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Original article

Design and synthesis of biaryl aryl stilbenes/ethylenes as antimicrotubule agents

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ABSTRACT

Two new series of compounds *E*-2,3,4-trimethoxy-6-styrylbiphenyls and 2,3,4-trimethoxy-6-(1-phenylvinyl)biphenyls were designed, synthesized and evaluated for antitubulin activity. A common intermediate 4,5,6-trimethoxybiphenyl-2-carbaldehydes was employed to generate the two scaffolds. Majority of the analogs inhibited cell proliferation and those functionalized with 3,4-(1,3-dioxolane) and 3,4-difluoro groups were identified as effective inhibitors in both the series. Treatments with **19b**, **19c**, **22b** and **22c** arrested cells at G2/M phase, disrupted microtubule network, accumulated tubulin in the soluble fraction and manifested an increased expression of the G2/M marker, Cyclin B1. Molecular docking analysis demonstrated the interaction of these compounds at the colchicine binding site of tubulin.

1. Introduction

Microtubules are key components of cytoskeleton involved in a wide variety of cellular functions such as cell division, morphology, regulation of motility, signaling and various intracellular processes [1]. Primary role of microtubules is the formation of mitotic spindle by the polymerization of tubulin resulting in chromosomal separation. Consequently, perturbation of tubulin assembly/disassembly is a popular target for new chemotherapeutic agents [2,3]. Microtubule stabilizing taxanes and vinca alkaloids, which recognize taxoid and vinca alkaloid sites on tubulin, are routinely used in the clinics [4,5]. Another chemotherapeutic target site on tubulin is the colchicine binding site, whose ligands generally inhibit tubulin polymerization. A number of natural products and their derivatives that recognize the colchicine site such as colchicine (**1**), podophyllotoxin (**2**), combretastatin A-4 (**3**), ZD6126 (**4**), curacin A (**5**), AVE8062A (**6**), ABT-751 (**7**), steganacine (**8**) and nocodazole (**9**) are in clinical trials [6–9]. The biaryl configuration is important for effective binding of colchicine and allocolchicinoids with tubulin, which is also present in a wide range of cytotoxic natural products such as steganacine (**8**), steganone (**10**), eupomatilone (**11**), buflavine (**12**), dibenzocyclooctadiene lignans and many synthetic derivatives (Fig. 1) [10,11].

Recently, we found nitrovinyl biphenyls (**13**) and nitrovinyl stilbenes (**14**) as novel antimitotic agents with biphenyl and stilbene pharmacophores, respectively [11,12]. In continuity of our previous investigations devoted to design and synthesis of new scaffolds for tubulin target, we became interested in the synthesis of biaryl aryl stilbenes **19a**–**k** with the combination of biphenyl and stilbene pharmacophores. Next we focused our attention for the synthesis of 1,1-biaryl aryl ethylenes **22a**–**k** (Fig. 1) with inspiration of recent demonstration that the bioisosteric replacement of the (*Z*)-1,2-ethylene group with a 1,1-ethylene bridge resulted in retention of biological activities [13].

2. Chemistry

Scheme 1 outlines the synthetic route followed for the synthesis of novel compounds (*E*)-2,3,4-trimethoxy-6-styrylbiphenyls **19a**–**k** and 2,3,4-trimethoxy-6-(1-phenylvinyl)biphenyls **22a**–**k**. The preparation of 2-bromo-3,4,5-trimethoxybenzaldehyde **16** was achieved by the bromination of commercially available 3,4,5-

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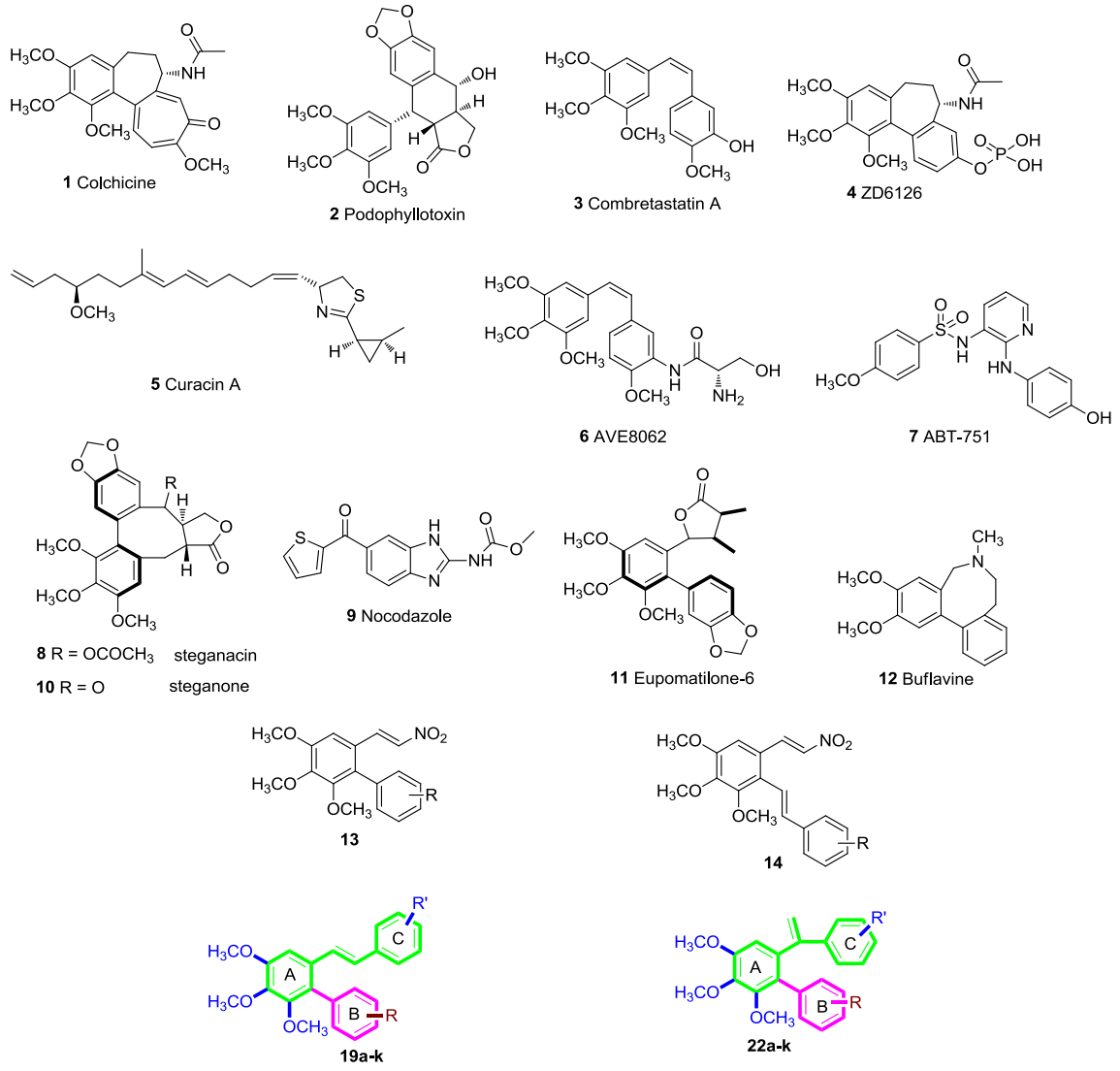


Fig. 1. Antiproliferative activity of natural compounds having biphenyl pharmacophore, biaryl aryl stilbenes **19a**–**k** and biaryl aryl ethylenes **22a**–**k**.

trimethoxybenzaldehyde **15** using Br_2 at room temperature [11]. Suzuki cross-coupling of **16** with aryl boronic acids under palladium catalysis afforded the key intermediates 4,5,6-trimethoxybiphenyl-2-carbaldehydes **17a**–**i** [11].

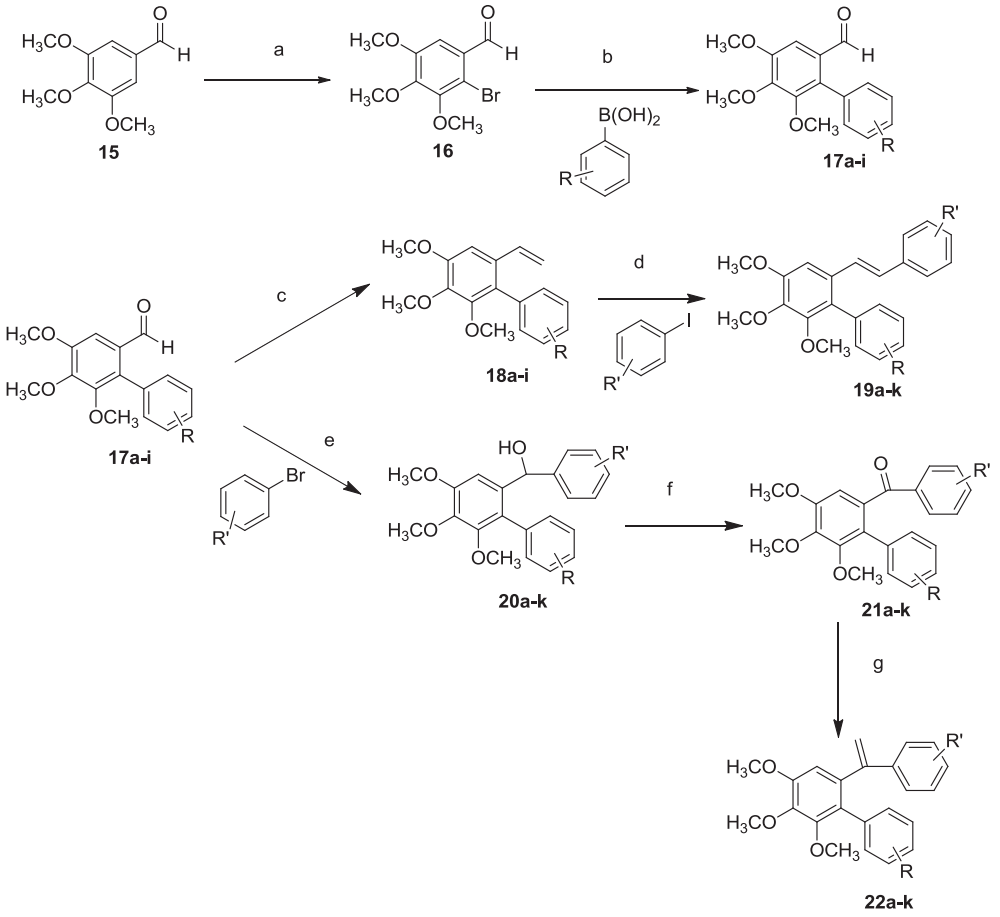
The target compounds **19a**–**k** were obtained by the Wittig reaction of **17a**–**i** with methylenetriphenylphosphorane to generate intermediate compounds 2,3,4-trimethoxy-6-vinylbiphenyls **18a**–**i** [14] followed by Heck coupling with aryl halides in the presence of $Pd(OAc)_2$ [15].

Having achieved the preparation of **19a**–**k**, we next focused our attention for the synthesis of another series **22a**–**k**. Intermediates **17a**–**i** treated with different aryl magnesium halides yielded phenyl(4,5,6-trimethoxy-biphenyl-2-yl)methanols **20a**–**k** [16], which on further oxidation with PCC yielded phenyl(4,5,6-trimethoxy-biphenyl-2-yl)methanone **21a**–**k** [17]. Wittig reaction of **21a**–**k** with methylenetriphenylphosphorane [16] generated the target compounds **22a**–**k**.

3. Results and discussion

3.1. In vitro cytotoxic activity

(*E*)-2,3,4-Trimethoxy-6-styrylbiphenyls **19a**–**k** were evaluated for their antiproliferative activity against a panel of four different human tumor cells from lung, cervix, neuroblastoma and prostate using the MTT assay. The results of this study are summarized in Table 1, the synthesized compounds exhibited significant antiproliferative activities against these cell lines in a concentration-dependent manner. The SAR studies of stilbene analogs revealed that the 4-methoxy group is essential for the activity [18]. This observation was substantiated by loss of efficacy of the compounds **19j** and **19k** without 4-methoxy group or replaced with methyl group on the stilbene pharmacophore (C-ring). Consequently, SAR studies of the biphenyl pharmacophore were conducted with the methoxy group at 4th position on the C-ring. Compounds **19b** and



Scheme 1. Synthesis of 2,3,4-trimethoxy-6-(1-phenylvinyl)biphenyl and (*E*)-2,3,4-trimethoxy-6-styrylbiphenyls. a) Br_2, CH_3COOH, rt, 2 h; b) $Pd(PPh_3)_4$, H_2O: C_2H_5OH (1:1) 80 °C, 6 h; c) $CH_3P(Ph)_3Br$, ^tBuOK, THF, rt, 24 h; d) $Pd(OAC)_2$, K_3PO_4, DMA,140 °C, 12 h; e) Mg, THF, 2 h; f) PCC,DCM, rt, 2 h; g) $CH_3P(Ph)_3Br$, *n*-BuLi, THF, −78°, 12 h.

19c having 3,4-(1,3-dioxolane) and 3,4-difluoro groups, respectively exhibited IC_{50} values below 10 μM against all 4 cancer cell lines. The compounds **19f** substituted with phenyl extension and **19h** bearing 3-methyl-4-fluoro groups exhibited <20 μM against all the cell lines, except DU145. The derivatives **19d** devoid of any substitution and **19g** with 4-chloro group exhibited antiproliferative activity at concentration of 11 μM and 15 μM against SK-N-SH cell line. The analogs **19a**, **19e** and **19i** bearing 4-methoxy group, 4-tertiary butyl group and 3,4-dimethoxy group exhibited antiproliferative activity at higher concentrations (28–45 μM) against all the cell lines except **19a** on the HeLa cell lines.

Similar results were found with other series of compounds **22a–k** containing same substituents on B and C rings. The compounds **22b** with 3,4-(1,3-dioxolane) and **22c** with 3,4-difluro groups demonstrated IC_{50} values below 8 μM against all 4 cancer cell lines. The compound **22f** with phenyl extension exhibited IC_{50} values of 15 μM against A549, 6 μM against SK-N-SH cell lines. Interestingly, compound **22d** with no substitution on B ring exhibited IC_{50} values of 11 μM against HeLa and 8 μM against DU145 cell lines. The congeners **22a** and **22h** with 4-methoxy group and devoid of any substitution on both the rings had an IC_{50} value of 14 μM and 17 μM, respectively against A549 cell line. The compounds **22e**, **22i** and **22j** exhibited less antiproliferative activity (24–40 μM) against all 4 cell lines. However, the compound **22k** with 4-trifluoromethyl group exhibited at concentration of 13 μM against SK-N-SH cell line (Table 2). The SAR studies of both the series conclude that the 3,4-disubstitution with small size and high electronegative groups may be important for effective antiproliferative activity.

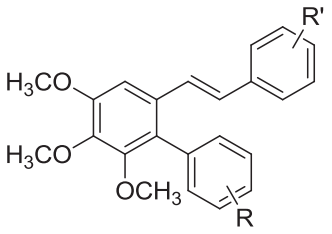
3.2. Inhibition of in vitro tubulin polymerization

Cell viability assays revealed that all compounds exhibited effective antiproliferative activity against a majority of cell lines tested. To investigate the antiproliferative activities of these compounds like nitrovinyl biphenyls and nitrovinyl stilbenes [11,12], we evaluated their antitubulin effects at 5 μM concentrations on tubulin assembly. Interestingly, biaryl aryl stilbene compounds **19b** and **19c** inhibited tubulin polymerizations by 62% and 55%, respectively (Table 1). In comparison, 1,1-biaryl aryl ethylenes containing the similar substitutions on B ring, congeners **22b** and **22c** inhibited tubulin polymerization by 56% and 53%, respectively (Table 2). The tubulin inhibition studies are in consonance with the results of antiproliferative effect of the compounds. Thus, we determined the IC_{50} value of compounds **19b**, **19c**, **22b** and **22c** for their ability to inhibit tubulin polymerization. As expected, compounds **19b** which demonstrated the maximum inhibition of tubulin assembly manifested the lowest IC_{50} (6.8 μM). However, compounds **19c**, **22b** and **22c** demonstrated IC_{50} values of 9.2, 8.6 and 11.2 μM, respectively (Table 3). The obtained results support the findings that the compounds inhibit tubulin assembly in the order of **19b**>**22b**>**19c**>**22c**.

