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Conformationally restricted naphthalene derivatives type *isocombretastatin A-4* and *isoerianin* analogues: Synthesis, cytotoxicity and antitubulin activity

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Abstract

A novel series of dihydronaphthalene, tetrahydronaphthalene and naphthalene derivatives as restricted-analogues of *isoCA-4* were designed, synthesized and evaluated for their anticancer properties. High cell growth inhibition against four tumor cell lines was observed at a nanomolar level with dihydronaphthalenes **1d,e** and **1h**, tetrahydronaphthalene **2c** and naphthalene **3c**. Structure activity relationships are also considered. These compounds exhibited a significant inhibitory activity toward tubulin polymerization ($IC_{50} = 2-3 \mu M$), comparable to that of *isoCA-4*. The effect of the lead compounds **1e** and **2c** on the cancer cells tested was associated with cell cycle arrest in the G₂/M phase. Docking studies reveal that these compounds showed a binding mode similar to those observed with their non-constraint *isoCA-4* and *isoerianin* congeners.

Keywords: Combretastatin A-4, *isoCA-4*, Cytotoxicity, Antimitotic, Tubulin, Restricted analogues

1. Introduction

Microtubules found in cytoskeleton of almost all eukaryotic cell types are hollow tubes formed by self-assembly of α and β tubulin heterodimers. They are directly involved in a variety of cellular functions, such as cell movement, transport of organelles inside the cell, maintenance of cell shape as well as mitosis and cell replication. Consequently, perturbation of tubulin assembly/disassembly is a popular target for new chemotherapeutic agents.[1,2] The vinca alkaloids, typified by vinblastine and vincristine which inhibit microtubules assembly[3] as well as the taxanes, such as paclitaxel and docetaxel which promoted microtubules polymerization and inhibits microtubules depolymerization,[4,5] are the mostly used antimicrotubules agents introduced in clinical oncology.[6] However, despite their potent antitumor activities, these drugs have undesirable side effects[7,8] and are subject to multidrug resistance.[9,10] These last decades, there has been a strong enthusiasm for discovering tubulin polymerization inhibitors of small size, easy synthesis and low side effects. Combretastatin A-4 (CA-4, Figure 1), a *cis*-stilbene extracted from the South African willow *Combretum caffrum*[11,12] is arguably the most studied substance that displays a nanomolar level of cytotoxicity against a variety of human cancer cells, including multidrug resistant cell lines.[13,14] CA-4 binds at or near colchicine binding site of β -tubulin and strongly interferes with the assembly of tubulin, leading to cell death.[15] It also exerts highly selective effects in proliferating endothelial cells and, as a consequence, demonstrates strong suppressive activity on tumor blood flow leading to tumor necrosis.[16] Two derivatives are currently in clinical trials: CA-4 disodium phosphate CA-4P,[17,18] a water soluble prodrug of CA-4 and the aminocombretastatin prodrug AVE-8062 (**3**).[19,20] To date, CA-4P[21] either as a single agent or in combination therapy is undergoing several advanced clinical trials worldwide for the treatment of age-related macular degeneration or anaplastic thyroid cancer.

Despite its remarkable anticancer activity, the main disadvantage of CA-4 is the ready isomerization of the *Z*-double bond to its inactive *trans*-form during storage, administration[22] and metabolism.[23] In an ongoing project aimed at developing novel tubulin assembly inhibitors,[24,25,26,27,28,29] we recently discovered *isocombretastatin* A-4 (*iso*CA-4), a structural isomer of the natural product, which holds biological activities comparable to that of CA-4.[30] This substance having a 1,1-diarylethylene scaffold is easy to synthesize[31,32,33] at a multi grams scale without the need to control the olefin geometry and then definitively solving the *Z* double bond isomerization problem.[34]

