 H), 6.55 (d, *J* = 7.8 Hz, 2 H), 6.04 (s, 1 H), 3.77 (s, 3 H), 2.81 (s, 4 H); ^{13}C NMR ($CDCl_3$) δ 156.6, 150.3, 142.0, 134.4, 133.6, 130.0, 125.7, 124.9, 114.8, 112.7, 56.0, 37.9, 37.6; MS (ESI) 475 $(M+Na)^+$.

*Macrocyclic derivative (**119**).*

This compound was prepared from **117** in 95% yield by following GP 4, white solid; mp 178-179 ˚C. ^{1}H NMR ($CDCl_3$) δ 7.05-7.03 (m, 2 H), 6.95 (t, *J* = 9.0 Hz, 2 H), 6.74 (s, 1 H), 6.73 (d, *J* = 8.4 Hz, 2 H), 6.56 (d, *J* = 9.0 Hz, 2 H), 6.09 (d, *J* = 8.4 Hz, 1 H), 6.01 (d, *J* = 1.8 Hz, 2 H), 5.95 (dd, *J* = 1.8 Hz, 8.4 Hz, 1 H), 3.91 (s, 3 H), 3.79 (s, 3 H), 3.77 (s, 3 H), 2.80 (d, *J* = 3.6 Hz, 4 H), 2.79 (s, 4 H); ^{13}C NMR ($CDCl_3$) δ 156.2, 150.1, 150.0, 148.8, 145.5, 142.5, 142.4, 134.5, 134.3, 134.2, 134.0, 130.1, 125.4, 125.3, 124.1, 124.0, 121.7, 115.4, 114.1, 112.6, 112.5, 112.0, 56.0, 55.9, 55.8, 38.5, 38.0, 37.6, 37.5; MS (ESI) 505 $(M+Na)^+$.

*Macrocyclic derivative (**120**).*

This compound was prepared from **118** in 74% yield by following GP 5, white solid; mp 257-258 ˚C. ^{1}H NMR ($CDCl_3$) δ 7.02 (dd, *J* = 7.8 Hz, 18.0 Hz, 2 H, Ar-H), 6.80 (d, *J* = 8.4 Hz, 2 H, Ar-H), 6.67 (d, *J* = 7.8 Hz, 2 H, Ar-H), 6.06 (s, 1 H, Ar-H), 5.30 (s, 1 H, -OH), 2.81 (m, 4 H, $-CH_2-$); ^{13}C NMR ($CDCl_3$) δ 155.2, 146.1, 141.1, 135.5, 133.9, 130.4, 130.0, 125.8, 121.7, 116.2, 116.1, 37.7, 37.5; MS (ESI) 423 $(M-H)^-$; HRMS calcd for $C_{28}H_{24}O_4Na$ 447.1567, found: 447.1554 $(M+Na)^+$.

*Macrocyclic derivative (**121**).*

This compound was prepared from **119** in 80% yield by following GP 5, white solid; mp 195-196 ˚C. ^{1}H NMR ($CDCl_3$) δ 7.06-6.97 (m, 3 H, Ar-H), 6.97 (d, *J* = 7.8 Hz, 1 H, Ar-H), 6.77 (d, *J* = 8.4 Hz, 3 H, Ar-H), 6.69 (d, *J* = 6.6 Hz, 2 H, Ar-H), 6.34 (d, *J* = 6.6 Hz, 1 H, Ar-H), 6.10 (s, 2 H, Ar-H), 6.06 (s, 1 H, Ar-H), 5.46 (s, 1 H, -OH), 5.33 (s, 1H, -OH), 5.32 (s, 1H, -OH), 2.80-2.79 (m, 8 H, $-CH_2-$); ^{13}C NMR ($CDCl_3$) δ 155.1, 145.9, 145.8, 145.7, 141.9, 141.1, 140.8, 140.5, 137.3, 135.6, 134.3, 133.9,

130.4, 126.1, 125.4, 121.7, 121.1, 120.9, 116.6, 116.5, 116.3, 116.1, 115.1, 38.0, 37.6, 37.4, 37.2; MS (ESI) 439 $(M-H)^-$; HRMS calcd for $C_{28}H_{24}O_5Na$ 463.1516, found: 463.1509 $(M+Na)^+$.