3.3. Antimitotic effects of compounds *19b*, *19c*, *22b* and *22c*

Molecules exhibiting effects on tubulin polymerization causes the alteration of the cell cycle parameters [12]. To elucidate antitubulin activity of the most active compounds **19b**, **19c**, **22b** and

Table 1
In vitro antiproliferative activity of compounds **19a**–**k** on A549, HeLa, SK-N-SH and DU145 human cancer cells and tubulin polymerization.[a]



Compound	R	R′	IC_{50}[b] (μm)				Tubulin polymerization (% inhibition)[c]
			A549	HeLa	SK-N-SH	DU145	
19a	4-OCH_3	4-OCH_3	35 ± 1.2	19 ± 1.8	36 ± 1.6	34 ± 3.1	20
19b	3,4-(1,3-Dioxolane)	4-OCH_3	6.3 ± 0.5	8.7 ± 1.1	8.0 ± 8.0	7.3 ± 0.8	62
19c	3,4 Difluoro	4-OCH_3	7.5 ± 0.4	9.2 ± 0.1	6.9 ± 0.1	7.5 ± 0.9	55
19d	H	4-OCH_3	36 ± 0.7	26 ± 3.5	11 ± 0.2	51 ± 0.3	22
19e	4-$C(CH_3)_3$	4-OCH_3	32 ± 3.2	28 ± 2.5	30 ± 3.6	45 ± 1.9	33
19f	Phenyl	4-OCH_3	14 ± 1.1	13 ± 1.4	16 ± 2.4	32 ± 1.2	50
19g	4-Cl	4-OCH_3	30 ± 2.6	49 ± 3.8	15 ± 1.2	35 ± 3.8	26
19h	3-CH_3, 4-F	4-OCH_3	18 ± 1.3	17 ± 1.7	19 ± 2.7	23 ± 1.1	48
19i	3,4-$(OCH_3)_2$	4-OCH_3	28 ± 1.6	45 ± 4.4	42 ± 2.9	34 ± 2.2	33
19j	H	H	79 ± 8.4	89 ± 5.8	63 ± 4.5	82 ± 8.8	41
19k	H	4-CH_3	54 ± 3.4	45 ± 4.2	31 ± 2.4	101 ± 8.9	47

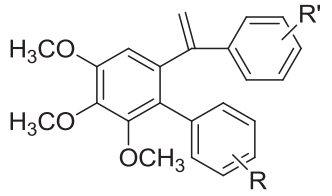
[a] Cell lines were treated with different concentrations of compounds for 48 h as described under Materials and methods. Cell viability was measured employing MTT assay.
[b] IC_{50} values are indicated as the mean ± SD of three independent experiments.
[c] Compounds were preincubated with tubulin (2 mg/ml) at a final concentration of 5 μM.

22c, we analyzed their cell cycle effects. Flow cytometry can be used to quantitatively determine the population of cells in each phase of the cell cycle by measuring the DNA content of individual cells. HeLa cells were treated with the compounds **19b**, **19c**, **22b** and **22c** at 10 μM concentrations for duration of 24 h. Later, cells were harvested and analyzed by flow cytometry. Majority population of cells arrested at the G2/M phase with 73.02% (**19b**) 71.16% (**19c**), 73.00% (**22b**) and 70.02% (**22c**) accumulation (Fig. 2). Over all these results suggest that compounds **19b**, **19c**, **22b** and **22c** more effectively inhibit tubulin polymerization in vitro and in cellular assays as compared to other compounds in the both series.

3.4. Effects of *19b*, *19c*, *22b* and *22c* on cellular microtubules and nuclear morphology

Microtubule depolymerizing drugs prevent the organization of the mitotic spindle and result in improper chromosome separation [6]. To identify the effect of compounds **19b**, **19c**, **22b** and **22c** on

Table 2
In vitro antiproliferative activity of compounds **22a**–**k** on A549, HeLa, SK-N-SH and DU145 human cancer cells and tubulin polymerization.[a]



Compound	R	R′	IC_{50}[b] (μm)				Tubulin polymerization (% inhibition)[c]
			A549	HeLa	SK-N-SH	DU145	
22a	4-OCH_3	4-OCH_3	14 ± 3.5	72 ± 2.1	75 ± 2.6	37 ± 2.1	40
22b	3,4-(1,3-Dioxolane)	4-OCH_3	5.0 ± 3.6	5.4 ± 1.8	6.1 ± 1.5	6.0 ± 1.1	56
22c	3,4 Difluoro	4-OCH_3	6.5 ± 4.2	5.9 ± 4.8	7.5 ± 1.9	6.8 ± 2.6	53
22d	H	4-OCH_3	22 ± 1.6	11 ± 2.5	31 ± 3.2	8.0 ± 0.9	49
22e	4-$C(CH_3)_3$	4-OCH_3	27 ± 1.1	39 ± 2.6	24 ± 1.8	39 ± 2.8	23
22f	Phenyl	4-OCH_3	15 ± 0.7	35 ± 3.5	6.0 ± 2.9	46 ± 6.2	21
22g	4-Cl	4-OCH_3	29 ± 1.9	30 ± 3.6	15 ± 3.6	33 ± 7.1	40
22h	H	H	17 ± 3.8	42 ± 1.1	34 ± 2.8	36 ± 2.6	40
22i	H	4-CH_3	35 ± 0.8	28 ± 2.9	31 ± 2.4	28 ± 1.8	32
22j	H	4-Cl	40 ± 6.2	34 ± 2.5	25 ± 1.3	29 ± 3.1	51
22k	H	4-CF_3	48 ± 2.2	32 ± 1.4	13 ± 2.1	31 ± 4.5	49

[a] Cell lines were treated with different concentrations of compounds for 48 h as described under Materials and methods. Cell viability was measured employing MTT assay.
[b] IC_{50} values are indicated as the mean ± SD of three independent experiments.
[c] Compounds were preincubated with tubulin (2 mg/ml) at a final concentration of 5 μM.

Table 3
Antitubulin activity of compounds **19b**, **19c**, **22b** and **22c**.[a]

Compound	Anti-tubulin activity, IC_{50} (5 μM)
1	1.7 ± 0.51
19b	6.8 ± 0.89
19c	9.2 ± 1.20
22b	8.6 ± 0.16
22c	11.2 ± 0.75

[a] Effect of congeners on tubulin polymerization. IC_{50} values for **19b**, **19c**, **22b**, **22c** and colchicine were determined from the tubulin polymerization assays.

tubulin cytoskeleton by immunohistochemistry, human cervical cancer cells were treated with the compounds at 10 μM concentrations for 24 h and the cells were stained with antitubulin antibody. The tubulin network was severely disrupted in cells treated with all 4 compounds. DAPI was employed to stain nucleus. In contrast, cells treated with DMSO demonstrated a normal and intact tubulin organization (Fig. 3).

3.5. Distribution of soluble versus polymerized tubulin in cells

Microtubules are in dynamic equilibrium with tubulin dimers as tubulin is polymerized into microtubules, which are depolymerized to tubulin. Microtubule disrupting agents target this dynamic equilibrium. Microtubule stabilizing (paclitaxel) drugs promote polymerization [4], whereas, microtubule depolymerization agents (nocodazole and colcemid) inhibit polymerization thereby increase the cytosolic pool of tubulin heterodimers [12]. To gain further insight on the specific property of compounds **19b** and **22b** due to their potent cytotoxic effect and inhibition of tubulin assembly, we analyzed the levels of soluble and polymerized fractions of tubulin in HeLa cells by treatment with 10 μM of compounds **19b** and **22b** for 24 h. Subsequently, soluble (free tubulin) and polymerized (microtubules) fractions of tubulin were collected. Nocodazole and paclitaxel were employed at 1 μM concentrations. Nocodazole treated cells demonstrated marked shift in tubulin from the polymerized to soluble fraction. In contrast, the tubulin protein was more in the polymerized fraction than the soluble portion of paclitaxel treated cells. The DMSO treated cells exhibited an equal distribution of tubulin among the two fractions similar to nocodazole, cells treated with **19b** and **22b** contained higher amounts of tubulin in the soluble fraction (Fig. 4A). Therefore, our results suggest that **19b** and **22b** function as microtubule-destabilizing agents under both in vitro and intracellular conditions.

3.6. Cell cycle related expression of cyclin B1

Cyclin B1/CDc2 complex regulates the progression of cell cycle at G2/M. Cyclin B1 levels peak during metaphase [19]. To determine that the cell population obtained after treatment with compounds was indeed arrested at G2/M phase, we performed immunoblot analysis of cyclin B1. HeLa cells were treated with 10 μM of **19b**, **19c**, **22b** and **22c** for duration of 24 h. Paclitaxel was employed at 1 μM concentration. Cells treated with compounds exhibited marked increase in cyclin B1 protein expression. Under similar experimental conditions, paclitaxel employed as positive control also induced the expression of cyclin B1 (Fig. 4B).

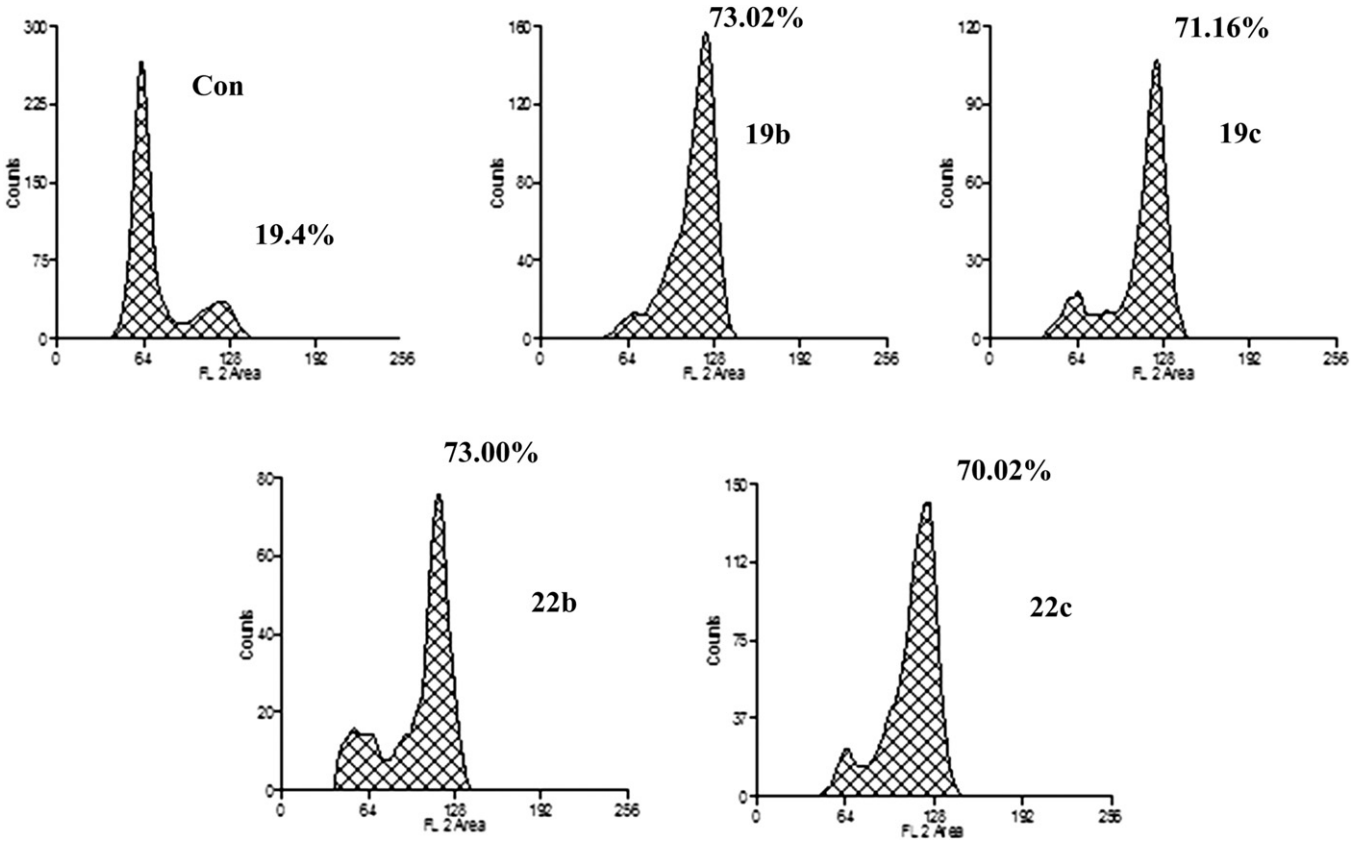


Fig. 2. Antimitotic effects of **19b**, **19c**, **22b** and **22c** by FACS analysis. Cell cycle arrest at G2/M phase by compound **19b**, **19c**, **22b** and **22c**. HeLa cells were harvested after treatment with compounds at 10 μM for 24 h. Untreated cells and DMSO treated cells served as controls. The percentage of cells in each phase of cell cycle was quantified by flow cytometry and the values indicate the number of cells stalled at G2/M phase.

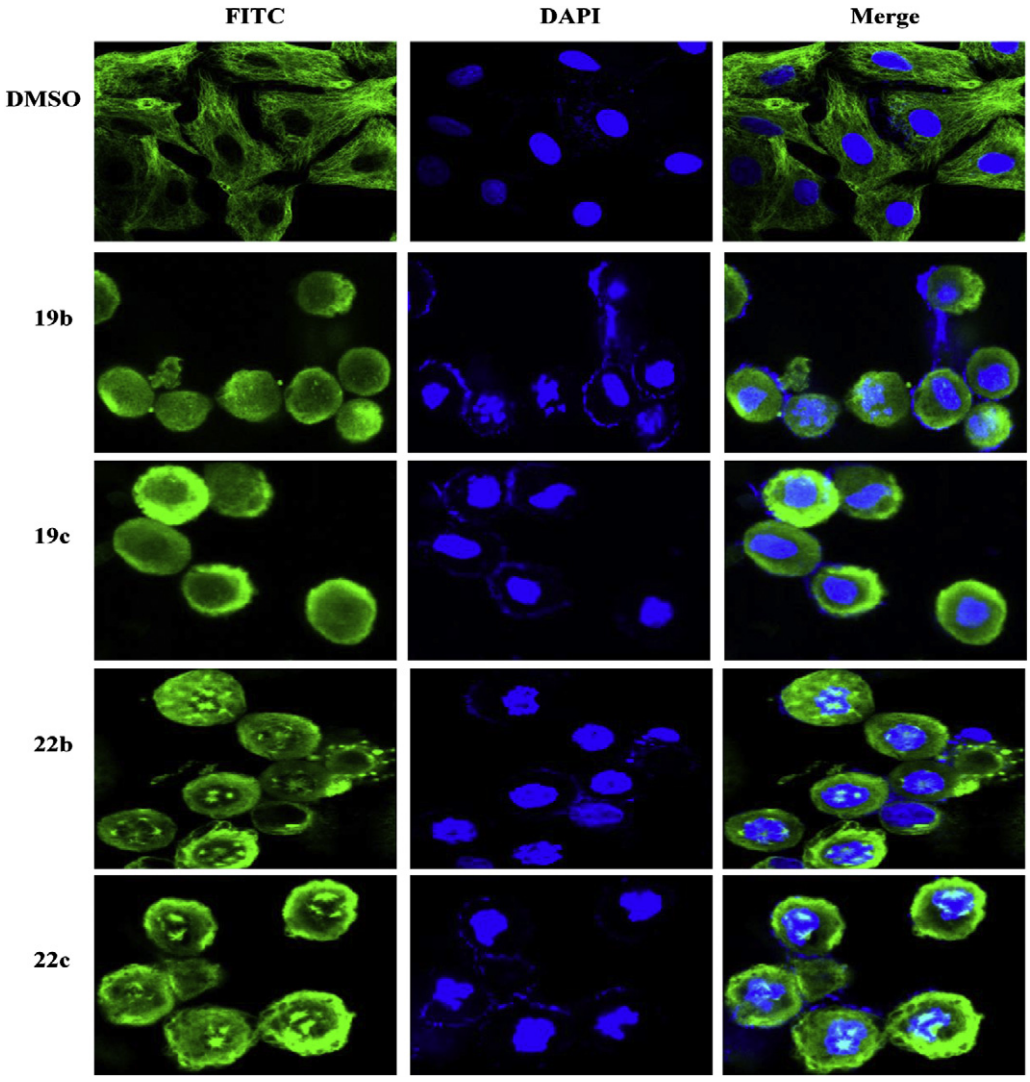


Fig. 3. Effect of **19b**, **19c**, **22b** and **22c** on microtubules and nuclear condensation. HeLa cells were independently treated with **19b**, **19c**, **22b** and **22c** at 10 μM concentrations for 24 h. Following the termination of experiment, cells were fixed and stained for tubulin. DAPI was used as counter stain. The merged images of cells stained for tubulin and DAPI are represented. The photographs were taken using Olympus fluorescence microscope equipped with FITC and DAPI filter settings. Data is the representative of five different fields of view.

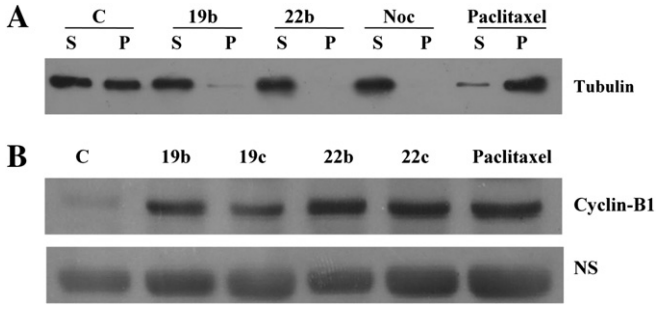


Fig. 4. Distribution of tubulin in polymerized vs soluble fractions as analyzed by Immunobloting in **19b** and **22b** treated HeLa cells. Panel A, A549 cells were treated with 10 μM of **19b** and **22b** for 24 h. Nocodazole and paclitaxel were used at 1 μM concentrations for 24 h treatments. The fractions containing soluble and polymerized tubulin were collected and separated by SDS-PAGE. Tubulin was detected by Immunoblot analysis. Panel B, Hela cells were treated with 10 μM concentrations of Compound **19b**, **19c**, **22b** and **22c** for 24 h. Paclitaxel was treated at 1 μM concentrations for 24 h. Subsequently, whole lysates were prepared and analyzed for Cyclin-B1. A non-specific (NS) band at 90 kDa was used as control.