<Figure 1>

By structural modifications on the B-ring, we have also identified other promising antiproliferative agents such as *iso*NH₂CA-4 and *iso*FCA-4 (Figure 1).[35,36] We also demonstrated that the bioisosteric replacement of the (*Z*)-1,2-ethylene by the 1,1-ethylene could be apply successfully to natural combretastatins CA-2, CA-3 and CA-5.[30] On the basis of these bioisosteric considerations, we also showed that isoerianin derivatives having a 1,1-diarylethane scaffold were as active as the natural product erianin.[37] A set of molecular docking calculations was performed with *iso*CA-4 as well as *isoerianin* which showed a binding pose similar to those observed with CA-4 and the co-crystallized DAMA-colchicine in the colchicine binding site.[38] In addition, the dihedral angles between the planes of the two A/B-aromatic nucleus in *iso*CA-4 and *isoerianin* (68° and 77°, respectively)[30,37] were found to be close to that of CA-4 (53°).[39] From all of these considerations, we are planning to rationalize the synthesis of three new series of rigid analogues of *iso*CA-4 and *isoerianin* namely, 4-aryldihydronaphtalenes **1** (e.g.; dihedral angle = 69° for **1e**), 4-aryltetrahydronaphtalenes **2** (e.g.; dihedral angle = 79° for **2c**) and 1-arylnaphtalenes **3** (e.g.; dihedral angle = 70° for **3d**) with reduced mobility of the B-ring. We hypothesized that constrained analogues **1-3** with dihedral angles close to those of *iso*CA-4 and *isoerianin* would be as active as their non restricted congeners. In this paper we would like to describe the synthesis and evaluation of compounds **1-3** in terms of inhibition of tubulin assembly along with cytotoxicity studies against various cancer cell lines.

<Scheme 1>

Reagents and conditions: (i) *p*TsNHNH₂ (1.2 equiv), PTSA (0.2 equiv), MgSO₄ (1 equiv), EtOH, 50 °C. (ii) ArI (1.1 equiv), Pd₂dba₃ (10 mol%), XPhos (20 mol%), LiOtBu (2.2 equiv), dioxane 90 °C in a sealed tube. (iii) 3,4,5-trimethoxyiodobenzene (1.1 equiv), Pd₂dba₃ (10 mol%), XPhos (20 mol%), LiOtBu (2.2 equiv), dioxane 90 °C in a sealed tube. (iv) NaN₃ (2 equiv), CuI 10 mol%, DMEDA (15 mol%), sodium ascorbate (5 mol%), DMSO/H₂O: 5/1, 60 °C. (v) KOH (5 equiv), Pd₂dba₃ (10 mol%), *t*BuXPhos (20 mol%), dioxane/H₂O: 1/1, 90 °C in a sealed tube. (vi) Alkyne (1.2 equiv), PdCl₂(PPh₃)₂ (5 mol%), PPh₃ (10 mol%), CuI (10 mol%), Et₂NH (2 equiv), DMF, MWI, 120 °C. (vii) Methyl acrylate (10 equiv), PEPPSI (5 mol%), K₂CO₃ (2 equiv), NMP 140 °C in a sealed tube. (viii) H₂, Pd/C in MeOH. (ix) DDQ (1.2 equiv), CH₂Cl₂, 20 °C.

2. Results and discussion

2.1. Chemistry.

Scheme 1 outlines the convergent synthetic routes followed for the synthesis of the novel restricted analogues **1-3**. The projected incorporation of a variety of substituents at the C3' position of the B-ring trusts in the tractability of a C–Br bond, which can further be engaged into diverse coupling reactions. Thus, the preparation of the pivotal brominated precursors **1a** and **1b** was achieved from 5-bromo-6-methoxytetralone **4b**[40] which was heated in EtOH at 50 °C with TsNHNH₂ in the presence of PTSA. The resulting *N*-tosylhydrazone **5b** was next coupled with aryl iodides under palladium catalysis[30,41,42] to afford the key intermediates **1a,b**. By securing the required skeleton for the dihydronaphthalene analogues, the stage was ready for the installation of various functionalities in place of the bromine atom. The C(sp²)–NH₂ bond of **1d** and **1i** was formed from **1a** and **1b**, respectively, using sodium azide as the amino source[43,44] in the presence of a catalytic amount of CuI. Treating **1a,b** with KOH in the presence of Pd₂dba₃, *t*BuXPhos in a mixture dioxane/H₂O: 1/1 at 90 °C[45] delivered in good yields the C3'-hydroxy substituted analogues **1e** (63%) and **1h** (62%). For the introduction of alkyne substituents on the B-aromatic ring,[36] we examined the Sonogashira-Linstrumelle reaction[46] of **1a** with propargylic and homopropargylic alcohols. The coupling reaction of these alcohols with **1a** proceeded in the presence of PdCl₂(PPh₃)₂ and CuI catalysts under microwave irradiation (MWI) at 120 °C to give the corresponding alkynes **1f,g** in good yields. Similarly, **1a** underwent Heck coupling with methyl acrylate using [1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene](3-chloropyridyl)palladium(II) dichloride (PEPPSI) as the catalyst in NMP at 140 °C to afford the corresponding 3' methyl (*E*)-cinnamate **1j** in an unoptimized 35% yield.