4.2.1. Antiproliferative studies

Human breast adenocarcinoma cell line HCC1428 and human colonic cancer cell line HT29 were purchased from the Shanghai Institute for Biological Sciences (SIBS), China Academy of Sciences (China). Human myelogenous leukemia k562 cell line was purchased from the Department of Pharmacology, Institute of Hematology of the Chinese Academy of Medical Sciences, Tianjin (China). The cells were cultured in RPMI-1640 (HyClone) medium containing 10% FBS (Sijiqing Company, Ltd.), 100 units/mL of penicillin G, and 100 μg/mL of streptomycin in a stable environment with 37 □ and 5% CO_2. HeLa (cervical carcinoma) was obtained from the American Type Culture Collection (ATCC) and cultured at 37 □ and 5% CO_2 in DMEM medium supplemented as described above. The PC-3/Doc cell line was obtained from Yuan's group at Shandong University. The antiproliferative activity of the marchantin C analogues on the five tumor cell lines was measured by the MTT method, as previously described [40]. Briefly, after treatment with the candidate drug for 48 h, the absorbance of the soluble MTT product was measured at 570 nm. All experiments were performed at least three times.

4.2.2. Cell growth curve

The cell growth curves of HCC1428 cells treated by the indicated concentrations of compound **47** for 84 h were created by the xCELLigence system from Roche according to the manufacturer's protocol. The cells were incubated in RPMI-1640 medium containing 2% FBS at 37 □ and 5% CO_2 throughout.

4.2.3. Cell cycle analysis

The cell cycle distribution was measured by flow cytometric analysis. HCC1428 cells were seeded into 6-well plates and then treated with varying concentrations of compound **47**. Adherent cells were detached with trypsin and collected by centrifugation, followed by washing, fixation, and PI staining. The cell cycle distribution was examined by a FACScan flow cytometer (Becton–Dickinson, USA), and the data were analyzed using the ModFit program (Becton–Dickinson, USA)

4.2.4. Immunofluorescence

For the immunofluorescence studies, HCC1428 cells were seeded on 12-mm round glass cover slips and placed at the bottom of 24-well plates. After the experimental treatment, the cells were fixed

with cold methanol/acetone (1:1) for 5 min followed by incubating with 3% goat serum (in 0.1% Triton X-100) for 20 min to prevent nonspecific antibody binding. The cells were then immunostained for α-tubulin using mouse anti-α-tubulin antibody followed by FITC-conjugated goat anti-rabbit secondary antibody. The DNA was counterstained with DAPI (4 μg/mL) for 15 min at room temperature. The samples were mounted on microscope slides with mounting medium and analyzed by confocal microscopy.

4.2.5. Tubulin polymerization assay

An *in vitro* assay for monitoring the time-dependent polymerization of tubulin to microtubules was performed. Bovine brain tubulin (>97% pure tubulin) was suspended with 10 mL of G-PEM buffer (80 mM PIPES, 2 mg $MgCl_2$, 0.5 mM EGTA, 1.0 mM GTP, pH 6.9) in 0.1% DMSO at 4 □, with and without test compound, using the HTS-Tubulin Polymerization Assay Kit (Cat. BK004P) according to the manufacturer's protocol (Cytoskeleton, Inc., Denver, CO, USA). The polymerization of tubulin was measured by the change in absorbance at 340 nm every 1 min for 1 h using a spectrophotometer (Thermo Fisher Scientific, Inc., USA) in a stable environment at 37 □.

4.3. Molecular modeling

The crystal structure of tubulin in complex with colchicine was downloaded from the Protein Data Bank (PDB code 1SA0) [41]. Hydrogens were added and minimized using the Amber force field and the Amber charges. Modeled analogues were constructed in SYBYL-X, and the energy was minimized with the Amber force field and Amber charges [42]. The docking of compound **47** into the colchicine-binding site of tubulin was performed using the GOLD program. For the genetic algorithm (GA) runs, a maximum number of 100,000 GA operations were performed on a single population of 100 individuals. The operator weights for crossover, mutation, and migration were set to 95, 95, and 10, respectively, which are the standard default settings recommended by the authors. The maximum distance between hydrogen bond donors and acceptors for hydrogen bonding was set to 3.5 Å. After docking, the best-docked conformation of **47** was merged into the ligand-free protein. The new ligand–protein complex was subsequently subjected to energy minimization using the Amber force field with Amber charges. During the energy minimization, the structure of **47** and a surrounding 6 Å sphere were allowed to move, while the structures of the remaining proteins were frozen. The energy minimization was performed using the Powell method with a 0.05 kcal/(mol Å) energy gradient convergence criterion and a distance-dependent dielectric function.

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Fig. 1. Modification strategy for macrocyclic bisbibenzyl analogues

Fig. 2. Key NOESY correlations (dashed blue arrows) for compound **47**.

Fig. 3. Three-dimensional structures of compounds **42**, **55**, **77**, **88**, **96**, **109**, **120** and marchantin C; The IC_{50} represents the average IC_{50} value of each compound against four human cancer cell lines; The aromatic carbons that are included in the macrocyclic ring are indicated by a blue cross symbol.