3.7. Docking study

The possible binding mode for effective compounds with tubulin was investigated by docking simulations, using the Autodock4 [20]. Results suggest that the docking position of trimethoxyphenyl group of all molecules showed a similar binding mode to that of A-ring of colchicines. Some of the amino acids in β-chain are Cys241, Leu242, Ala250, Leu255, Val318 and I378 that are in contact with A-ring of trimethoxyphenyl group (Fig. 5). The 4-substituted methoxy oxygen atom on the C-ring of compounds **19b** and **19c** formed hydrogen bonds with the side chains, amine of Lys254 (3.3 Å) of β-chain and Asn101 (3.1 Å) of α-chain. However, any other substitution at this position except methoxy was unsuitable for making similar hydrogen bonds (Fig. 5A). In contrast, 4-methoxyphenyl group of compounds **22b** and **22c** bend toward B-ring because of π–π stacking. The oxygen atom of 4-methoxy group of compounds **22b** and **22c** participated in hydrogen bonding with Asn101 of α-chain, as Lys254 of β-chain is quite far to form hydrogen bond (Fig. 5B). The B-ring of biphenyl moiety is embedded between the helix 8 and strand 9 of β-chain which is

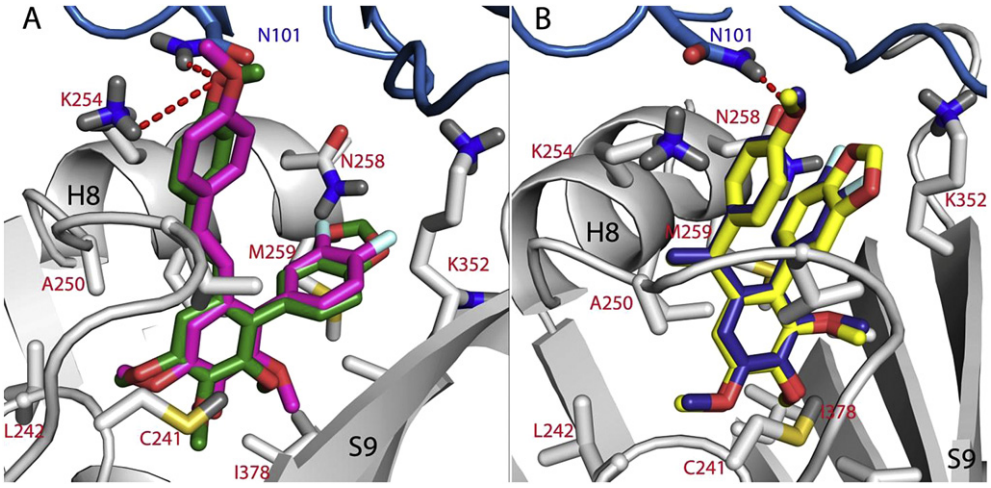


Fig. 5. (A) Possible binding mode of compound **19b**, **19c** in colchicine binding domain present in β-tubulin. Green and pink sticks represent compound **19b** and **19c** respectively. The red dot lines are the potential H-bond between Asn101 (3.1 Å), Lys254 (3.3 Å). H-atoms are displayed in gray color sticks. (B) Docking pose of Compound **22b** (yellow stick) and **22c** (blue sticks) in colchicine binding site of tubulin. Final figure for docking pose was generated by PyMol [22]. For the sake of clarity, hydrogen atoms involved only in the hydrogen bond are shown in the figure as dark gray sticks. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

similar to B-ring of colchicine. B-ring of compounds creates hydrophobic contacts with Met259, Ala316 and Lys352. The 3,4-(1,3-dioxolane) moiety of compounds **19b**, **22b** and 3,4-difluoro substitution of compound **19c**, **22c** form electrostatic attraction with side chain of Asn258 and main chain of Lys352 of β-chain.

4. Conclusion

In the present study, two new series of biaryl aryl stilbenes and 1,1-biaryl aryl ethylenes were designed, synthesized and evaluated for antitubulin activity. Two series of compounds were synthesized from a common intermediate 4,5,6-trimethoxybiphenyl-2-carbaldehydes. Majority of these compounds demonstrated significant antiproliferative activity against the cancer cell lines employed. We have identified four new compounds **19b**, **19c**, **22b** and **22c** as effective cytotoxic agents and inhibitors of tubulin polymerization. These compounds accumulated cells in the G2/M phase, inhibited tubulin assembly and disrupted microtubules as other antitubulin agents. Compounds **19b** and **22b** increased the amount of tubulin in soluble fraction, a feature of microtubule depolymerizing agents. Increased expression of cyclin B1 in cells treated with **19b**, **19c**, **22b** and **22c** corroborated cell cycle arrest at G2/M phase. Molecular docking analysis of both series demonstrated that the compounds occupied colchicine binding site in tubulin. Due to their relative ease of synthesis, the compounds of these series are further amenable for structural modifications and will be useful as templates for the design of new anticancer agents.

5. Experimental section

5.1. Chemistry

5.1.1. Materials and methods

All chemicals were purchased from Sigma–Aldrich and S.D Fine Chemicals, Pvt. Ltd. India and used as received. ACME silica gel (100–200 mesh) was used for column chromatography and thin-layer chromatography was performed on Merck-precoated silica gel 60-F_{254} plates. All the other chemicals and solvents were obtained from commercial sources and purified using standard methods. The IR spectra of all compounds were recorded on a Perkin–Elmer, Spectrum GX FTIR spectrometer. The IR values are reported in reciprocal centimeters (cm^{-1}). The ^1H, ^{13}C NMR spectra were recorded on a Bruker-Avance 300 MHz Spectrometer. Chemical shifts (δ) are reported in ppm, using TMS ($\delta = 0$) as an internal standard in $CDCl_3$. ESI mass spectra were recorded on a Finnigan LCQ Advantagemax spectrometer. High-resolution mass spectra (HRMS) were recorded on QSTAR XL Hybrid MS/MS mass spectrometer. Combustion elemental analyses were recorded on a Vario EL analyzer. All products reported showed ^1H NMR and ^{13}C NMR spectra in agreement with the assigned structures. The purity of compounds was determined by combustion elemental analyses and HRMS and all tested compounds yielded data consistent with a purity of at least 95% compared with the theoretical values.

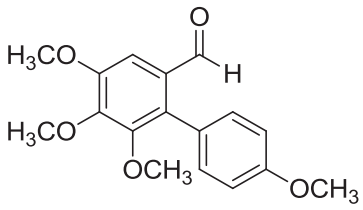
5.1.2. Synthesis of 2-bromo-3,4,5-trimethoxybenzaldehyde (**16**) [11]

A 500 mL round bottom flask was charged with 3,4,5-trimethoxybenzaldehyde **15** (25.5 mmol), methylene chloride (100 mL) and acetic acid (200 μL). The flask was cooled to 0 °C in an ice-bath and bromine (25.5 mmol) in methylene chloride (10 mL) was added dropwise *via* addition funnel over 15 min. After stirring at 0 °C for 30 min, aqueous sodium thiosulfate was added and the mixture was extracted three times with methylene chloride. The combined organic layers were washed with saturated aqueous sodium bicarbonate, brine and dried over sodium sulfate. Removal of the solvent under reduced pressure gave a solid, which was recrystallized (EtOAc/hexane) to give **16** (91%) as colorless needles. mp. 67–69 °C. IR (KBr): 2981, 1690, 1579, 1481, 1385, 1286, 1199, 1166, 1045, 922 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 3.92 (s, 6H), 3.99 (s, 3H), 7.31 (s, 1H), 10.30 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 56.1, 61.1, 61.2, 107.3, 115.5, 128.7, 148.6, 150.6, 152.9, 190.9.

5.1.3. General procedure A for the synthesis of biphenyls (**17a–i**)

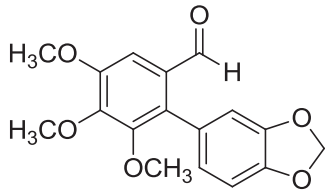
To a solution of 2-bromo-3,4,5-trimethoxybenzaldehyde **16** (1 mmol) in 3 mL ethanol, appropriate aryl boronic acid (1.1 mmol), $Pd(PPh_3)_4$ (1 mol %) sodium carbonate (1.2 mmol, dissolve in a minimum amount of water) was added. The reaction mixture was heated at 80 °C for 6 h. The solvent was removed by rotary evaporation and the product was extracted with ethyl acetate (3 × 10 mL), the organics were washed with water (2 × 10 mL), and dried over anhydrous sodium sulfate. The solvent was evaporated, and the residue was purified by column chromatography on silica gel, eluting with hexane/EtOAc mixture.

*5.1.3.1. 4,4′,5,6-Tetramethoxybiphenyl-2-carbaldehyde (**17a**) [11].*



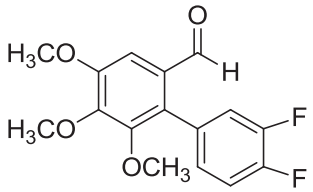
Following the general procedure A, compound **17a** was purified by column chromatography, eluting with hexane–EtOAc (9.5:0.5). 91% yield. White solid. mp. 87–91 °C. IR (KBr): 2940, 1683, 1587, 1464, 1324, 1141, 1087, 996 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 3.56 (s, 3H), 3.86 (s, 3H), 3.96 (s, 3H), 3.97 (s, 3H), 6.93 (d, 2H, $J = 8.3$ Hz), 7.22 (d, 2H, $J = 9.0$ Hz), 7.29 (s, 1H), 9.63 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.1, 55.9, 60.8, 60.9, 105.0, 113.3, 124.6, 129.7, 132.1, 134.1, 151.1, 152.7, 159.2, 191.3. ESI MS (*m*/*z*): 303 $(M + H)^+$.

*5.1.3.2. 2-(Benzo[d][1,3]dioxol-5-yl)-3,4,5-trimethoxybenzaldehyde (**17b**) [11].*



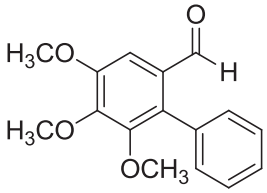
Following the general procedure A, compound **17b** was purified by column chromatography, eluting with hexane–EtOAc (9:1). 95% yield. White solid. mp. 140–143 °C. IR (KBr): 2937, 1682, 1581, 1468, 1329, 1252, 1131, 1093, 1003 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 3.62 (s, 3H), 3.95 (s, 3H), 3.96 (s, 3H), 6.04 (s, 2H), 6.70 (dd, 1H, $J = 2.3$ Hz, 8.3 Hz), 6.81 (d, 1H, $J = 2.3$ Hz), 6.85 (d, 1H, $J = 8.3$ Hz), 7.28 (s, 1H), 9.65 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 56.0, 60.9, 61.0, 101.2, 105.1, 107.8, 111.2, 124.7, 126.2, 129.9, 133.8, 147.4, 151.1, 152.9, 191.1. ESI MS (*m*/*z*): 317 (M + H), 339 $(M + Na)^+$.

*5.1.3.3. 3′,4′-Difluoro-4,5,6-trimethoxybiphenyl-2-carbaldehyde (**17c**) [11].*



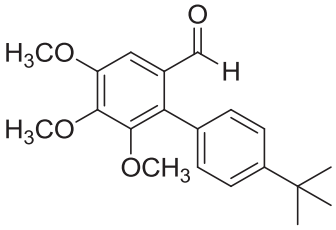
Following the general procedure A, compound **17c** was purified by column chromatography, eluting with hexane–EtOAc (9.5:0.5). 90% yield. White solid. mp. 64–69 °C. IR (KBr): 2939, 1686, 1588, 1483, 1396, 1331, 1136, 1089 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 3.62 (s, 3H), 3.96 (s, 3H), 3.97 (s, 3H), 7.00 (s, 1H), 7.16–7.23 (m, 2H), 7.30 (s, 1H), 9.62 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 56.1, 61.0, 61.1, 105.5, 116.7, 120.0, 127.2, 129.5, 147.6, 148.3, 150.9, 151.6, 153.5, 190.3. ESI MS (*m*/*z*): 309 $(M + H)^+$.

*5.1.3.4. 4,5,6-Trimethoxybiphenyl-2-carbaldehyde (**17d**) [11].*



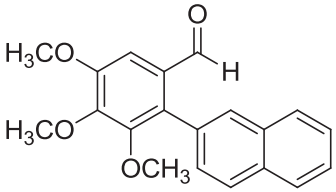
Following the general procedure A, compound **17d** was purified by column chromatography, eluting with hexane–EtOAc (9.5:0.5). 89% yield. White solid. mp. 91–94 °C. IR (KBr): 2849, 1678, 1584, 1330, 1096 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 3.57 (s, 3H), 3.96 (s, 3H), 3.97 (s, 3H), 7.28–7.33 (m, 3H), 7.38–7.45 (m, 3H), 9.61 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.9, 60.9, 105.0, 127.7, 127.8, 129.5, 130.8, 132.6, 134.3, 147.4, 150.9, 152.9, 190.9. ESI MS (*m*/*z*): 273 $(M + H)^+$.

*5.1.3.5. 4′-tert-Butyl-4,5,6-trimethoxybiphenyl-2-carbaldehyde (**17e**) [11].*



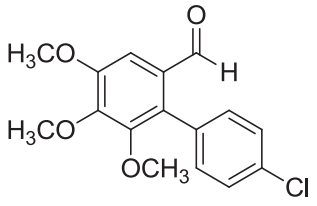
Following the general procedure A, compound **17e** was purified by column chromatography, eluting with hexane–EtOAc (9.5:0.5). 92% yield. White solid. mp. 99–101 °C. IR (KBr): 2961, 1680, 1483, 1483, 1389, 1330, 1146, 1088, 999 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.38 (s, 9H), 3.59 (s, 3H), 3.96 (s, 3H), 3.97 (s, 3H), 7.22 (d, 2H, $J = 8.3$ Hz), 7.31 (s, 1H), 7.42 (d, 2H, $J = 9.0$ Hz), 9.60 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 31.2, 34.5, 56.0, 60.0, 61.9, 105.0, 107.4, 124.8, 129.7, 130.6, 134.5, 147.5, 150.7, 151.2, 152.8, 191.4. ESI MS (*m*/*z*): 329 $(M + H)^+$.

*5.1.3.6. 3,4,5-Trimethoxy-2-(naphthalene-2-yl)benzaldehyde (**17f**).*



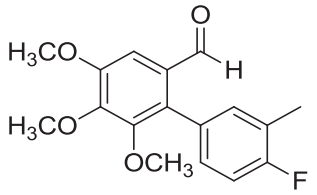
Following the general procedure A, compound **17f** was purified by column chromatography, eluting with hexane–EtOAc (9:1). 88% yield. White solid. mp. 132–134 °C. IR (KBr): 2930. 2850, 1683, 1480, 1316, 1137, 1083, 1003, 828, 763 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 3.57 (s, 3H), 3.99 (s, 3H), 4.00 (s, 3H), 7.36 (s, 1H), 7.40–7.58 (m, 3H), 7.74 (s, 1H), 7.81–7.93 (m, 3H), 9.61 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 56.1, 61.0, 105.3, 126.4, 127.4, 127.7, 128.0, 128.7, 129.9, 130.3, 132.7, 134.2, 147.6, 151.3, 153.2, 190.7. ESI MS (*m*/*z*): 323 $(M + H)^+$.

*5.1.3.7. 4′-Chloro-4,5,6-trimethoxybiphenyl-2-carbaldehyde (**17g**).*



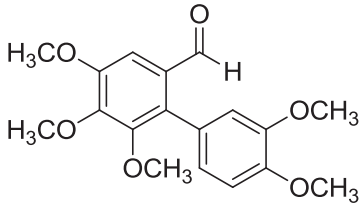
Following the general procedure A, compound **17g** was purified by column chromatography, eluting with hexane–EtOAc (9:1). 90% yield. Liquid. IR (neat): 2929, 2848, 1683, 1472, 1327, 1143, 1091, 844, 723 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 3.60 (s, 3H), 3.98 (s, 6H), 7.27 (d, 2H, $J = 6.8$ Hz), 7.32 (s, 1H) 7.42 (d, 2H, $J = 6.8$ Hz), 9.62 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 56.0, 61.0, 105.5, 128.2, 129.6, 131.3, 132.3, 132.9, 134.2, 147.6, 151.0, 153.3, 190.1. ESI MS (*m*/*z*): 307 $(M + H)^+$.

*5.1.3.8. 4′-Fluoro-4,5,6-trimethoxy-3′-methylbiphenyl-2-carbaldehyde (**17h**).*



Following the general procedure A, compound **17h** was purified by column chromatography, eluting with hexane–EtOAc (9.5:0.5). 88% yield. Liquid. IR (neat): 2937, 2849, 1684, 1482, 1329, 1136, 1093, 1017, 829,760 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 2.33 (s, 3H), 3.62 (s, 3H), 3.96 (s, 3H), 4.00 (s, 3H), 7.05–7.19 (m, 3H), 7.35 (s, 1H), 9.65 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.5, 56.0, 61.0, 105.1, 114.4, 124.6, 128.2, 129.7, 133.5, 133.9, 147.5, 151.0, 153.0, 159.3, 162.6, 191.0. ESI MS (*m*/*z*): 327 $(M + Na)^+$.