Having achieved the preparation of dihydronaphthalenes **1**, we next focused our attention on their catalytic reduction to give restricted *isoerianin* analogues **2**. Thus, 4-aryltetrahydronaphthalenes **2a-e** were obtained in acceptable yields using H₂ in the presence of Pd/C in MeOH. Finally, aromatization of compound **1a** into naphthalene derivative **3a** was attempted using a variety of oxidizing species, including Pd/C, SeO₂, *o*-chloranil, *p*-chloranil, and SO₃-pyridine complex. However, the oxidation reactions were unsuccessful and gave **3a** in very poor yields (<10 %). After several trials, we found that the oxidation of **1a** with DDQ in CH₂Cl₂ afforded the desired naphthalene **3a** but in a moderate 33% yield. Introduction of various substituents on **3a** was next achieved in a similar manner as described above for **1d-j** from **1a,b**. Using a similar route for the synthesis of **1d**, dihydronaphthalene **1l** bearing a NH₂ substituent at the C-7 position was prepared from 7-bromo-6-methoxytetralone **4c**[47] for structure-activity relation study (Scheme 2).

<Scheme 2>

Reagents and conditions: (i) *p*TsNHNH₂ (1.2 equiv), PTSA (0.2 equiv), MgSO₄ (1 equiv), EtOH, 50 °C. (ii) 3,4,5-trimethoxyiodobenzene (1.1 equiv), Pd₂dba₃ (10 mol%), XPhos (20 mol%), LiOtBu (2.2 equiv), dioxane 90 °C in a sealed tube. (iii) NaN₃ (2 equiv), CuI (10 mol%), DMEDA (15 mol%), sodium ascorbate (5 mol%), DMSO/H₂O: 5/1, 60 °C.

<Table 1>

2.2. Biological results.

In vitro antiproliferative activity of the synthesized naphthalene derivatives **1-3** was first determined against the human colon carcinoma cell line (HCT116) using CA-4[48] and *iso*CA-4[30] and *isoerianin*[37] as reference compounds. The results of this study are summarized in Table 1. On the exception of the amino derivative **3c** ($GI_{50} = 55$ nM), naphthalene compounds **3** displayed only modest antiproliferative activity, which was affected with halogen (Br, **3a**), alkynol (**3e**, **3f**), alkene (**3g**) and alkyl (**3h**) substituents at the C5 position. In contrast, dihydronaphthalenes **1** were significantly more active than their aromatic congeners. In particular, dihydronaphthalenes **1d** and **1e**[49] bearing the greatest resemblance to *iso*NH₂CA-4 and *iso*CA-4, respectively, displayed a high antiproliferative activity at a nanomolar level ($GI_{50} = 7$ and 85 nM). By comparison with **1d**, the introduction of an amino substituent at the C7 position failed to improve the cytotoxic activity profile of **1l**. One note that compounds **1h** and **1i** bearing two methoxy groups on the A-ring retained an important cytotoxicity in comparison with **1e** and **1d**, respectively. Nevertheless, on the contrary with previous reports,[36] decreased cytotoxic activity was observed with dihydronaphthalenes **1f,g** and **1j** bearing alkynol or alkene substituents at the C5 position.

The reduction of **1** into tetrahydronaphthalenes **2** as restricted *isoerianin* analogues led to compounds that displayed similar cytotoxic activities in comparison with *isoerianin* ($GI_{50} = 28$ nM) and with their dihydronaphthalenes precursors. For example, **2c** with a GI_{50} value of 20 nM was slightly more active than restricted *iso*CA-4 **1e** (85 nM), while the amino derivative **2b** was about ten fold less active than its dihydronaphthalene analogue **1d**. These results indicated that rigidifying *iso*CA-4 or *isoerianin* with the dihydro- or tetrahydronaphthalene system did not alter the reported SAR. These preliminary *in vitro* cytotoxic results prompted us to evaluate the most promising molecules in these series against other human cancer cell lines. The GI_{50} values of selected compounds obtained with K562 (chronic myelogenous leukemia), H1299 (non-small lung human carcinoma) and MDA-MB231 (human breast) cell lines are summarized in Table 2.

<Table 2>

Results from the cytotoxicity study provide evidence that dihydronaphthalenes **1d**, **1e**, **1h**, **1i** which retained a high level of cytotoxicity against HCT116 (Table 1) cells were also strongly cytotoxic against H1299, MDA-MB231 and K562 cancer cell lines. Similarly, tetrahydronaphthalenes **2a-c** as well as naphthalene derivative **3c** displayed an equivalent level of cytotoxicity against the three tested cancer cells ($30 < GI_{50} < 150$ nM).