Fig. 4. HCC1428 cells were treated with compound **47** as indicated. Cells were then plated 2000 cells/well into E-plate 16 and analyzed using a xCELLigence RTCA DP instrument. Results are representatives of three independent experiments.

Fig. 5. Compound **47** induced HCC1428 cells cycle arrest at the G_2/M phase. HCC1428 cells were treated with 3 μM and 6 μM concentrations of compound **47** for 24 h, and then trypsinized, fixed and stained with PI to measure the cell cycle profile by flow cytometry. Control cells were treated with DMSO alone. The results are representatives of three independent experiments.

Fig. 6. HCC1428 cells were treated with compound **47** and **77** as indicated for 24 h and then fixed and immunostained with monoclonal anti-α-tubulin antibody (red) and DAPI (blue). One micromolar concentrations of Vincristine (VCR) and same amount of DMSO were used as controls. Results are representatives of three independent experiments. Bar = 10 μm.

Fig. 7. Effect of compound **47** on tubulin polymerization *in vitro*. Purified bovine brain tubulin was incubated in the presence of Taxol, VCR, DMSO (control), and compound **47** under the indicated concentrations at 37℃, and absorbance readings were recorded every minute for 1 h.

Fig. 8. Proposed binding mode of compound **47** in the colchicine binding site (PDB code 1SA0). (A) The binding mode of **47** (cyan) in the binding site with hydrogen bonds are shown as dotted red lines, and the distance between ligand and protein is less than 3 Å. (B) Docking of **47** (grey) into the binding site, and overlaid with a model of DAMA-colchicine (magenta stick). The methoxyl group could fit well into the hydrophobic pocket formed by residues Gln 247, Leu 248, Lys 352 and Ala 354.

Scheme 1. Synthesis of macrocyclic compounds **32-47**. *Reagents and conditions*: (a) CuO, K_2CO_3, Py, reflux, (yields 63%-76%); (b) i. $NaBH_4$, THF, 0 ℃ to r.t.; ii. PPh_3HBr, MeCN, reflux, (yields 78%-89%, two steps); (c) i. K_2CO_3, 18-crown-6, DCM, reflux; ii. Pd/C (10%), H_2, Et_3N, EtOAc, r.t. (yields 71%-80%, two steps); (d) i. $LiAlH_4$, THF, -40 ℃ to r.t.; ii. HCl/EtOH (1:10), r.t. (yields 80%-86%, two steps); (e) PPh_3HBr, MeCN, reflux, (yields 86%-93%); (f) NaOMe, DCM, r.t. (yields 80%-88%); (g) Pd/C (10%), H_2, EtOAc, r.t. (yields 95%-99%); (h) BBr_3, DCM, -40 ℃ to r.t. (yields 51%-86%).

Scheme 2. Synthesis of macrocyclic compounds **53-55**. *Reagents and conditions*: (a) CuO, K_2CO_3, Py, reflux, (yield 65%); (b) i. K_2CO_3, 18-crown-6, DCM, reflux; ii. Pd/C (10%), H_2, Et_3N, EtOAc, r.t. (yield 83%, two steps); (c) i. $LiAlH_4$, THF, -40 ℃ to r.t.; ii. HCl/EtOH (1:10), r.t. (yield 85%, twp steps); (d) PPh_3HBr, MeCN, reflux, (yield 92%); (e) NaOMe, DCM, r.t. (yield 80%); (f) Pd/C (10%), H_2, EtOAc, r.t. (yields 96%); (g) BBr_3, DCM, -40 ℃ to r.t. (yield 86%).

Scheme 3. Synthesis of macrocyclic compounds **63-65**. *Reagents and conditions*: (a) CuO, K_2CO_3, Py, reflux, (yield 61%); (b) $LiAlH_4$, THF, -40 ℃ to r.t. (yield 88%); (c) PPh_3HBr, MeCN, reflux, (yield 90%); (d) i. K_2CO_3, 18-crown-6, DCM, reflux; ii. Pd/C (10%), H_2, Et_3N, EtOAc, r.t. (yield 80%, two steps); (e) i. $LiAlH_4$, THF, -40 ℃ to r.t.; ii. HCl/EtOH (1:10), r.t. (yield 87%, twp steps); (f) NaOMe, DCM, r.t. (yield 73%); (g) Pd/C (10%), H_2, EtOAc, r.t. (yields 92%); (h) BBr_3, DCM, -40 ℃ to r.t. (yield 82%).