*5.1.3.9. 3′,4,4′,5,6-Pentamethoxybiphenyl-2-carbaldehyde (**17i**).*

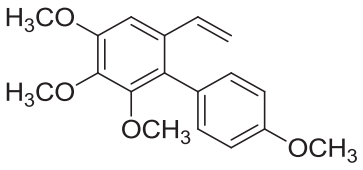


Following the general procedure A, compound **17i** was purified by column chromatography, eluting with hexane–EtOAc (9:1). 85% yield. White solid. mp. 92–95 °C. IR (KBr): 2934, 1680, 1585, 1463, 1324, 1249, 1137, 1090, 1008 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 3.59 (s, 3H), 3.88 (s, 3H), 3.93 (s, 3H), 3.96 (s, 3H), 3.98 (s, 3H), 3.98 (s, 3H), 6.80 (dd, 1H, $J = 1.9$ Hz, 7.8 Hz), 6.84 (s, 1H), 6.90 (d, 1H, $J = 8.8$ Hz), 7.30 (s, 1H), 9.64 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.7, 55.8, 55.9, 60.9, 104.9, 110.4, 113.9, 123.6, 124.9, 129.7, 134.0, 147.4, 148.2, 148.6, 151.0, 152.7, 191.2. ESI MS (*m*/*z*): 355 $(M + Na)^+$.

*5.1.4. General procedure B for the synthesis of styrenes (**18a–i**)*

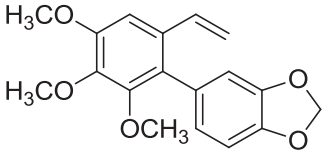
Methyl triphenylphosphonium bromide (1.2 equiv) and ^tBuOK (2.0 equiv) in dry THF were stirred for 1 h. The aldehyde (1.0 equiv) was added, dropwise and the reaction mixture stirred was for 24 h. After the completion of the reaction, the solvent was removed by rotary evaporation and the product was extracted with ethyl acetate (3 × 10 mL), the organics were washed with water (2 × 10 mL), and dried over anhydrous sodium sulfate. The solvent was evaporated, and the residue was purified by column chromatography on silica gel, eluting with hexane/EtOAc mixture.

*5.1.4.1. 2,3,4,4′-Tetramethoxy-6-vinylbiphenyl (**18a**).*



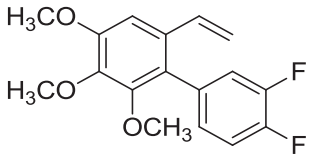
Following the general procedure B, compound **18a** was purified by column chromatography, eluting with hexane–EtOAc (9.7:0.3). 85% yield. White solid. mp. 57–59 °C. IR (KBr): 2932, 2834, 1584, 1453, 1326, 1238, 1093, 918, 822, 784 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 3.53 (s, 3H), 3.84 (s, 3H), 3.88 (s, 3H), 3.92 (s, 3H), 5.03 (d, 1H, $J = 10.8$ Hz), 5.49 (d, 1H, $J = 17.4$ Hz), 6.41 (dd, 1H, $J = 10.8$ Hz, 17.4 Hz), 6.84–6.91 (m, 3H), 7.08–7.15 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.1, 55.9, 60.7, 60.9, 93.0, 103.8, 113.2, 113.4, 124.2, 128.1, 131.7, 132.2, 135.5, 142.0, 151.4, 152.5, 158.4. ESI MS (*m*/*z*): 323 $(M + Na)^+$.

*5.1.4.2. 5-(2,3,4-Trimethoxy-6-vinylphenyl)benzo[d][1,3]dioxole (**18b**).*



Following the general procedure B, compound **18b** was purified by column chromatography, eluting with hexane–EtOAc (9.2:0.8). 88% yield. White solid. mp. 53–55 °C. IR (KBr): 2929, 1593, 1474, 1324, 1231, 1126, 1036, 929, 804 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 3.58 (s, 3H), 3.88 (s, 3H), 3.92 (s, 3H), 5.05 (d, 1H, $J = 11.3$ Hz), 5.49 (d, 1H, $J = 16.9$ Hz), 5.99 (s, 2H), 6.43 (dd, 1H, $J = 11.3$ Hz, 16.9 Hz), 6.59–6.70 (m, 2H), 6.78–6.83 (m, 1H), 6.86 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.9, 60.9, 100.9, 103.8, 107.8, 111.1, 113.6, 124.0, 128.0, 129.6, 132.2, 135.5, 142.0, 146.4, 147.1, 151.3, 152.6. ESI MS (*m*/*z*): 337 $(M + Na)^+$.

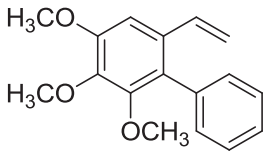
*5.1.4.3. 3′, 4′-Difluoro-2,3,4-trimethoxy-6-vinylbiphenyl (**18c**).*



Following the general procedure B, compound **18c** was purified by column chromatography, eluting with hexane–EtOAc (9.7:0.3).

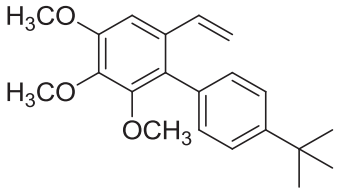
84% yield. Liquid IR (neat): 2931, 2852, 1595, 1484, 1331, 1137, 1071, 914, 802, 768 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 3.59 (s, 3H), 3.88 (s, 3H), 3.93 (s, 3H), 5.09 (d, 1H, $J = 10.9$ Hz), 5.52 (d, 1H, $J = 17.3$ Hz), 6.35 (dd, 1H, $J = 10.9$ Hz, 17.3 Hz), 6.86 (s, 1H), 6.88–6.99 (m, 1H), 7.00–7.22 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.9, 60.8, 60.9, 104.1, 114.4, 116.4, 119.6, 126.2, 127.0, 132.1, 132.9, 135.0, 142.1, 147.7, 148.1, 151.1, 153.1. ESI MS (m/z): 329 $(M + Na)^+$.

*5.1.4.4. 2,3,4-Trimethoxy-6-vinylbiphenyl (**18d**).*



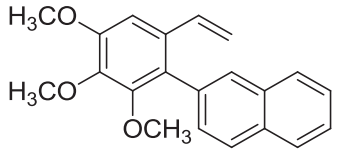
Following the general procedure B, compound **18d** was purified by column chromatography, eluting with hexane–EtOAc (9.7:0.3). 83% yield. White solid. mp. 64–66 °C. IR (KBr): 2972, 2854, 1596, 1449, 1329, 1148, 1095, 846, 708 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 3.54 (s, 3H), 3.89 (s, 3H), 3.93 (s, 3H), 5.04 (d, 1H, $J = 10.5$ Hz), 5.50 (d, 1H, $J = 17.3$ Hz), 6.38 (dd, 1H, $J = 10.5$ Hz, 17.3 Hz), 6.89 (s, 1H), 7.15–7.23 (m, 2H), 7.28–7.41 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.9, 60.8, 60.9, 103.8, 113.6, 126.8, 127.7, 128.6130.6, 131.9, 135.4, 136.1, 142.1, 151.2, 152.7. ESI MS (m/z): 271 $(M + H)^+$.

*5.1.4.5. 4′-tert-Butyl-2,3,4-trimethoxy-6-vinylbiphenyl (**18e**).*



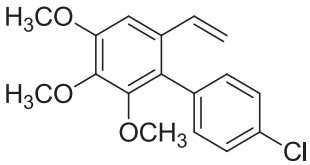
Following the general procedure B, compound **18e** was purified by column chromatography, eluting with hexane–EtOAc (9.7:0.3). 85% yield. White solid. mp. 61–63 °C. IR (KBr): 2959, 2866, 1589, 1480, 1327, 1146, 1088, 926, 815 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.38 (s, 9H), 3.56 (s, 3H), 3.89 (s, 3H), 3.93 (s, 3H), 5.04 (d, 1H, $J = 11.1$ Hz), 5.50 (d, 1H, $J = 17.1$ Hz), 6.41 (dd, 1H, $J = 11.1$ Hz, 17.1 Hz), 6.89 (s, 1H), 7.11 (d, 2H, $J = 8.1$ Hz), 7.36 (d, 2H, $J = 8.1$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 31.5, 34.6, 55.9, 60.8, 103.9, 113.2, 124.6, 128.6, 130.3, 132.1, 133.0, 135.8, 142.2, 149.4, 151.1, 152.6. ESI MS (m/z): 327 $(M + H)^+$.

*5.1.4.6. 2-(2,3,4-Trimethoxy-6-vinylbiphenyl)naphthalene (**18f**).*



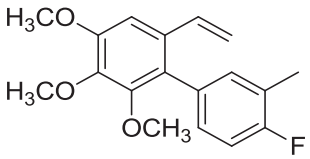
Following the general procedure B, compound **18f** was purified by column chromatography, eluting with hexane–EtOAc (9.2:0.8). 83% yield. White solid. mp. 67–69 °C. IR (KBr): 2926, 1658, 1548, 1431, 1354, 1199, 1086, 931, 746 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 3.54 (s, 3H), 3.91 (s, 3H), 3.95 (s, 3H), 5.02 (d, 1H, $J = 10.9$ Hz), 5.53 (d, 1H, $J = 17.3$ Hz), 6.41 (dd, 1H, $J = 10.9$ Hz, 17.3 Hz), 6.93 (s, 1H), 7.32–7.39 (m, 1H), 7.40–7.51 (m, 2H), 7.66 (s, 1H), 7.76–7.89 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.9, 60.7, 60.9, 104.3, 113.6, 125.8, 127.1, 127.7, 128.0, 128.5, 129.1, 129.2, 132.2, 132.5, 133.2, 133.7, 135.7, 142.4, 151.6, 152.9. ESI MS (m/z): 343 $(M + Na)^+$.

*5.1.4.7. 4′-Chloro-2,3,4-trimethoxy-6-vinylbiphenyl (**18g**).*



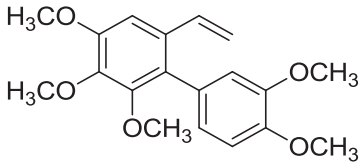
Following the general procedure B, compound **18g** was purified by column chromatography, eluting with hexane–EtOAc (9.2:0.8). 86% yield. Liquid. IR (neat): 2936, 2834, 1590, 1478, 1328, 1093, 916, 816, 764 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 3.55 (s, 3H), 3.88 (s, 3H), 3.93 (s, 3H), 5.06 (d, 1H, $J = 10.8$ Hz), 5.51 (d, 1H, $J = 17.3$ Hz), 6.36 (dd, 1H, $J = 10.8$ Hz, 17.3 Hz), 6.87 (s, 1H), 7.15 (d, 2H, $J = 8.3$ Hz), 7.35 (d, 2H, $J = 8.3$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.9, 60.7, 60.8, 104.1, 114.0, 127.1, 128.0, 132.0, 132.1, 132.9, 134.5, 135.3, 142.2, 151.2, 152.9. ESI MS (m/z): 305 $(M + H)^+$.

*5.1.4.8. 4′-Fluoro-2,3,4-trimethoxy-3′-methyl-6-vinylbiphenyl (**18h**).*



Following the general procedure B, compound **18h** was purified by column chromatography, eluting with hexane–EtOAc (9.7:0.3). 82% yield. Liquid. IR (neat): 2926, 2851, 1589, 1482, 1328, 1136, 1093, 990, 801, 754 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 2.30 (s, 3H), 3.60 (s, 3H), 3.91 (s, 3H), 3.94 (s, 3H), 5.09 (d, 1H, $J = 10.9$ Hz), 5.56 (d, 1H, $J = 17.5$ Hz), 6.41 (dd, 1H, $J = 10.9$ Hz, 17.5 Hz), 6.94 (s, 1H), 6.99–7.08 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.5, 55.9, 60.8, 60.9, 103.7, 113.7, 114.4, 124.0, 127.6, 129.5, 131.5, 132.0, 133.6, 135.2, 142.0, 151.2, 152.7, 162.0. ESI MS (m/z): 303 $(M + H)^+$.

*5.1.4.9. 2,3,3′,4,4′-Pentamethoxy-6-vinylbiphenyl (**18i**).*



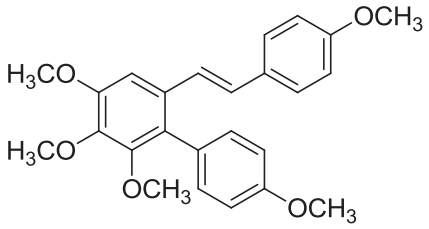
Following the general procedure B, compound **18i** was purified by column chromatography, eluting with hexane–EtOAc (9.2:0.8). 81% yield. White solid. mp. 83–85 °C. IR (KBr): 2933, 2835, 1587, 1484, 1246, 1140, 1096, 1922, 798 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 3.56 (s, 3H), 3.86 (s, 3H), 3.89 (s, 3H), 3.91 (s, 3H), 3.92 (s, 3H), 5.04 (d, 1H, $J = 10.8$ Hz), 5.49 (d, 1H, $J = 17.8$ Hz), 6.43 (dd, 1H, $J = 10.8$ Hz, 17.8 Hz), 6.71–6.75 (m, 2H), 6.84–6.88 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.7, 55.9, 60.9, 103.8, 110.5, 113.4, 119.4, 122.9, 128.2, 128.4, 132.1, 135.4, 142.0, 147.8, 148.1, 151.1, 152.5. ESI MS (m/z): 353 $(M + Na)^+$.

*5.1.5. General procedure C for the synthesis of stilbenes (**19a–k**)*

Taken the aryl halide (1.0 equiv), and styrene (1.2 equiv) into 3 ml of DMA in a 50 mL round bottom flask, then added 0.05 mol% $Pd(OAc)_2$ and 1.4 equiv of K_3PO_4 and the reaction mixture was subjected to reflux at 140 °C for 12 h [15]. After the completion of the reaction, reaction mixture was extracted with ethyl acetate (3 × 10 mL), the organics were washed with water (2 × 10 mL), and dried over anhydrous sodium sulfate. The solvent was evaporated, and the residue was purified by column chromatography on silica gel, eluting with hexane/EtOAc mixture and it is observed that

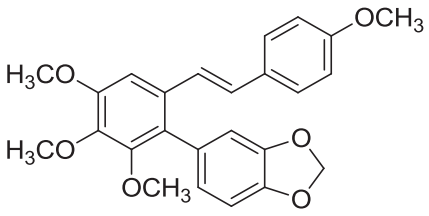
along with the desired products, some unidentified products are also formed.

*5.1.5.1. (E)-2,3,4,4′-Tetramethoxy-6-(4-methoxystyryl)biphenyl (**19a**).*



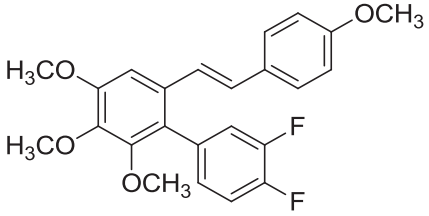
Following the general procedure C, compound **19a** was purified by column chromatography, eluting with hexane–EtOAc (9.5:0.5). 88% yield. White solid. mp. 137–139 °C. IR (KBr): 2931, 2835, 1511, 1455, 1344, 1246, 1094, 829, 775 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 3.54 (s, 3H), 3.77 (s, 3H), 3.87 (s, 3H), 3.90 (s, 3H), 3.96 (s, 3H), 6.65 (d, 1H, J = 15.8 Hz), 6.73–6.80 (m 3H), 6.88–6.94 (m, 2H), 6.96 (s, 1H), 7.15–7.21 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.1, 55.2, 56.0, 60.7, 61.0, 103.7, 113.2, 114.0, 125.4, 127.5, 127.8, 128.1, 128.2, 130.2, 131.9, 132.2, 141.7, 151.5, 152.5, 158.4, 159.0. ESI MS (m/z): 429 $(M + Na)^+$. HRMS (EI, 70 eV): calcd for $C_{25}H_{26}O_5Na$: 429.1677, found: 429.1665.

*5.1.5.2. (E)-5-(2,3,4-Trimethoxy-6-(4-methoxystyryl)phenyl)benzo[d][1,3]dioxole (**19b**).*



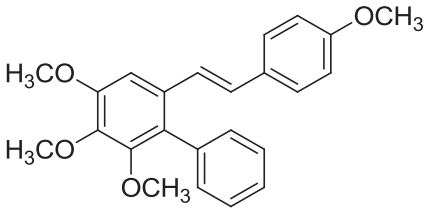
Following the general procedure C, compound **19b** was purified by column chromatography, eluting with hexane–EtOAc (9:1). Liquid. 90% yield. IR (neat): 2927, 1601, 1510, 1471, 1241, 1122, 1036, 931, 811 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 3.60 (s, 3H), 3.78 (s, 3H), 3.90 (s, 3H), 3.96 (s, 3H), 6.02 (s, 2H), 6.63–6.69 (m, 2H), 6.74–6.78 (m, 3H), 6.79–6.83 (m, 2H), 6.95 (s, 1H), 7.18–7.23 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 56.0, 56.1, 60.8, 60.9, 100.9, 103.8, 107.8, 111.3, 114.0, 124.3, 125.3, 127.6, 128.0, 128.1, 129.8, 130.2, 132.3, 141.7, 146.5, 147.2, 151.3, 152.7, 159.1. ESI MS (m/z): 443 $(M + Na)^+$. HRMS (EI, 70 eV): calcd for $C_{25}H_{24}O_6Na$: 443.1470, found: 443.1470.