To confirm that the antiproliferative activities of these compounds, like those in the *iso*CA-4[30] and *isoerianin* series,[37] were related to an interaction with the microtubule system, these selected compounds were evaluated for their inhibitory effects on tubulin assembly (Table 2). Except for dihydronaphthalenes **2a** and **2b**, the results demonstrated that the drug cytotoxicity correlated with the inhibition of tubulin polymerization. For instance, dihydronaphthalenes **1d,e**, **1h,i**, tetrahydronaphthalene **2c** and naphthalene **3c** were found to be as active as *iso*CA-4 and CA-4, displaying an IC_{50} at a micromolar level. One note that naphthol derivative **3d**, bearing the greatest resemblance to *iso*CA-4, showed a reduced antitubulin activity ($IC_{50} = 6.9$ μ M) which was consistent with the results of the growth inhibitory effect (310 nM $< GI_{50} < 500$ nM).

Because molecules exhibiting effects on tubulin polymerization causes the alteration of cell cycle parameters, the effect of tetrahydronaphthalene **2c**, dihydronaphthalene **1e**, and naphthalene **3d** on MDA-MB231, K562, HCT116 and H1299 cellular cycle was investigated. The fluorescent propidium iodide intercalates with the DNA and hence, the amount of fluorescence measured per cell is proportional to the DNA content. Cells were harvested after 24 h and analyzed for DNA content by flow cytometry. Table 3 shows that a significant increased in G₂/M peak is observed after treatment of the four cell lines with tetrahydronaphthalene **2c** at a low concentration (5.10^{-9} M). Similarly, dihydronaphthalene **1e** as

well as naphthalene derivative **3d** arrest the majority of cells in the G₂/M phase of the cell cycle but at concentrations smoothly superiors (10⁻⁸ M and 5.10⁻⁷ M, respectively).

<Table 3>

2.3. Docking study.

These results clearly demonstrated that tubulin is the target of these compounds; however, the specific binding site on tubulin was not investigated, for example, by use of a radiolabeled colchicine displacement assay. Nevertheless, a set molecular docking calculations was performed with 5-OH naphthalene derivatives to investigate the possible binding mode of **2c**, **1e** and **3d** which were docked in the colchicine binding site of tubulin. For this purpose, the X-ray structure of tubulin DAMA-colchicine complex (Code PDB: 1sa0)[38] was used. Figure 2 illustrates from one hand, the docking-derived superimposition of **2c** and **1e**, with *isoCA-4* (blue), and on the other hand, the superimposition of **3d** with *isoerianin* (green). As expected, these compounds showed a binding pose similar to the one observed with the reference compounds *isoCA-4* and *isoerianin* with the trimethoxyphenyl ring placed in proximity of Cys241 and the OH substituent of the B-ring (naphthalene, dihydro- and tetrahydronaphthalene) which forms a hydrogen-bond with Val181. These binding parallels and the dihedral angles values of **2c** (79°), **1e** (69°) and **3d** (70°) probably rationalise the potency observed for these drugs in their tubulin effects which are seen to be close to that reported for *isoCA-4* (dihedral angle = 68°)[30] and *isoerianin* (dihedral angle = 77°).[37]

<Figure 2>

3. Conclusion

We designed and synthesized by a convergent strategy, three new classes of synthetic inhibitors of tubulin polymerization based on the molecular skeleton of dihydronaphthalenes **1**, tetrahydronaphthalenes **2** and naphthalenes **3**. These restricted analogues of *isoCA-4* and *isoerianin* were evaluated for their antiproliferative activity against various human cancer cell lines. The lead compounds, dihydronaphthalenes **1e-h**, tetrahydronaphthalenes **2b,c** and to a lesser extent naphthalene **3c** displayed potent cytotoxicities with GI₅₀ ranging from 15 to 110 nM. In these three series, six of the most cytotoxic compounds were evaluated for effects on tubulin polymerization and the IC₅₀ values in a nearly range of 3 μM are comparable to that of *isoCA-4*. The three most potent inhibitors of tubulin assembly having the greatest resemblance to *isoCA-4*, **2c**, **1e** and **3d** induced a prevalent block of cells in G₂/M phase of the cell cycle at nanomolar concentrations. In addition, docking studies revealed that these compounds adopted an orientation similar to that of *isoCA-4* and *isoerianin* in the colchicine binding-site. Biological results obtained in this study demonstrate that structural restrictions at this portion of *isoCA-4* offers various permises for the design of novel heterocycle-containing restricted *isoCA-4* derivatives. Synthesis and biological evaluation of such compounds are under investigation in our laboratory and will be reported in due course.