Scheme 4. Synthesis of macrocyclic compounds **73-78**. *Reagents and conditions*: (a) CuO, K_2CO_3, Py, reflux, (yield 70%); (b) i. K_2CO_3, 18-crown-6, DCM, reflux; ii. Pd/C (10%), H_2, Et_3N, EtOAc, r.t. (yield 80-86%); (c) i. $LiAlH_4$, THF, -40 ℃ to r.t.; ii. HCl/EtOH (1:10), r.t.; iii. PPh_3HBr, MeCN, reflux, (yield 70-74%, three steps); (d) NaOMe, DCM, r.t. (yields 71-77%); (e) Pd/C (10%), H_2, EtOAc, r.t. (yields 92-96%); (f) BBr_3, DCM, -40 ℃ to r.t. (yields 79-82%).

Scheme 5. Synthesis of macrocyclic compounds **87-88**. *Reagents and conditions*: (a) CuO, K_2CO_3, Py, reflux, (yield 75%); (b) HCl/EtOH (1:10), r.t. (yield 79%); (c) $NaBH_4$, THF, 0 ℃ to r.t. (yield 86%); (d) PPh_3HBr, MeCN, reflux, (yield 88%); (e) i. K_2CO_3, 18-crown-6, DCM, reflux; ii. Pd/C (10%), H_2, Et_3N, EtOAc, r.t. (yield 83%, two steps); (f) i. $LiAlH_4$, THF, -40 ℃ to r.t.; ii. HCl/EtOH (1:10), r.t., (yield 73%, two steps); (g) i. NaOMe, DCM, r.t.; ii. Pd/C (10%), H_2, EtOAc, r.t. (yields 75%); (h) BBr_3, DCM, -40 ℃ to r.t. (yields 73%).

Scheme 6. Synthesis of macrocyclic compounds **95-96**. *Reagents and conditions*: (a) CuO, K_2CO_3, Py, reflux, (yield 76%); (b) i. HCl/EtOH (1:10), r.t.; ii. $NaBH_4$, THF, 0 ℃ to r.t. (yield 61%, two steps); (c) PPh_3HBr, MeCN, reflux, (yield 82%); (d) i. K_2CO_3, 18-crown-6, DCM, reflux; ii. Pd/C (10%), H_2, Et_3N, EtOAc, r.t. (yield 88%); (e) i. $LiAlH_4$, THF, -40 ℃ to r.t.; ii. HCl/EtOH (1:10), r.t., (yield 72%, two steps); (f) i. NaOMe, DCM, r.t.; ii. Pd/C (10%), H_2, EtOAc, r.t. (yields 77%); (g) BBr_3, DCM, -40 ℃ to r.t. (yields 79%).

Scheme 7. Synthesis of macrocyclic compounds **105-110**. *Reagents and conditions*: (a) CuO, K_2CO_3, Py, reflux, (yields 54-73%); (b) i. K_2CO_3, 18-crown-6, DCM, reflux; ii. Pd/C (10%), H_2, Et_3N, EtOAc, r.t.; iii. $LiAlH_4$, THF, -40 ℃ to r.t. (yields 64-76%, three steps); (c); i. HCl/EtOH (1:10), r.t.; ii. PPh_3HBr, MeCN, reflux, (yields 74-81%, two steps); (d) NaOMe, DCM, r.t. (yields 81-86%); (e) Pd/C (10%), H_2, EtOAc, r.t. (yields 93-96%); (f) BBr_3, DCM, -40 ℃ to r.t. (yields 73-80%).

Scheme 8. Synthesis of macrocyclic compounds **116-121**. *Reagents and conditions*: (a) CuO, K_2CO_3, Py, reflux, (yields 77%); (b) i. K_2CO_3, 18-crown-6, DCM, reflux; ii. Pd/C (10%), H_2, Et_3N, EtOAc, r.t. (yields 66-75%, two steps); (c) i. $LiAlH_4$, THF, -40 ℃ to r.t.; ii. HCl/EtOH (1:10), r.t.; iii. PPh_3HBr, MeCN, reflux, (yields 66-70%, three steps); (d) NaOMe, DCM, r.t. (yields 83-87%); (e) Pd/C (10%), H_2, EtOAc, r.t. (yields 95-96%); (f) BBr_3, DCM, -40 ℃ to r.t. (yields 74-80%).

Table 1. In Vitro Cytotoxicity of marchantin C derivatives in four cancer cell lines

Highlights

- Novel marchantin C derivatives were synthesized and evaluated as anticancer agents
- Derivatives showed improved anticancer activity compared to positive controls
- Derivatives were also effective in multidrug-resistant cancer cell line
- A focused structure-activity relationship was discussed
- The anticancer mechanism could be attributed to the inhibition of tubulin polymerization