*5.1.5.3. (E)-3′, 4′-Difluoro-2,3,4,-trimethoxy-6-(4-methoxystyryl) biphenyl (**19c**).*



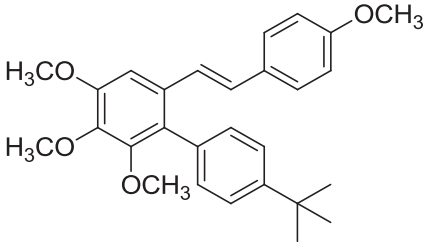
Following the general procedure C, compound **19c** was purified by column chromatography, eluting with hexane–EtOAc (9.5:0.5). 86% yield. White solid. mp. 98–100 °C. IR (KBr): 2926, 2850, 1599, 1509, 1451, 1336, 1265, 1084, 821, 765 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 3.60 (s, 3H), 3.78 (s, 3H), 3.89 (s, 3H), 3.97 (s, 3H), 6.56 (d, 1H, J = 16.2 Hz), 6.70–6.85 (m 3H), 6.89–7.02 (m, 2H), 7.106–7.23 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.2, 56.0, 60.8, 103.9, 114.0, 116.4, 119.7, 124.5, 126.1, 127.1, 127.6, 128.8, 129.9, 132.1, 133.1, 141.6, 147.7, 148.1, 151.2, 153.1, 159.2. ESI MS (m/z): 435 $(M + Na)^+$. HRMS (EI, 70 eV): calcd for $C_{24}H_{22}O_4F_2Na$: 435.1383, found: 435.1394.

*5.1.5.4. (E)-2,3,4,-Trimethoxy-6-(4-methoxystyryl)biphenyl (**19d**).*



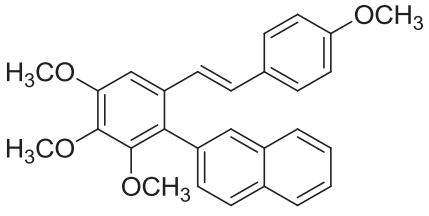
Following the general procedure C, compound **19d** was purified by column chromatography, eluting with hexane–EtOAc (9.5:0.5). 84% yield. White solid. mp. 102–104 °C. IR (KBr): 2929, 2834, 1505, 1456, 1399, 1245, 1091, 831, 702 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 3.55 (s, 3H), 3.76 (s, 3H), 3.90 (s, 3H), 3.97 (s, 3H), 6.60 (d, 1H, J = 15.8 Hz), 6.73–6.77 (m, 3H), 6.97 (s, 1H), 7.11–7.17 (m, 2H), 7.24–7.27 (m, 2H), 7.30–7.35 (m, 1H), 7.36–7.41 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.1, 56.0, 60.7, 60.9, 104.0, 114.0, 125.4, 126.9, 127.6, 127.8, 128.0, 128.7, 130.3, 131.0, 132.0, 136.2, 141.9, 151.4, 152.8, 159.1. ESI MS (m/z): 399 $(M + Na)^+$. HRMS (EI, 70 eV): calcd for $C_{24}H_{24}O_4Na$: 399.1572, found: 399.1577.

*5.1.5.5. (E)-4′-tert-Butyl-2,3,4,-trimethoxy-6-(4-methoxystyryl) biphenyl (**19e**).*



Following the general procedure C, compound **19e** was purified by column chromatography, eluting with hexane–EtOAc (9.5:0.5). 88% yield. Liquid. IR (neat): 2924, 2853, 1605, 1510, 1460, 1336, 1249, 1093, 831, 770 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.39 (s, 9H), 3.56 (s, 3H), 3.76 (s, 3H), 3.90 (s, 3H), 3.96 (s, 3H), 6.63 (d, 1H, J = 16.0 Hz, 1H), 6.72–6.80 (m, 3H), 6.96 (s, 1H), 7.14–7.22 (m, 4H), 7.34–7.44 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 29.6, 31.4, 34.5, 55.2, 56.0, 60.8, 60.9, 104.0, 114.0, 124.6, 125.6, 127.6, 127.9, 128.6, 129.1, 130.4, 132.2, 133.0, 141.8, 149.5, 151.5, 152.6, 159.0. ESI MS (m/z): 455 $(M + Na)^+$. HRMS (EI, 70 eV): calcd for $C_{28}H_{32}O_4Na$: 455.2198, found: 455.2200.

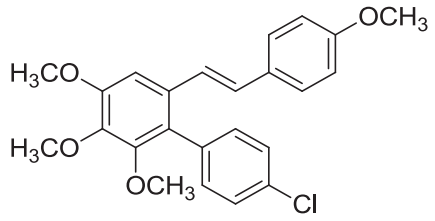
*5.1.5.6. (E)-2-(2,3,4-Trimethoxy-6-(4-methoxystyryl)phenyl)naphthalene (**19f**).*



Following the general procedure C, compound **19f** was purified by column chromatography, eluting with hexane–EtOAc (9:1). 85% yield. Liquid. IR (neat): 2924, 2853, 1632, 1510, 1402, 1250, 1092, 828, 772 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 3.54 (s, 3H), 3.73 (s, 3H), 3.93 (s,

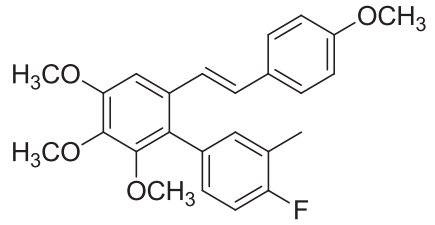
3H), 3.99 (s, 3H), 6.65 (d, 1H, $J = 16.6$ Hz), 6.96–6.86 (m, 3H), 7.01 (m, 1H), 7.07–7.19 (m, 2H), 7.35–7.58 (m, 3H), 7.70–7.94 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.1, 56.1, 60.8, 61.0, 96.2, 104.1, 114.0, 125.4, 125.8, 125.9, 127.2, 127.6, 127.8, 128.2, 128.3, 128.5, 129.4, 129.9, 130.2, 131.3, 132.3, 135.9, 141.9, 151.8, 152.9, 159.2. ESI MS (m/z): 449 $(M + Na)^+$. HRMS (EI, 70 eV): calcd for $C_{28}H_{26}O_4Na$: 449.1728, found: 449.1724.

*5.1.5.7. (E)-4′-Chloro-2,3,4,-trimethoxy-6-(4-methoxystyryl)biphenyl (**19g**).*



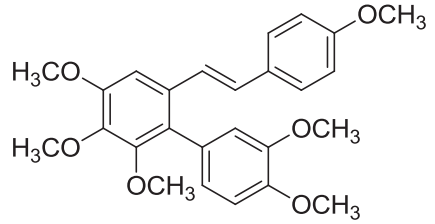
Following the general procedure C, compound **19g** was purified by column chromatography, eluting with hexane–EtOAc (9:1). 88% yield. White solid. mp. 124–126 °C. IR (KBr): 2930, 2833, 1596, 1474, 1399, 1248, 1091, 826, 769 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.56 (s, 3H), 3.78 (s, 3H), 3.90 (s, 3H), 3.96 (s, 3H), 6.58 (d, 1H, $J = 16.6$ Hz, 1H), 6.74–6.84 (m, 3H), 6.96 (m, 1H), 7.15–7.23 (m, 4H), 7.34–7.41(m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.1, 56.0, 60.7, 60.9, 104.0, 114.0, 124.9, 127.1, 127.6, 128.0, 128.6, 130.0, 132.0, 132.3, 132.9, 134.6, 141.8, 151.3, 153.0, 159.2. ESI MS (m/z): 433 $(M + Na)^+$. HRMS (EI, 70 eV): calcd for $C_{24}H_{23}O_4NaCl$: 433.1182, found: 433.1178.

*5.1.5.8. (E)-4′-Fluoro-2,3,4-trimethoxy-3′-methyl-6-styrylbiphenyl (**19h**).*



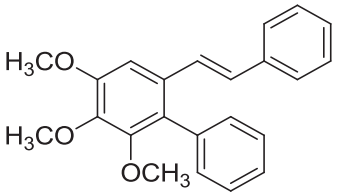
Following the general procedure C, compound **19h** was purified by column chromatography, eluting with hexane–EtOAc (9.5:0.5). 87% yield. Liquid. IR (neat): 2922, 2852, 1605, 1459, 1340, 1246, 1092, 826, 758 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.31 (s, 3H), 3.61 (s, 3H), 3.80 (s, 3H), 3.93 (s, 3H), 3.98 (s, 3H), 6.65 (d, 1H, $J = 15.8$ Hz), 6.80–6.91 (m, 3H), 7.02–7.16 (m, 4H), 7.21–7.25 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.6, 55.2, 56.2, 60.8, 61.0, 103.7, 114.0, 114.5, 119.0, 124.0, 125.0, 127.5, 128.1, 129.6, 130.1, 132.1, 132.9, 133.9, 141.7, 151.3, 152.7, 159.1, 162.1. ESI MS (m/z): 409 $(M + H)^+$. HRMS (EI, 70 eV): calcd for $C_{25}H_{25}O_4FNa$: 431.1629, found: 431.1640.

*5.1.5.9. (E)-2,3,3′,4,4′-Pentamethoxy-6-(4-methoxystyryl)biphenyl (**19i**).*



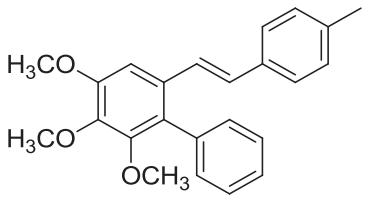
Following the general procedure C, compound **19i** was purified by column chromatography, eluting with hexane–EtOAc (9:1). 86% yield. White solid. mp. 135–137 °C. IR (KBr): 2931, 2834, 1598, 1458, 1258, 1171, 1093, 810, 760 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.62 (s, 3H), 3.79 (s, 3H), 3.85 (s, 3H), 3.94 (S, 3H), 3.95 (s, 3H), 3.98 (s, 3H) 6.74 (d, 1H, $J = 15.8$ Hz), 6.80–6.89 (m, 5H), 6.92–7.00 (m, 2H), 7.21–7.28 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.1, 55.7, 55.9, 60.8, 60.9, 103.6, 110.4, 113.9, 123.1, 125.3, 127.4, 127.8, 128.1, 28.5, 130.1, 130.9, 132.1, 141.6, 147.7, 148.0, 151.4, 152.5, 159.0. ESI MS (m/z): 437 $(M + H)^+$. HRMS (EI, 70 eV): calcd for $C_{26}H_{29}O_6$: 437.1958, found: 437.1960.

*5.1.5.10. (E)-2,3,4,-Trimethoxy-6-styrylbiphenyl (**19j**).*



Following the general procedure C, compound **19j** was purified by column chromatography, eluting with hexane–EtOAc (9.5:0.5). 87% yield. White solid. mp. 85–87 °C. IR (KBr): 2926, 2852, 1593, 1457, 1343, 1236, 1145, 1096, 962, 754 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.56 (s, 3H), 3.91 (s, 3H), 3.97 (s, 3H), 6.76–6.82 (m, 2H), 7.00 (s, 1H), 7.11–7.18 (m, 1H), 7.23–7.28 (m, 5H), 7.31–7.46 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 56.0, 60.7, 60.9, 104.3, 126.4, 127.0, 127.3, 127.5, 127.8, 128.6, 129.0, 129.7, 131.0, 131.7, 136.2, 137.5, 142.3, 151.3, 152.8. ESI MS (m/z): 369 $(M + Na)^+$. HRMS (EI, 70 eV): calcd for $C_{23}H_{22}O_3Na$: 369.1480, found: 369.1480.

*5.1.5.11. (E)-2,3,4-Trimethoxy-6-(4-methylstyryl)biphenyl (**19k**).*

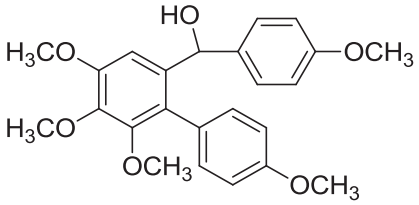


Following the general procedure C, compound **19k** was purified by column chromatography, eluting with hexane–EtOAc (9.5:0.5). 86% yield. White solid. mp. 95–97 °C. IR (KBr): 2926, 2855, 1588, 1446, 1395, 1142, 1090, 835, 754 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.31 (s, 3H), 3.55 (s, 3H), 3.91 (s, 3H), 3.97 (s, 3H), 6.65–6.73 (m, 1H), 6.76–6.84 (m, 1H), 6.96–7.06 (m, 3H), 7.09–7.15 (m, 2H),7.23–7.24 (m, 1H), 7.26–7.27 (m, 1H), 7.31–7.43 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.3, 56.0, 60.7, 60.9, 104.2, 108.7, 126.4, 126.6, 127.0, 127.8, 128.5, 128.8, 129.3, 131.0, 132.0, 134.7, 136.2, 142.1, 151.4, 152.8. ESI MS (m/z): 383 $(M + Na)^+$. HRMS (EI, 70 eV): calcd for $C_{24}H_{24}O_3Na$: 383.1623, found: 383.1631.

*5.1.6. General procedure D for the synthesis of biphenylmethanols (**20a–k**)*

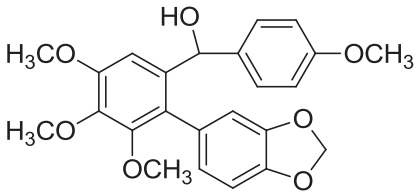
An aryl magnesium bromide prepared from arylbromide (1.5 mmol) and magnesium turnings (activated with iodine) in anhydrous tetrahydrofuran was slowly added to the corresponding aldehydes (1.0 mmol) in tetrahydrofuran at 0 °C. The reaction mixture was warmed up to room temperature, and stirring was continued for another 2 h. A saturated NH_4Cl solution was slowly added at 0 °C, the mixture was extracted with ethyl acetate and dried over anhydrous sodium sulfate. The solvent was evaporated, and the residue purified by column chromatography on silica gel, eluting with hexane/EtOAc mixture.

*5.1.6.1. (4-Methoxyphenyl)(4,4′,5,6-tetramethoxy-biphenyl-2-yl) methanol (**20a**).*



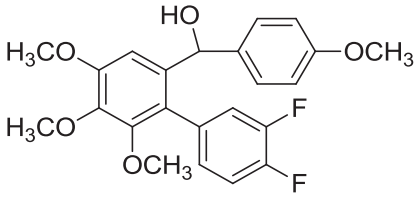
Following the general procedure D, compound **20a** was purified by column chromatography, eluting with hexane–EtOAc (7:3). 90% yield. Liquid. IR (neat): 3422, 2936, 2834, 1581, 1461, 1246, 1141, 1083, 824, 755 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 2.05 (brs, 1H), 3.57 (s, 3H), 3.78 (s, 3H), 3.84 (s, 3H), 3.88 (s, 3H), 3.89 (s, 3H), 5.64 (s, 1H), 6.78 (d, 2H, J = 9.0 Hz), 6.80–6.82 (m, 2H), 6.92–6.99 (m, 2H), 7.04 (d, 2H, J = 9.0 Hz), 7.15–7.25 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.1, 55.4, 56.2, 60.5, 61.0, 104.6, 110.6, 113.0, 114.1, 122.6, 126.5, 129.2, 132.8, 133.6, 141.5, 143.5, 148.2, 149.4, 152.7, 158.5. ESI MS (m/z): 393 $(M - OH)^+$.

*5.1.6.2. (2-(Benzo[d][1,3]dioxol-5-yl)-3,4,5-trimethoxyphenyl)(4-methoxyphenyl)methanol (**20b**).*



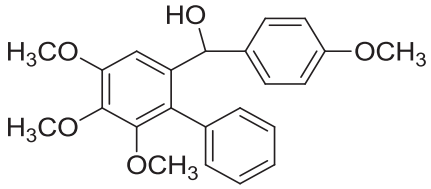
Following the general procedure D, compound **20b** was purified by column chromatography, eluting with hexane–EtOAc (7:3). 85% yield. White solid. mp. 121–123 °C IR (KBr): 3448, 2936, 2836, 1602, 1459, 1241, 1132, 1036, 935, 753.cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 2.04 (d, 1H, J = 3.4 Hz), 3.62 (s, 3H), 3.78 (s, 3H), 3.89 (s, 6H), 5.65 (d, 1H, J = 3.4 Hz), 5.93–6.04 (m, 2H), 6.26–6.42 (m, 1H), 6.69–6.98 (m, 5H), 7.01–7.10 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.1, 56.1, 60.8, 61.0, 101.0, 102.9, 104.4, 105.6, 114.0, 114.5, 126.4, 129.1, 129.6, 133.4, 141.4, 141.5, 144.2, 146.2, 147.1, 148.0, 152.6, 158.4. ESI MS (m/z): 407 $(M - OH)^+$.