4. Experimental

4.1 General considerations

Triethylamine was distilled from potassium hydroxide under argon prior to use. The compounds were all identified by usual physical methods, i.e. ¹H-NMR, ¹³C-NMR, IR, MS and elemental analysis. ¹H and ¹³C NMR spectra were measured in CDCl₃ with a Bruker Avance 300. ¹H chemical shifts are reported in ppm from an internal standard TMS or of residual chloroform (7.27 ppm). The following abbreviations are used: m (multiplet), s (singlet), d (doublet), br s (broad singlet), t (triplet). ¹³C chemical shifts are reported in ppm from the central peak of CDCl₃ (77.14). IR spectra were measured on a Bruker Vector 22 spectrophotometer (neat, cm⁻¹). Elemental analyses were performed with a Perkin-Elmer 240 analyser. Mass spectra were obtained with a LCT Micromass spectrometer. Analytical TLC was

performed on Merck precoated silica gel 60F plates. Merck silica gel 60 (230-400 mesh) was used for column chromatography.

4.2. Bromination of 6-methoxytetralone was achieved according to literature to give **4b** and **4c**.^[40]

4.2.1 5-Bromo-6-methoxytetralone (**4b**)

Yield: 49 %. TLC: Rf 0.52 (cyclohexane/EtOAc: 9/1). IR (neat) $\nu_{\max}/\text{cm}^{-1}$: 3904, 3232, 1664, 1568, 1458, 1415, 1352, 1327, 1280, 1232, 1188, 904, 826, 776, 729, 638. $^1\text{H NMR}$ (300 MHz, CDCl_3) δ ppm 8.06 (d, $J = 8.7$ Hz, 1H), 6.88 (d, $J = 8.7$ Hz, 1H), 3.97 (s, 3H), 3.03 (t, $J = 6.2$ Hz, 2H), 2.66 – 2.54 (m, 2H), 2.14 (m, 2H). $^{13}\text{C NMR}$ (75 MHz, CDCl_3) δ 196.9, 159.8, 145.6, 128.5, 127.7, 113.1, 109.7, 56.6, 38.1, 30.6, 22.6. MS (APCI, m/z) 255.1 ($[\text{M} + \text{H}]^+$, ^{79}Br), 257.0 ($[\text{M} + \text{H}]^+$, ^{81}Br).

4.2.2 7-Bromo-6-methoxytetralone (**4c**)

Yield: 7 %. Rf 0.45 (cyclohexane/ EtOAc: 9/1). IR (neat) $\nu_{\max}/\text{cm}^{-1}$: 3628, 3238, 1668, 1568, 1459, 1413, 1352, 1327, 1283, 1260, 1232, 1188, 902, 778, 733, 640. $^1\text{H NMR}$ (300 MHz, CDCl_3) δ ppm 8.21 (s, 1H), 6.69 (s, 1H), 3.94 (s, 3H), 2.91 (t, $J = 6.0$ Hz, 2H), 2.75 – 2.41 (m, 2H), 2.12 (m, 2H). $^{13}\text{C NMR}$ (75 MHz, CDCl_3) δ 196.0, 159.6, 159.4, 151.4, 145.9, 132.6, 110.8, 56.4, 38.5, 29.9, 23.2. MS (APCI, m/z) 255.0 ($[\text{M} + \text{H}]^+$, ^{79}Br), 257.0 ($[\text{M} + \text{H}]^+$, ^{81}Br).

4.3. General procedure for the formation of *N*-tosylhydrazones.

To a solution of tetralone **4b,c** (1 mmol), PTSA (0.2 mmol) and MgSO_4 (1 mmol) in ethanol (20 mL) was added 4-methylbenzenesulfonylhydrazide (1.2 mmol). The resulting mixture was stirred under reflux for 2 h. After cooling at room temperature, the medium was diluted with EtOAc and filtered over a pad of Celite. The solvent was next removed and the residue was purified by crystallization in ethanol to afford **5b,c**.

4.3.1. *N'*-(5-Bromo-6-methoxy-3,4-dihydronaphthalen-1(2H)-ylidene)-4-methylbenzenesulfonylhydrazide (**5b**)

Yield: 100 %. M.p. 212.1°C Rf 0.5 (cyclohexane/EtOAc: 7/3). IR (neat) $\nu_{\max}/\text{cm}^{-1}$: 2249, 1054, 1025, 1006, 821, 758, 623. $^1\text{H NMR}$ (300 MHz, DMSO) δ ppm 10.51-10.03 (br s, 1H), 7.85 – 7.73 (m, 3H), 7.40 (d, $J = 8.1$ Hz, 2H), 7.01 (d, $J = 8.9$ Hz, 1H), 3.85 (s, 3H), 2.75 (t, $J = 6.0$ Hz, 2H), 2.52 - 2.47 (m, 2H), 2.37 (s, 3H), 1.77 (m, 2H). $^{13}\text{C NMR}$ (75 MHz, DMSO) δ 156.21, 152.15, 143.14, 140.06, 136.50, 129.39 (2C), 127.61 (2C), 126.37, 124.76, 112.31, 110.58, 56.39, 29.29, 25.12, 21.03, 20.86.