*5.1.6.3. (3′,4′-Difluoro-4,5,6-trimethoxy-biphenyl-2-yl)(4-methoxyphenyl)methanol (**20c**).*



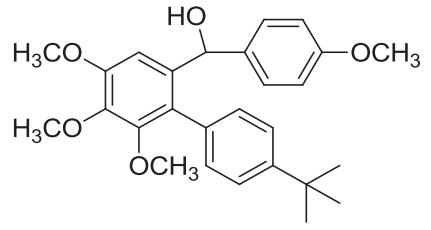
Following the general procedure D, compound **20c** was purified by column chromatography, eluting with hexane–EtOAc (7:3). 86% yield. Liquid. IR (neat): 3450, 2936, 2838, 1602, 1486, 1331, 1131, 1015, 832, 770 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 2.00 (brs, 1H), 3.60 (s, 3H), 3.78 (s, 3H), 3.89 (s, 3H), 3.91 (s, 3H), 5.55 (d, 1H, J = 2.3 Hz), 6.43–6.66 (m, 1H), 6.78 (d, 2H, J = 8.3 Hz), 6.92–7.23 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.0, 55.8, 60.7, 60.8, 72.1, 105.4, 113.5, 116.6, 118.9, 119.8, 125.8, 126.9, 127.8, 132.8, 135.5, 137.4, 141.1, 147.8, 150.8, 153.1, 158.7. ESI MS (m/z): 399 $(M - OH)^+$.

*5.1.6.4. (4-Methoxyphenyl)(4,5,6-trimethoxy-biphenyl-2yl)methanol (**20d**).*



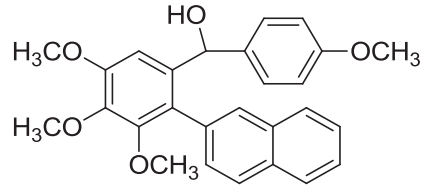
Following the general procedure D, compound **20d** was purified by column chromatography, eluting with hexane–EtOAc (7:3). 84% yield. Liquid. IR (neat): 3453, 2934, 2836, 1605, 1509, 1327, 1245, 1140, 1008, 840, 705 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 2.04 (brs, 1H), 3.58 (s, 3H), 3.77 (s, 3H), 3.89 (s, 3H), 3.90 (s, 3H), 5.61 (s, 1H), 6.77 (d, 2H, J = 9.0 Hz), 6.86–6.92 (m, 1H), 6.98 (s, 1H), 7.01 (d, 2H, J = 9.0 Hz), 7.27–7.46 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.1, 55.9, 60.8, 72.0, 105.3, 113.4, 127.0, 127.8, 127.9, 129.7, 130.6, 135.8, 136.0, 137.4, 141.2, 151.0, 152.8, 158.6. ESI MS (m/z): 252 $(M - OH)^+$.

*5.1.6.5. (4′-(tert-Butyl)-4,5,6-trimethoxy-biphenyl-2-yl)(4-methoxyphenyl)methanol (**20e**).*



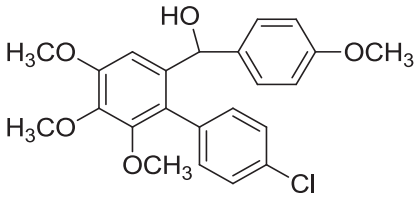
Following the general procedure D, compound **20e** was purified by column chromatography, eluting with hexane–EtOAc (7:3). 88% yield. White solid. mp. 113–115 °C. IR (KBr): 3456, 2939, 2867, 1599, 1456, 1399, 1238, 1140, 1001, 832, 697 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.36 (s, 9H), 1.97 (brs, 1H), 3.60 (s, 3H), 3.78 (s, 3H), 3.87 (s, 3H), 3.90 (s, 3H), 5.63 (s, 1H), 6.77 (d, 2H, J = 8.7 Hz), 6.85 (d, 1H, J = 6.5 Hz), 6.93 (s, 1H), 7.02 (d, 2H, J = 8.7 Hz),7.23 (d, 1H, J = 7.6 Hz),7.29 (d, 1H, J = 6.5 Hz), 7.43 (d, 1H, J = 7.6 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 31.3, 34.4, 55.1, 55.9, 60.7, 60.9, 72.0, 105.4, 113.4, 124.8, 127.7, 129.2, 130.1, 132.8, 135.9, 137.7, 141.3, 149.7, 151.1, 152.7, 158.6. ESI MS (m/z): 419 $(M - OH)^+$.

*5.1.6.6. (4-Methoxyphenyl)(3,4,5-trimethoxy-2-(naphthalen-2-yl) phenyl)methanol (**20f**).*



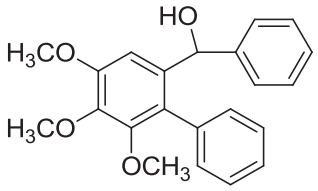
Following the general procedure D, compound **20f** was purified by column chromatography, eluting with hexane–EtOAc (7:3). 82% yield. White solid. mp. 117–119 °C IR (KBr): 3509, 2931, 2838, 1499, 1327, 1239, 1130, 1014, 830, 748 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 2.02 (brs, 1H), 3.57 (s, 3H), 3.77 (s, 3H), 3.92 (s, 6H), 5.48–5.74 (m, 1H), 6.66–6.83 (m, 2H), 6.89–7.19 (m, 4H), 7.40–7.67 (m, 3H), 7.72–7.95 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.1, 56.0, 60.8, 61.0, 72.1, 105.4, 113.5, 125.8, 127.2, 127.6, 127.8, 127.9, 128.1, 128.3, 128.4, 128.9, 129.7, 132.2, 132.8, 133.8, 135.9, 137.5, 141.3, 151.2, 153.0. ESI MS (m/z): 413 $(M - OH)^+$.

*5.1.6.7. (4′-Chloro-4,5,6-trimethoxy-biphenyl-2-yl)(4-methoxyphenyl)methanol (**20g**).*



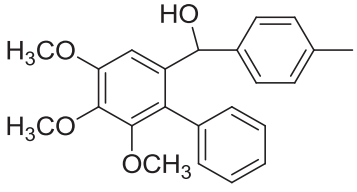
Following the general procedure D, compound **20g** was purified by column chromatography, eluting with hexane–EtOAc (7:3). 80% yield. White solid. mp. 100–102 °C. IR (KBr): 3477, 2913, 1604, 1479, 1328, 1256, 1138, 1020, 835, 734 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.97 (d, 1H, $J = 2.6$ Hz), 3.58 (s, 3H), 3.78 (s, 3H), 3.90 (s, 6H), 5.56 (d, 1H, $J = 2.6$ Hz), 6.74–6.82 (m, 3H), 6.97–7.01 (m, 2H), 7.02 (s, 1H), 7.19–7.25 (m, 1H), 7.27 (s, 1H), 7.32–7.49 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.1, 55.9, 60.7, 60.8, 72.1, 105.3, 113.5, 126.6, 127.9, 131.1, 132.0, 132.9, 134.4, 135.5, 137.3, 141.2, 150.9, 153.0, 158.7. ESI MS (m/z): 397 $(M - OH)^+$.

*5.1.6.8. Phenyl(4,5,6-trimethoxy-biphenyl-2-yl)methanol (**20h**).*



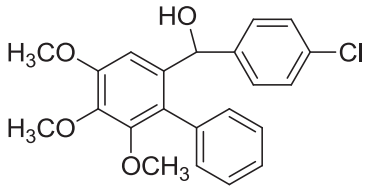
Following the general procedure D, compound **20h** was purified by column chromatography, eluting with hexane–EtOAc (7:3). 82% yield. White solid. mp. 93–95 °C. IR (KBr): 3481, 2933, 1595, 1483, 1324, 1236, 1137, 1019, 847, 706 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 2.09 (brs, 1H), 3.58 (s, 3H), 3.86 (s, 3H), 3.90 (s, 3H), 5.67 (s, 1H), 6.92 (s, 1H), 6.96 (d, 1H, $J = 6.9$ Hz), 7.08–7.15 (m, 2H), 7.17–7.48 (m, 7H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.9, 60.7, 60.9, 72.3, 105.7, 126.4, 127.0, 127.1, 128.0, 128.4, 129.8, 130.6, 136.0, 137.2, 141.4, 143.5, 151.0, 152.9. ESI MS (m/z): 333 $(M - OH)^+$.

*5.1.6.9. p-Tolyl(4,5,6-trimethoxy-biphenyl]-2-yl)methanol (**20i**).*



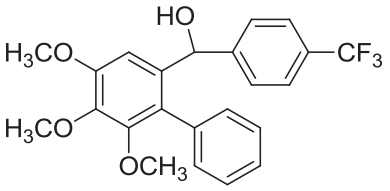
Following the general procedure D, compound **20i** was purified by column chromatography, eluting with hexane–EtOAc (7:3). 80% yield. Liquid. IR (neat): 3455, 2933, 1598, 1481, 1327, 1236, 1140, 1009, 843, 708 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 2.01 (brs, 1H), 2.31 (s, 3H), 3.58 (s, 3H), 3.87 (s, 3H), 3.90 (s, 3H), 5.63 (s, 1H), 6.95 (s, 1H), 6.09–7.09 (m, 5H), 7.28–7.38 (m, 3H), 7.39–7.46 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.9, 55.8, 60.7, 60.8, 72.1, 105.5, 126.3, 126.9, 127.8, 127.9, 128.7, 129.7, 130.6, 135.9, 136.7, 137.4, 141.2, 150.9, 152.8. ESI MS (m/z): 347 $(M - OH)^+$.

*5.1.6.10. (4-Chlorophenyl)(4,5,6-trimethoxy-biphenyl-2-yl)methanol (**20j**).*



Following the general procedure D, compound **20j** was purified by column chromatography, eluting with hexane–EtOAc (7:3). 78% yield. Liquid. IR (neat): 3448, 2935, 2835, 2598, 1483, 1327, 1236, 1140, 1010, 846, 705 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 2.10 (brs, 1H), 3.58 (s, 3H), 3.86 (s, 3H), 3.90 (s, 3H), 5.64 (s, 1H), 6.87 (s, 1H), 6.92–6.98 (m, 1H), 7.03 (d, 2H, $J = 8.3$ Hz), 7.21 (d, 2H, $J = 8.3$ Hz), 7.29–7.46 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.9, 60.8, 60.9, 71.7, 105.4, 127.1, 127.9, 128.0, 128.2, 129.7, 130.5, 132.8, 135.8, 136.8, 141.5, 141.9, 151.0, 153.0. ESI MS (m/z): 367 $(M - OH)^+$.

*5.1.6.11. (4-(Trifluoromethyl)phenyl)(4,5,6-trimethoxy-biphenyl-2-yl) methanol (**20k**).*

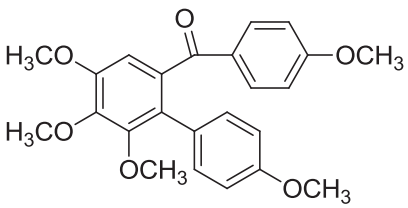


Following the general procedure D, compound **20k** was purified by column chromatography, eluting with hexane–EtOAc (7:3). 75% yield. Liquid. IR (neat): 3439, 2936, 1604, 1474, 1324, 1235, 1127, 1013, 843, 711 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 2.15 (d, 1H, 2.6 Hz), 3.59 (s, 3H), 3.85 (s, 3H), 3.90 (s, 3H), 5.73 (d, 1H, 2.6 Hz), 6.83 (s, 1H), 6.96–7.04 (m, 1H), 7.24 (d, 2H, $J = 8.3$ Hz), 7.30–7.46 (m, 4H), 7.50 (d, 2H, $J = 8.3$ Hz).^{13}C NMR (75 MHz, $CDCl_3$): δ 55.9, 60.8, 71.7, 105.6, 124.9, 126.6, 127.2, 128.1, 128.5, 129.0, 129.7, 130.5, 135.8, 136.6, 141.7, 147.6, 151.1, 153.1. ESI MS (m/z): 401 $(M - OH)^+$.

*5.1.7. General procedure E for the synthesis of diphenylmethanones (**21a–k**)*

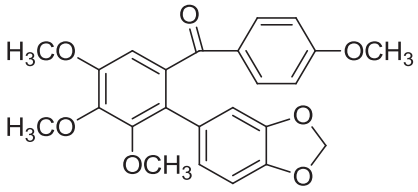
The biphenylmethanol (1 mmol) was dissolved in CH_2Cl_2 and PCC (1.5 mmol) was added to the solution by portions at RT. The resulting solution was stirred for 2 h and after filtration over Celite, the filtrate was evaporated and the residue was purified by flash chromatography on silica gel, eluting with hexane/EtOAc mixture.

*5.1.7.1. (4-Methoxyphenyl)(4,4′,5,6-tetramethoxy-biphenyl-2-yl) methanone (**21a**).*



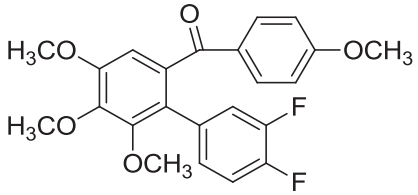
Following the general procedure E, compound **21a** was purified by column chromatography, eluting with hexane–EtOAc (9:1). 86% yield. White solid. mp. 99–101 °C. IR (KBr): 2935, 2839, 1650, 1598, 1458, 1338, 1259, 1166, 1092, 846, 786 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 3.59 (s, 3H), 3.71 (s, 3H), 3.79 (s, 3H), 3.88 (s, 3H), 3.98 (s, 3H), 6.69 (d, 2H, $J = 8.2$ Hz), 6.73 (d, 2H, $J = 9.1$ Hz), 6.76 (s, 1H), 7.11 (d, 2H, $J = 8.2$ Hz). 7.59 (d, 2H, $J = 9.1$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 54.9, 55.2, 56.0, 60.8, 60.9, 107.0, 113.1, 113.2, 127.3, 127.6, 130.1, 131.3, 132.1, 135.6, 143.5, 151.1, 152.2, 158.3, 163.1, 196.6. ESI MS (*m*/*z*): 431 $(M + Na)^+$.

*5.1.7.2. (2-(Benzo[d][1,3]dioxol-5-yl)-3,4,5-trimethoxyphenyl)(4-methoxyphenyl)methanone (**21b**).*



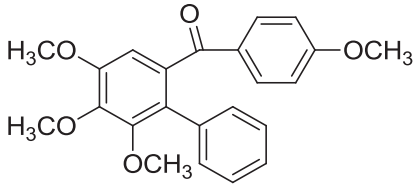
Following the general procedure E, compound **21b** was purified by column chromatography, eluting with hexane–EtOAc (9:1). 80% yield. Liquid. IR (neat): 2929, 2851, 1739, 1657, 1596, 1479, 1334, 1232, 1125, 1037, 846, 758 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 3.64 (s, 3H), 3.81 (s, 3H), 3.88 (s, 3H), 3.98 (s, 3H), 5.86 (s, 2H), 6.59–6.63 (m, 2H), 6.72–6.80 (m, 4H), 7.58–7.65 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.3, 56.0, 60.9, 61.0, 100.7, 107.1, 107.6, 110.8, 113.2, 123.9, 127.2, 129.1, 130.2, 132.1, 135.7, 143.6, 146.5, 146.8, 151.1, 152.4, 163.2, 196.4. ESI MS (*m*/*z*): 423 $(M + H)^+$.

*5.1.7.3. (3′,4′-Difluoro-4,5,6-trimethoxy-biphenyl-2-yl)(4-methoxyphenyl)methanone (**21c**).*



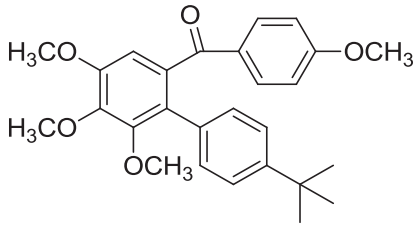
Following the general procedure E, compound **21c** was purified by column chromatography, eluting with hexane–EtOAc (9:1). 82% yield. Liquid. IR (neat): 2939, 2841, 1658, 1569, 1486, 1337, 1260, 1166, 1090, 846, 762 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 3.68 (s, 3H), 3.84 (s, 3H), 3.91 (s, 3H), 4.01 (s, 3H), 6.76–6.84 (m, 3H), 6.89–7.01 (m, 2H), 7.04–7.11 (m, 1H), 7.61 (d, 2H, $J = 8.3$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.3, 56.0, 60.9, 61.0, 107.3, 113.4, 116.3, 119.4, 125.5, 126.5, 129.9, 132.1, 132.3, 135.5, 143.6, 147.6, 147.8, 150.9, 152.9, 163.4, 196.0. ESI MS (*m*/*z*): 457 $(M + Na)^+$.