4.3.2. *N'*-(7-Bromo-6-methoxy-3,4-dihydronaphthalen-1(2H)-ylidene)-4-methylbenzenesulfonylhydrazide (**5c**)

Yield: 98 %. M.p. 236°C Rf 0.5 (cyclohexane/ EtOAc: 7/3). IR (neat) $\nu_{\max}/\text{cm}^{-1}$: 2249, 1054, 1025, 1016, 992, 821, 701, 654. $^1\text{H NMR}$ (300 MHz, DMSO) δ ppm 10.39 (br s, 1H), 7.92 – 7.70 (m, 3H), 7.42 (d, $J = 7.8$ Hz, 2H), 6.91 (s, 1H), 3.84 (s, 3H), 3.35 – 3.30 (m, 2H), 2.76 – 2.59 (m, 2H), 2.38 (s, 3H), 1.85 – 1.65 (m, 2H). $^{13}\text{C NMR}$ (75 MHz, DMSO) δ 156.3, 152.1, 143.8, 141.8, 136.7, 129.9 (2C), 128.8, 127.9 (2C), 126.0, 112.5, 109.3, 56.8, 29.1, 25.9, 21.5, 21.4.

4.4. General procedure for the coupling of *N*-tosylhydrazones with aryl iodides.

To a dioxane (2 mL) solution of *N*-tosylhydrazone (0.24 mmol), *t*BuOLi (0.53 mmol), Pd_2dba_3 (0.02 mmol), and XPhos (0.04 mmol) was added the required aryl iodide (0.24 mmol). The mixture was stirred at 90 °C for 5 h. CH_2Cl_2 (5 mL) was then added to the cooled mixture which was filtered over a pad of Celite. After concentration, the residue was purified by silica gel chromatography to yield **1a-c**, **1k**.

4.4.1. 8-Bromo-7-methoxy-4-(3,4,5-trimethoxyphenyl)-1,2-dihydronaphthalene (**1a**)

Yield: 76 %. Rf 0.4 (cyclohexane/EtOAc: 7/3). IR (neat) $\nu_{\max}/\text{cm}^{-1}$: 2931, 1591, 1421, 1331, 1267, 1204, 1154, 1062, 994, 906, 857, 729, 648. $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 6.90 (d, $J = 8.5$ Hz, 1H), 6.60 (d, $J = 8.5$ Hz, 1H), 6.45 (s, 2H), 5.91 (t, $J = 4.6$ Hz, 1H), 3.81 (s, 6H), 3.77 (s, 6H), 2.96 (t, $J = 7.9$ Hz, 2H), 2.33 (dt, $J = 4.8$ Hz, $J = 7.9$ Hz, 2H). $^{13}\text{C NMR}$ (75 MHz, CDCl_3) δ 154.9, 153.0 (2C), 139.2, 138.2, 137.3, 136.4, 129.8, 125.4, 125.4, 113.6, 108.8, 105.9 (2C), 60.9, 56.3, 56.1 (2C), 28.1, 23.0. MS (APCI, m/z) 405.7 ($[\text{M} + \text{H}]^+$, ^{79}Br), 407.2 ($[\text{M} + \text{H}]^+$, ^{81}Br). Anal. Calcd for $\text{C}_{20}\text{H}_{21}\text{BrO}_4$: C 59.27, H 5.22, found C 59.10, H 5.09.

4.4.2. 8-Bromo-4-(3,5-dimethoxyphenyl)-7-methoxy-1,2-dihydronaphthalene (**1b**)

Yield: 84 %. Rf 0.47 (cyclohexane/EtOAc: 7/3). IR (neat) ν_{\max} / cm^{-1} : 2931, 1591, 1421, 1267, 1204, 1154, 1062, 906, 729, 648. ^1H NMR (300 MHz, CDCl_3) δ 6.98 (d, $J = 8.5$ Hz, 1H), 6.66 (d, $J = 8.5$ Hz, 1H), 6.49 – 6.40 (m, 3H), 6.00 (t, $J = 4.7$ Hz, 1H), 3.88 (s, 3H), 3.79 (s, 6H), 3.12 – 2.94 (m, 2H), 2.49 – 2.28 (m, 2H). ^{13}C NMR (75 MHz, CDCl_3) δ 160.62 (2C), 154.9, 142.8, 139.2, 138.1, 129.7, 125.5, 115.8, 113.6, 108.8, 106.9 (2C), 99.4, 56.3, 55.3 (2C), 28.1, 23.0. MS (APCI, m/z) 375.15 ($[\text{M} + \text{H}]^+$, ^{79}Br), 377.36 ($[\text{M} + \text{H}]^+$, ^{81}Br). Anal. Calcd for $\text{C}_{19}\text{H}_{19}\text{BrO}_3$: C 60.81, H 5.10, found C 60.54, H 4.99.