*5.1.7.4. (4-Methoxyphenyl)(4,5,6-trimethoxy-biphenyl-2-yl)methanone (**21d**).*



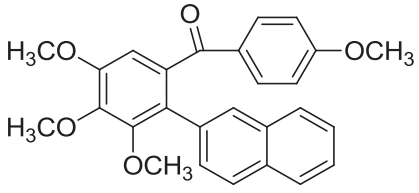
Following the general procedure E, compound **21d** was purified by column chromatography, eluting with hexane–EtOAc (9:1). 80% yield. White solid. mp. 73–75 °C. IR (KBr): 2936, 2840, 1659, 1597, 1481, 1336, 1256, 1166, 1005, 848, 752 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 3.63 (s, 3H), 3.82 (s, 3H), 3.92 (s, 3H), 4.02 (s, 3H), 6.76 (d, 2H, $J = 8.1$ Hz), 6.82 (s, 1H), 7.11–7.25 (m, 5H), 7.61 (d, 2H, $J = 8.1$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.3, 56.0, 60.9, 61.0, 107.2, 113.1, 126.9, 127.5, 127.7, 130.2, 130.5, 132.1, 135.3, 135.6, 143.6, 151.0, 152.4, 163.1, 196.4. ESI MS (*m*/*z*): 379 $(M + H)^+$.

*5.1.7.5. (4′-(tert-Butyl)-4,5,6-trimethoxy-biphenyl-2-yl)(4-methoxyphenyl)methanone (**21e**).*



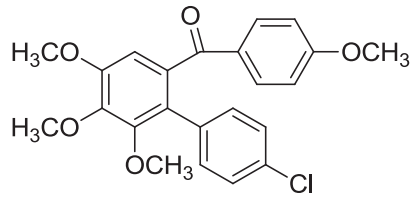
Following the general procedure E, compound **21e** was purified by column chromatography, eluting with hexane–EtOAc (9:1). 84% yield. White solid. mp. 154–156 °C. IR (KBr): 2962, 1737, 1658, 1594, 1483, 1326, 1250, 1164, 1011, 843, 765 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.19 (s, 9H), 3.64 (s, 3H), 3.77 (s, 3H), 3.90 (s, 3H), 3.98 (s, 3H), 6.69 (d, 2H, $J = 8.3$ Hz), 6.83 (s, 1H), 7.05–7.16 (m, 4H), 7.53 (d, 2H, $J = 8.3$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 31.0, 34.2, 55.2, 56.0, 61.0, 107.3, 112.9, 124.4, 128.0, 129.9, 130.5, 131.9, 132.3, 135.7, 143.7, 149.5, 151.0, 152.5, 162.8, 196.8. ESI MS (*m*/*z*): 457 $(M + Na)^+$.

*5.1.7.6. (4-Methoxyphenyl)(3,4,5-trimethoxy-2-(naphthalen-2-yl)phenyl)methanone (**21f**).*



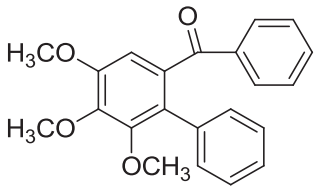
Following the general procedure E, compound **21f** was purified by column chromatography, eluting with hexane–EtOAc (9:1). 79% yield. White solid. mp. 114–116 °C IR (KBr): 2929, 2850, 1744, 1646, 1594, 1463, 1337, 1252, 1133, 1085, 789, 608 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 3.58 (s, 3H), 3.72 (s, 3H), 3.92 (s, 3H), 4.01 (s, 3H), 6.62–6.71 (m, 2H), 6.84 (s, 1H), 7.34–7.43 (m, 3H), 7.55–7.72 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.2, 56.1, 60.9, 61.0, 107.3, 113.1, 125.6, 125.7, 127.0, 127.3, 127.6, 127.9, 128.4, 129.3, 130.1, 132.0, 132.1, 132.8, 133.1, 135.8, 143.6, 151.3, 152.6, 163.1, 196.4. ESI MS (*m*/*z*): 429 $(M + H)^+$.

*5.1.7.7. (4′-Chloro-4,5,6-trimethoxy-biphenyl-2-yl)(4-methoxyphenyl)methanone (**21g**).*



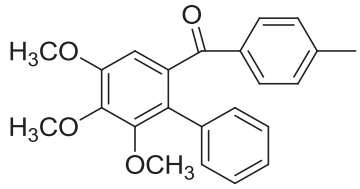
Following the general procedure E, compound **21g** was purified by column chromatography, eluting with hexane–EtOAc (9:1). 76% yield. White solid. mp. 83–85 °C. IR (KBr): 2935, 2840, 1654, 1596, 1483, 1332, 1258, 1170, 1088, 842, 762 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 3.60 (s, 3H), 3.81 (s, 3H), 3.89 (s, 3H), 3.98 (s, 3H), 6.76 (d, 2H, J = 8.7 Hz) 6.78 (s, 1H), 7.09–7.17 (m, 4H), 7.59 (d, 2H, J = 8.7 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.3, 56.0, 60.9, 61.0, 107.3, 113.5, 126.4, 127.8, 130.0, 131.5, 132.1, 132.9, 133.9, 135.5, 143.6, 151.0, 152.7, 163.4, 196.1. ESI MS (m/z): 413 $(M + H)^+$.

*5.1.7.8. Phenyl (4,5,6-trimethoxy-biphenyl-2-yl)methanone (**21h**).*



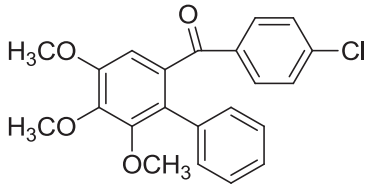
Following the general procedure E, compound **21h** was purified by column chromatography, eluting with hexane–EtOAc (9:1). 75% yield. White solid. mp. 104–106 °C. IR (KBr): 2934, 1656, 1587, 1454, 1338, 1273, 1138, 1088, 843, 756 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 3.62 (s, 3H), 3.93 (s, 3H), 4.02 (s, 3H), 6.88 (s, 1H), 7.08–7.22 (m, 5H), 7.23–7.29 (m, 2H), 7.35–7.41 (m, 1H), 7.59 (d, 2H, J = 8.8 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 56.1, 60.9, 61.0, 107.5, 126.5, 127.5, 127.8, 128.2, 129.6, 130.3, 130.6, 132.5, 135.3, 137.4, 144.0, 151.0, 152.5, 198.0. ESI MS (m/z): 371 $(M + Na)^+$.

*5.1.7.9. p-Tolyl(4,5,6-trimethoxy-biphenyl-2-yl)methanone (**21i**).*



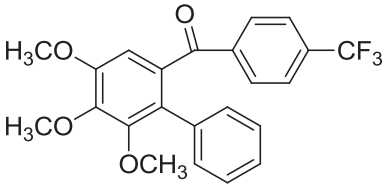
Following the general procedure E, compound **21i** was purified by column chromatography, eluting with hexane–EtOAc (9:1). 78% yield. White solid. mp. 108–110 °C. IR (KBr): 2926, 2851, 1658, 1596, 1475, 1327, 1226, 1132, 849, 762 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 2.31 (s, 3H), 3.60 (s, 3H), 3.89 (s, 3H), 3.99 (s, 3H), 6.80 (s, 1H), 7.04 (d, 2H, J = 8.0 Hz), 7.09–7.20 (m, 5H), 7.50 (d, 2H, J = 8.0 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.5, 56.0, 60.9, 61.0, 107.3, 126.9, 127.5, 128.0, 128.6, 129.9, 130.3, 134.7, 135.3, 135.5, 143.5, 143.7, 151.1, 152.4, 197.5. ESI MS (m/z): 363 $(M + H)^+$.

*5.1.7.10. (4-Chlorophenyl)(4,5,6-trimethoxy-biphenyl-2-yl)methanone (**21j**).*



Following the general procedure E, compound **21j** was purified by column chromatography, eluting with hexane–EtOAc (9:1). 74% yield. White solid. mp. 93–95 °C. IR (KBr): 2925, 2853, 1743, 1660, 1582, 1462, 1327, 1222, 1134, 1092, 849, 699 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 3.60 (s, 3H), 3.91 (s, 3H), 4.00 (s, 3H), 6.84 (s, 1H), 7.09–7.16 (m, 5H), 7.18 (d, 2H, J = 8.2 Hz), 7.48 (d, 2H, J = 8.2 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 56.0, 60.9, 61.0, 107.4, 127.1, 127.6, 128.0, 129.9, 130.3, 130.8, 134.7, 135.5, 135.7, 138.7, 144.2, 151.0, 152.6, 196.8. ESI MS (m/z): 405 $(M + Na)^+$.

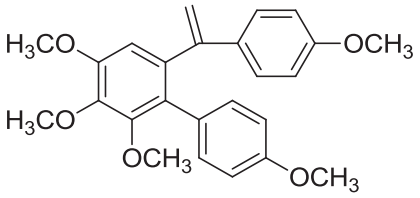
*5.1.7.11. (4-(Trifluoromethyl)phenyl)(4,5,6-trimethoxy-biphenyl-2-yl) methanone (**21k**).*



Following the general procedure E, compound **21k** was purified by column chromatography, eluting with hexane–EtOAc (9:1). 72% yield. White solid. mp. 85–87 °C. IR (KBr): 2936, 2854, 1815, 1656, 1584, 1482, 1327, 1221, 1163, 1066, 853, 745 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 3.60 (s, 3H), 3.93 (s, 3H), 4.02 (s, 3H), 6.91 (s, 1H), 7.06–7.15 (m, 5H), 7.44 (d, 2H, J = 8.3 Hz), 7.59 (d, 2H, J = 8.3 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 56.0, 60.8, 60.9, 107.7, 124.7, 125.2, 127.2, 127.6, 128.4, 129.5, 130.4, 133.0, 134.4, 135.0, 140.5, 144.5, 150.9, 152.7, 197.1. ESI MS (m/z): 439 $(M + Na)^+$.

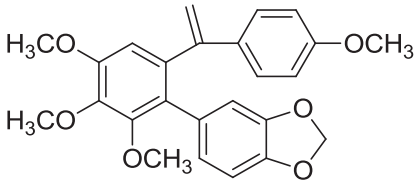
*5.1.8. General procedure F for the synthesis of phenylvinylbiphenyls (**22a**–**k**).* The methyl triphenylphosphonium bromide (2.0 mmol) was suspended in dry THF and cooled to −78 °C under nitrogen. *n*-Butyl lithium (1.6 M in hexanes, 0.75 mol per mol of phosphonium salt) was added dropwise, and the resulting yellow solution was stirred for 1 h. Then diphenylmethanones (1.0 mmol) in THF was added and warmed to room temperature. The resulting solution was stirred for 12 h and after completion of reaction, saturated NH_4Cl solution was slowly added at 0 °C and extracted with extracted with ethyl acetate and dried over anhydrous sodium sulfate. The solvent was evaporated, and the residue was purified by column chromatography on silica gel, eluting with hexane/EtOAc mixture.

*5.1.8.1. 2,3,4,4′-Tetramethoxy-6-(1-(4-methoxyphenyl)vinyl)biphenyl (**22a**).*



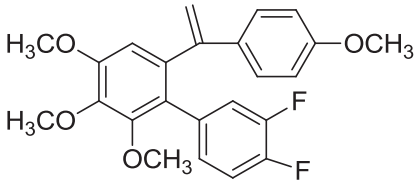
Following the general procedure F, compound **22a** was purified by column chromatography, eluting with hexane–EtOAc (9:1). 86% yield. Liquid. IR (neat): 2933, 2836, 1510, 1459, 1344, 1246, 1096, 834 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): 3.58 (s, 3H), 3.74 (s, 3H), 3.75 (s, 3H), 3.88 (s, 3H), 3.95 (s, 3H), 5.00 (s, 1H), 5.38 (s, 1H), 6.62–6.71 (m, 5H), 6.93–7.01 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 54.8, 54.9, 55.8, 60.6, 60.7, 109.3, 112.5, 112.9, 114.0, 127.7, 128.0, 128.9, 131.1, 133.9, 137.5, 141.4, 148.5, 151.3, 151.8, 157.8, 158.0. ESI MS (m/z): 429 $(M + Na)^+$. HRMS (EI, 70 eV): calcd for $C_{25}H_{26}O_5Na$: 429.1677, found: 429.1691.

*5.1.8.2. 5-(2,3,4-Trimethoxy-6-(1-(4-methoxyphenyl)vinyl)phenyl) benzo[d][1,3]dioxole (**22b**).*



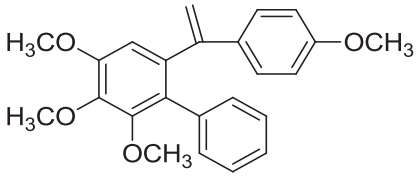
Following the general procedure F, compound **22b** was purified by column chromatography, eluting with hexane–EtOAc (9:1). 88% yield. Liquid. IR (neat): 2933, 1600, 1507, 1474, 1240, 1123, 1036, 932, 837. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.58 (s, 3H), 3.75 (s, 3H), 3.88 (s, 3H), 3.92 (s, 3H), 4.98 (s, 1H), 5.34 (s, 1H), 5.85 (s, 2H), 6.45 (m, 1H), 6.53 (d, 1H, J = 9.0 Hz), 6.58–6.65 (m, 3H), 6.68–6.82 (m, 1H), 6.92 (d, 2H, J = 9.0 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.2, 56.0, 60.9, 100.5, 107.2, 109.4, 110.9, 113.0, 113.4, 114.2, 123.7, 127.9, 130.4, 134.0, 137.6, 141.5, 145.7, 146.4, 148.7, 151.3, 152.0, 158.7. ESI MS (m/z): 443 $(M + Na)^+$. HRMS (EI, 70 eV): calcd for $C_{25}H_{24}O_6Na$: 443.1470, found: 443.1456.

*5.1.8.3. 3′,4′-Difluoro-2,3,4-trimethoxy-6-(1-(4-methoxyphenyl) vinyl)biphenyl (**22c**).*



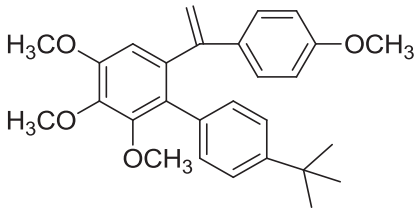
Following the general procedure F, compound **22c** was purified by column chromatography, eluting with hexane–EtOAc (9:1). 85% yield. Liquid. IR (neat): 2926, 2853, 1601, 1513, 1458, 1348, 1257, 1092, 832, 769 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.59 (s, 3H), 3.74 (s, 3H), 3.89 (s, 3H), 3.94 (s, 3H), 5.05 (s, 1H), 5.39 (s, 1H), 6.64 (d, 2H, J = 9.0 Hz), 6.69–6.74 (m, 2H), 6.80–6.88 (m 2H), 6.91 (d, 2H, J = 9.0 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.0, 55.9, 60.8, 109.5, 113.0, 114.4, 115.7, 119.2, 125.9, 126.4, 127.7, 132.0, 133.5, 137.5, 141.5, 147.2, 148.5, 150.5, 151.0, 152.5, 158.8. ESI MS (m/z): 435 $(M + Na)^+$. HRMS (EI, 70 eV): calcd for $C_{24}H_{22}O_4FNa$: 435.1383, found: 435.1393.

*5.1.8.4. 2,3,4-Trimethoxy-6-(1-(4-methoxyphenyl)vinyl)biphenyl (**22d**).*



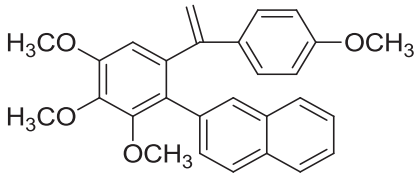
Following the general procedure F, compound **22d** was purified by column chromatography, eluting with hexane–EtOAc (9:1). 84% yield. Liquid. IR (neat): 2931, 1605, 1507, 1474, 1396, 1249, 1065, 836, 762 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.58 (s, 3H), 3.75 (s, 3H), 3.89 (s, 3H), 3.96 (s, 3H), 5.00 (d, 1H, J = 1.5 Hz), 5.37 (d, 1H, J = 1.5 Hz), 6.65 (d, 2H, J = 9.0 Hz), 6.68 (s, 1H), 6.96 (d, 2H, J = 9.0 Hz), 7.01–7.16 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.0, 55.9, 60.8, 60.9, 109.3, 112.9, 114.2, 126.0, 127.0, 127.8, 130.1, 132.0, 133.9, 136.9, 137.3, 141.5, 148.4, 151.2, 152.0, 158.6. ESI MS (m/z): 399 $(M + Na)^+$. HRMS (EI, 70 eV): calcd for $C_{24}H_{24}O_4Na$: 399.1572, found: 399.1571.

*5.1.8.5. 4′-(tert-Butyl)-2,3,4-trimethoxy-6-(1-(4-methoxyphenyl) vinyl)biphenyl (**22e**).*



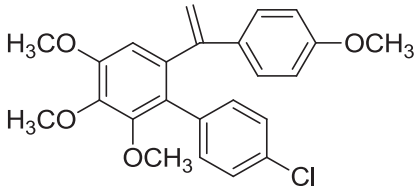
Following the general procedure F, compound **22e** was purified by column chromatography, eluting with hexane–EtOAc (9:1). 86% yield. White solid. mp. 98–100 °C. IR (KBr): 2924, 2853, 1604, 1509, 1461, 1344, 1250, 1097, 834 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.25 (s, 9H), 3.61 (s, 3H), 3.72 (s, 3H), 3.90 (s, 3H), 3.95 (s, 3H), 5.05 (d, 1H, J = 1.5 Hz), 5.31 (d, 1H, J = 1.5 Hz), 6.59 (d, 2H, J = 9.0 Hz), 6.72 (s, 1H), 6.84–6.94 (m, 4H), 7.08 (d, 2H, J = 8.3 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 31.2, 34.2, 55.1, 56.0, 60.8, 60.9, 109.3, 112.8, 114.3, 123.8, 128.0, 128.4, 129.7, 133.6, 134.2, 137.7, 141.5, 148.5, 149.2, 151.3, 151.9, 158.5. ESI MS (m/z): 455 $(M + Na)^+$. HRMS (EI, 70 eV): calcd for $C_{28}H_{32}O_4Na$: 455.2198, found: 455.2194.