4.4.3. 7-Methoxy-4-(3,4,5-trimethoxyphenyl)-1,2-dihydronaphthalene (**1c**)

Yield: 75%. Rf 0.57 (cyclohexane/EtOAc: 8/2). IR (neat) ν_{\max} / cm^{-1} : 2934, 2834, 1589, 1496, 1453, 1421, 1358, 1301, 1278, 1249, 1203, 1150, 1117, 1062, 1039, 1000. ^1H NMR (300 MHz, CDCl_3) δ 6.93 (d, $J = 8.5$ Hz, 1H), 6.71 (d, $J = 2.6$ Hz, 1H), 6.59 (dd, $J = 2.6$ Hz, $J = 8.5$ Hz, 1H), 6.49 (s, 2H), 5.89 (t, $J = 4.7$ Hz, 1H), 3.82 (s, 3H), 3.77 (s, 6H), 3.74 (s, 3H), 2.76 (t, $J = 7.9$ Hz, 2H), 2.31 (m, 2H). ^{13}C NMR (75 MHz, CDCl_3) δ 158.6, 152.9, 139.5, 138.6 (2C), 137.1, 136.7, 128.1, 126.7, 124.8, 113.8, 110.8, 105.7 (2C), 60.9, 56.1 (2C), 55.3, 28.8, 23.4. MS (APCI, m/z) 327.9 $[\text{M} + \text{H}]^+$. Anal. Calcd for $\text{C}_{20}\text{H}_{22}\text{O}_4$: C 73.60, H 6.79, found C 73.54, H 6.69.

4.4.4. 6-Bromo-7-methoxy-4-(3,4,5-trimethoxyphenyl)-1,2-dihydronaphthalene (**1k**)

Yield: 78 %. Rf 0.47 (cyclohexane/EtOAc: 8/2). IR (neat) ν_{\max} / cm^{-1} : 2934, 2833, 1580, 1505, 1490, 1465, 1449, 1411, 1360, 1337, 1255, 1237, 1166, 1126, 1018, 1003, 907, 730, 646. ^1H NMR (300 MHz, CDCl_3) δ 6.78 (s, 1H), 6.66 (s, 1H), 6.53 (s, 2H), 6.00 (t, $J = 4.6$ Hz, 1H), 3.92 (s, 3H), 3.90 (s, 3H), 3.85 (s, 6H), 2.81 (t, $J = 7.8$ Hz, 2H), 2.39 (m, 2H). ^{13}C NMR (75 MHz, CDCl_3) δ 154.5, 153.1 (2C), 138.7, 137.7, 137.3, 135.9, 130.1, 129.3, 125.7, 111.7, 108.6, 105.6 (2C), 60.9, 56.3, 56.1 (2C), 28.5, 23.2. MS (APCI, m/z) 405.1 ($[\text{M} + \text{H}]^+$, ^{79}Br), 407.4 ($[\text{M} + \text{H}]^+$, ^{81}Br). Anal. Calcd for $\text{C}_{20}\text{H}_{21}\text{BrO}_4$: C 59.27, H 5.22, found C 59.00, H 5.03.

4.5. Synthesis of **3a** and **3b**.

A CH_2Cl_2 solution (30 mL) of **1a** or **1c** (500 mg, 4.93 mmol) and DDQ (1.34 g, 5.91 mmol) was stirred at room temperature for 1 h. The medium was next washed three times with water and brine. The organic layer was dried over MgSO_4 , filtered and evaporated to dryness. Purification by flash chromatography afforded **3a,b**.