*5.1.8.6. 2-(2,3,4-Trimethoxy-6-(1-(4-methoxyphenyl)vinyl)phenyl) naphthalene (**22f**).*



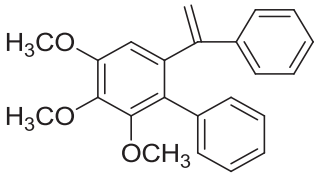
Following the general procedure F, compound **22f** was purified by column chromatography, eluting with hexane–EtOAc (9:1). 82% yield. Liquid. IR (neat): 2934, 1613, 1513, 1463, 1088, 794. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.54 (s, 3H), 3.67 (s, 3H), 3.92 (s, 3H), 3.96 (s, 3H), 4.99 (s, 1H), 5.29 (s, 1H), 6.50 (d, 2H, J = 9.0 Hz), 6.68 (s, 1H), 6.87 (d, 2H, J = 9.0 Hz), 7.11–7.14 (m, 1H), 7.34–7.37 (m, 2H), 7.46 (m, 1H), 7.51–7.55 (m, 1H), 7.59–7.63 (m, 1H), 7.67–7.72 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.1, 56.0, 60.9, 61.0, 109.4, 113.0, 114.5, 125.3, 125.7, 126.3, 127.3, 127.8, 128.8, 129.1, 130.2, 131.9, 132.8, 134.0, 134.4, 137.7, 141.6, 148.5, 151.5, 152.2, 158.7. ESI MS (m/z): 449 $(M + Na)^+$. HRMS (EI, 70 eV): calcd for $C_{28}H_{26}O_4Na$: 449.1728, found: 449.1724.

*5.1.8.7. 4′-Chloro-2,3,4-trimethoxy-6-(1-(4-methoxyphenyl)vinyl) biphenyl (**22g**).*



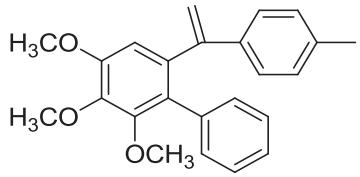
Following the general procedure F, compound **22g** was purified by column chromatography, eluting with hexane–EtOAc (9:1). 80% yield. Liquid. IR (neat): 2926, 2852, 1599, 1479, 1395, 1250, 1093, 833, 763 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.58 (s, 3H), 3.76 (s, 3H), 3.90 (s, 3H), 3.95 (s, 3H), 5.01 (d, 1H, J = 0.8 Hz), 5.39 (d, 1H, J = 0.8 Hz), 6.61–6.72 (m, 3H), 6.91–6.99 (m, 4H), 7.08 (d, 2H, J = 8.3 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 54.9, 55.8, 60.7, 109.4, 112.9, 114.3, 126.9, 127.1, 127.7, 131.5, 131.9, 133.6, 135.1, 137.3, 141.5, 148.3, 151.0, 152.2, 158.7. ESI MS (m/z): 433 $(M + Na)^+$. HRMS (EI, 70 eV): calcd for $C_{24}H_{23}O_4ClNa$: 433.1182, found: 433.1180.

*5.1.8.8. 2,3,4-Trimethoxy-6-(1-phenylvinyl)biphenyl (**22h**).*



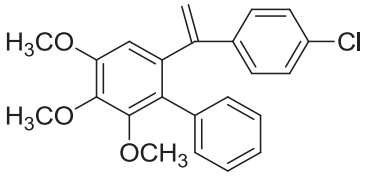
Following the general procedure F, compound **22h** was purified by column chromatography, eluting with hexane–EtOAc (9:1). 79% yield. White solid. mp. 85–87 °C. IR (KBr): 2924, 2853, 1594, 1459, 1397, 1260, 1139, 1096, 761 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 3.58 (s, 3H), 3.89 (s, 3H), 3.96 (s, 3H), 5.12 (d, 1H, J = 1.5 Hz), 5.45 (d, 1H, J = 1.5 Hz), 6.71 (s. 1H), 6.95–7.05 (m, 4H), 7.06–7.12 (m, 6H).^{13}C NMR (75 MHz, $CDCl_3$): δ 56.0, 60.8, 60.9, 109.4, 115.9, 126.0, 126.7, 126.9, 127.0, 127.5, 128.5, 130.3, 136.6, 137.2, 141.2, 141.6, 149.3, 151.2, 152.1. ESI MS (m/z): 369 $(M + Na)^+$. HRMS (EI, 70 eV): calcd for $C_{23}H_{22}O_3Na$: 369.1480, found: 369.1467.

*5.1.8.9. 2,3,4-Trimethoxy-6-(1-(p-tolyl)vinyl)-biphenyl (**22i**).*



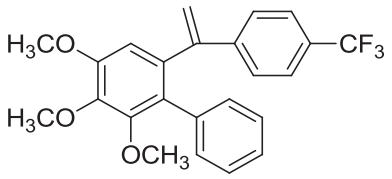
Following the general procedure F, compound **22i** was purified by column chromatography, eluting with hexane–EtOAc (9:1). 81% yield. Liquid. IR (neat): 2929, 2853, 1634, 1479, 1397, 1261, 1096, 828, 766 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 2.26 (s, 3H), 3.58 (s, 3H), 3.88 (s, 3H), 3.96 (s, 3H), 5.01 (s, 1H), 5.42 (s, 1H), 6.67 (s, 1H), 6.88–6.96 (m, 4H), 7.00–7.15 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.9, 55.9, 60.7, 60.8, 109.3, 115.2, 126.0, 126.5, 127.0, 128.3, 128.5, 129.8, 130.2, 136.6, 137.2, 138.3, 141.5, 148.7, 151.2, 152.0. ESI MS (m/z): 383 $(M + Na)^+$. HRMS (EI, 70 eV): calcd for $C_{24}H_{24}O_3Na$: 383.1623, found: 383.1663.

*5.1.8.10. 6-(1-(4-Chlorophenyl)vinyl)-2,3,4-trimethoxybiphenyl (**22j**).*



Following the general procedure F, compound **22j** was purified by column chromatography, eluting with hexane–EtOAc (9:1). 78% yield. Liquid. IR (neat): 2924, 2853, 1591, 1479, 1339, 1260, 1141, 1095, 837 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 3.60 (s, 3H), 3.93 (s, 3H), 3.96 (s, 3H), 5.19 (s, 1H), 5.44 (s, 1H), 6.73 (s, 1H), 6.92 (d, 2H, J = 7.9 Hz), 6.98–7.03 (m, 2H), 7.06 (d, 2H, J = 8.9 Hz), 7.09–7.15 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.9, 60.7, 60.8, 109.3, 116.2, 126.2, 127.0, 127.5, 127.9, 128.3, 130.2, 132.6, 136.4, 136.6, 139.7, 141.8, 148.5, 151.2, 152.1. ESI MS (m/z): 403 $(M + Na)^+$. HRMS (EI, 70 eV): calcd for $C_{24}H_{21}O_3ClNa$: 403.1076, found: 403.1062.

*5.1.8.11. 2,3,4-Trimethoxy-6-(1-(4-(trifluoromethyl)phenyl)vinyl) biphenyl (**22k**).*



Following the general procedure F, compound **22k** was purified by column chromatography, eluting with hexane–EtOAc (9:1). 76% yield. White solid. mp. 80–82 °C. IR (KBr): 2929, 2854, 1596, 1480, 1327, 1146, 1098, 843, 703 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 3.58 (s, 3H), 3.93 (s, 3H), 3.96 (s, 3H), 5.30 (s, 1H), 5.49 (s, 1H), 6.74 (s, 1H), 6.90–6.99 (m, 2H), 7.01–7.10 (m, 5H),7.30 (d, 2H, J = 7.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 56.0, 60.9, 109.4, 117.6, 124.4, 126.3, 127.0, 127.1, 128.5, 128.9, 129.5, 129.9, 130.3, 136.4, 142.0, 145.0, 148.8, 151.4, 152.3. ESI MS (m/z): 437 $(M + Na)^+$. HRMS (EI, 70 eV): calcd for $C_{24}H_{21}O_3F_3Na$: 437.1340, found: 437.1340.

5.2. Biology

5.2.1. Materials and methods. Cell cultures, maintenance and antiproliferative evaluation

All cell lines used in this study were purchased from the American Type Culture Collection (ATCC, United States). A549, SK-N-SH, and HeLa were grown in Dulbecco's modified Eagle's medium (containing 10% FBS in a humidified atmosphere of 5% CO2 at 37 °C). DU145 cells were cultured in Eagle's minimal essential medium (MEM) containing non-essential amino acids, 1 mM sodium pyruvate, 10 mg/mL bovine insulin, and 10% FBS. Cells were trypsinized when sub-confluent from T25 flasks/60 mm dishes and seeded in 96-wel plates. The synthesized test compounds were evaluated for their in vitro antiproliferative in four different human cancer cell lines. A protocol of 48 h continuous drug exposure was used, and a MTT cell proliferation assay was used to estimate cell viability or growth. The cell lines were grown in their respective media containing 10% fetal bovine serum and were seeded into 96-well microtiter plates in 200 μL aliquots at plating densities depending on the doubling time of individual cell lines. The microtiter plates were incubated at 37 °C, 5% CO_2, 95% air, and 100% relative humidity for 24 h prior to addition of experimental drugs. Aliquots of 2 μL of the test compounds were added to the wells already containing 198 μL of cells, resulting in the required final drug concentrations. For each compound, four concentrations (1, 10, 100, and 1000 μM) were evaluated, and each was done in triplicate wells. Plates were incubated further for 48 h, and the assay was terminated by the addition of 10 μL of 5% MTT and incubated for 60 min at 37 °C. Later, the plates were air-dried. Bound stain was subsequently eluted with 100 μL of DMSO, and the absorbance was read on a multimode plate reader (Tecan M200) at a wavelength of 560 nm. Percent growth was calculated on a plate by plate basis for test wells relative to control wells. The above determinations were repeated thrice. The growth inhibitory effects of the compounds were analyzed by generating dose response curves as a plot of the percentage surviving cells versus compound concentration. The sensitivity of the cancer cells to the test compound was expressed in terms of IC_{50}, a value defined as the concentration of compound that produced 50% reduction as compared to the control absorbance. IC_{50} values are indicated as means ± SD of three independent experiments.

5.2.2. Analysis of cell cycle

HeLa cells in 60 mm dishes were incubated for 24 h in the presence or absence of test compounds **19b**, **19c**, **22b** and **22c** (10 μM). Cells were harvested with Trypsin-EDTA, fixed with ice-cold 70% ethanol at 4 °C for 30 min, ethanol was removed by centrifugation and cells were stained with 1 mL of DNA staining solution [0.2 mg of Propidium Iodide (PI), and 2 mg RNase A] for 30 min as described earlier. The DNA contents of 20,000 events were measured by flow cytometer (BD FACSCanto II). Histograms were analyzed using FCS express 4 plus [12].

5.2.3. Tubulin polymerization assay

An in vitro assay for monitoring the time-dependent polymerization of tubulin to microtubules was performed employing a fluorescence-based tubulin polymerization assay kit (BK011, Cytoskeleton, Inc.) according to the manufacturer's protocol. The reaction mixture in a final volume of 10 μL in PEM buffer (80 mM PIPES, 0.5 mM EGTA, 2 mM $MgCl_2$, pH 6.9) in 384 well plates contained 2 mg/mL bovine brain tubulin, 10 μM fluorescent reporter, 1 mM GTP in the presence or absence of test compounds (3 μM final concentration) at 37 °C. Tubulin polymerization was followed by monitoring the fluorescence enhancement due to the incorporation of a fluorescence reporter into microtubules as polymerization proceeds. Fluorescence emission at 420 nm (excitation wavelength is 360 nm) was measured for 1 h at 1-min intervals in a multimode plate reader (Tecan M200). Colchicine was used as positive control under similar experimental conditions. To determine the IC_{50} values of the compounds against tubulin polymerization, the compounds were pre-incubated with tubulin at varying concentrations (1, 2, 3, 4 and 5 μM). Assays were performed under similar conditions as employed for polymerization assays as described above [21].

5.2.4. Western blot analysis of soluble versus polymerized tubulin and cyclin B1

Cells were seeded in 12-well plates at 1×10^5 cells per well in complete growth medium. Following treatment of cells with respective compounds (**19b**, **19c**, **22b**, **22c**, nocodazole and taxol) for a duration of 24 h, cells were washed with PBS and subsequently soluble and insoluble tubulin fractions were collected. To collect the soluble tubulin fractions, cells were permeablized with 200 μL of pre-warmed lysis buffer [80 mM Pipes-KOH (pH 6.8), 1 mM $MgCl_2$, 1 mM EGTA, 0.2% Triton X-100, 10% glycerol, 0.1% protease inhibitor cocktail (Sigma–Aldrich)] and incubated for 3 min at 30 °C. Lysis buffer was gently removed, and mixed with 100 μL of 3 × Laemmli's sample buffer (180 mM Tris–Cl pH 6.8, 6% SDS, 15% glycerol, 7.5% β-mercaptoethanol and 0.01% bromophenol blue). Samples were immediately heated to 95 °C for 3 min. To collect the insoluble tubulin fraction, 300 μL of 1 × Laemmli's sample buffer was added to the remaining cells in each well, and the samples were heated to 95 °C for 3 min. Equal volumes of samples were run on an SDS-10% polyacrylamide gel and were transferred to a nitrocellulose membrane employing semidry transfer at 50 mA for 1 h. Blots were probed with mouse anti-human α-tubulin diluted 1:2000 mL (Sigma) and stained with rabbit anti-mouse secondary antibody coupled with horseradish peroxidase, diluted 1:5000 mL (Sigma). Bands were visualized using an enhanced Chemiluminescence protocol (Pierce) and radiographic film (Kodak.). For cyclin B1 immunoblots, Cells were seeded in 12-well plates at 1×10^5 cells per well in complete medium and treated with different concentrations of **19b**, **19c**, **22b** and **22c** and nocodazole for 24 h. After treatment, cells were washed twice with phosphate-buffered saline and lysed in 1X SDS sample buffer. Proteins were separated, transferred, probed and analyzed similar to tubulin. The primary anti-cyclin B1 antibody was employed at 1:1500 (Sigma) and horseradish peroxidase coupled goat anti-rabbit secondary antibody diluted 1:5000 (Sigma) [11].

5.2.5. Immunohistochemistry of tubulin and analysis of nuclear morphology

HeLa cells were seeded on glass cover slip, incubated for 24 h in the presence or absence of test compounds **19b**, **19c**, **22b** and **22c** (10 μM). Cells grown on coverslips were fixed in 3.5% formaldehyde in phosphate-buffered saline (PBS) pH 7.4 for 10 min at room temperature. Cells were permeablized for 6 min in PBS containing 0.5% Triton X-100 (Sigma) and 0.05% Tween-20 (Sigma). The permeablized cells were blocked with 2% BSA (Sigma) in PBS for 1 h. Later, the cells were incubated with primary antibody for tubulin from (sigma) at (1:200) diluted in blocking solution for 4 h at room temperature. Subsequently the antibodies were removed and the cells were washed thrice with PBS. Cells were then incubated with FITC labeled anti-mouse secondary antibody (1:500) for 1 h at room temperature. Cells were washed thrice with PBS and mounted in medium containing DAPI. Images were captured using the Olympus confocal microscope and analyzed with Provision software [12].

5.2.6. Molecular modeling

Tubulin with colchicine (PDB code: 3E22) was selected as the receptor for docking simulation. After removing the ligand and solvent molecules, hydrogen atoms and Kollman charges were added to each protein atom. Coordinates of each compound were generated using Chemdraw11 followed by MM2 energy minimization. Docking was carried out by AutoDock4 in colchicines binding pocket [12]. Grid map in Autodock that defines the interaction of protein and ligands in binding pocket was defined. The grid map was used with 60 points in each *x*, *y*, and *z* direction, equally spaced at 0.375 Å. Docking was performed using the Lamarckian genetic algorithm. Each docking experiment was performed 100 times, yielding 100 docked conformations. Parameters used for the docking were as follows: population size of 150; random starting position and conformation; maximal mutation of 2 Å in translation and 50° in rotations; elitism of 1; mutation rate of 0.02 and crossover rate of 0.8; and local search rate of 0.06. Simulations were performed with a maximum of 1.5 million energy evaluations and a maximum of 50,000 generations. Final docked conformations were clustered using a tolerance of 1.0 Å root mean square deviation. The best model was picked based on the best stabilization energy.

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Appendix A. Supplementary information

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejmech.2012.12.008.

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