4.5.1. 1-Bromo-2-methoxy-5-(3,4,5-trimethoxyphenyl)naphthalene (**3a**)

Yield: 33 %. Rf 0.42 (cyclohexane/EtOAc: 7/3). IR (neat) ν_{\max} / cm^{-1} : 3663, 3324, 2974, 2934, 1672, 1659, 1579, 1499, 1088, 1045, 730, 700. ^1H NMR (300 MHz, CDCl_3) δ 8.28 (d, $J = 8.6$ Hz, 1H), 7.92 (d, $J = 9.2$ Hz, 1H), 7.59 (dd, $J = 8.6$, 7.0 Hz, 1H), 7.35 (dd, $J = 7.0$, 1.1 Hz, 1H), 7.23 (d, $J = 9.4$ Hz, 1H), 6.66 (s, 2H), 4.03 (s, 3H), 3.95 (s, 3H), 3.87 (s, 6H). ^{13}C NMR (75 MHz, CDCl_3) δ 153.8, 153.1 (2C), 140.7, 137.5, 136.2, 133.6, 128.3, 127.5, 127.3, 126.0, 125.3, 113.5, 109.1, 107.4 (2C), 61.1, 57.1, 56.3 (2C). MS (APCI, m/z) 403.1 ($[\text{M} + \text{H}]^+$, ^{79}Br), 405.1 ($[\text{M} + \text{H}]^+$, ^{81}Br). Anal. Calcd for $\text{C}_{20}\text{H}_{19}\text{BrO}_4$: C 59.57, H 4.75, found C 59.41, H 4.63.

4.5.2. 6-Methoxy-1-(3,4,5-trimethoxyphenyl)naphthalene (**3b**)

Yield: 99 %. Rf 0.3 (cyclohexane/EtOAc: 8/2). IR (neat) ν_{\max} / cm^{-1} : 2934, 1672, 1579, 1499, 1410, 1374, 1335, 1235, 1168, 1124, 1031, 1007, 910, 835, 789, 730, 700, 667, 647. ^1H NMR (300 MHz, CDCl_3) δ 7.86 (d, $J = 9.3$ Hz, 1H), 7.75 (d, $J = 8.2$ Hz, 1H), 7.48 (t, $J = 7.5$ Hz, 1H), 7.30 (d, $J = 7.1$ Hz, 1H), 7.21 (d, $J = 1.9$ Hz, 1H), 7.12 (dd, $J = 9.3$ Hz, $J = 1.9$ Hz, 1H), 6.70 (s, 2H), 3.95 (s, 6H), 3.88 (s, 6H). ^{13}C NMR (75 MHz, CDCl_3) δ 157.5, 152.9 (2C), 140.2, 137.3, 136.5, 135.1, 127.6, 127.1, 126.5, 125.9, 124.5, 118.7, 107.2 (2C), 106.1, 60.9, 56.2 (2C), 55.3. MS (APCI, m/z) 325.2 $[\text{M} + \text{H}]^+$. Anal. Calcd for $\text{C}_{20}\text{H}_{20}\text{O}_4$: C 74.06, H 6.21, found C 73.80, H 6.13.

4.6. General procedure for the preparation of anilines **1d**, **1i**, **1l** and **3c**.

A solution of **1a**, **1b**, **1k** or **3a** (1 mmol), NaN_3 (2 mmol), CuI (0.1 mmol), DMEDA (0.15 mmol) and sodium ascorbate (0.05 mmol) in a mixture of $\text{DMSO}/\text{H}_2\text{O}$: 5/1 was stirred at 60 °C in a sealed tube. After 12 h, the medium was cooled,

quenched with NH₄Cl and extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over MgSO₄, filtered and evaporated to dryness. Purification by flash chromatography afforded compounds **1d**, **1i**, **1l** and **3c**.

4.6.1. 2-Methoxy-5-(3,4,5-trimethoxyphenyl)-7,8-dihydronaphthalen-1-amine (**1d**)

Yield: 59 %. Rf 0.6 (cyclohexane/EtOAc: 5/5). IR (neat) $\nu_{\text{max}}/\text{cm}^{-1}$: 3663, 3324, 2974, 1659, 1088, 1045. ¹H NMR (300 MHz, CDCl₃) δ 6.52 (d, J = 8.4 Hz, 1H), 6.48 (s, 2H), 6.43 (d, J = 8.4 Hz, 1H), 5.84 (t, J = 4.6 Hz, 1H), 3.81 (s, 3H), 3.77 (s, 3H), 3.76 (s, 6H), 2.60 (t, J = 7.9 Hz, 2H), 2.34 (m, 2H), NH₂ not seen. ¹³C NMR (75 MHz, CDCl₃) δ 152.9 (2C), 147.2, 140.1, 137.3, 132.7, 128.3, 124.2, 121.2, 116.7, 107.2, 106.2 (2C), 61.0, 56.2 (2C), 55.7, 23.0, 21.7 (1C missing). MS (APCI, m/z) 342.2 [M + H]⁺. Anal. Calcd for C₂₀H₂₃NO₄: C 70.36, H 6.79, N 4.10 found C 70.01, H 6.48, N 3.98.

4.6.2. 5-(3,5-Dimethoxyphenyl)-1-amino-2-methoxy-1,2-dihydronaphthalene (**1i**)

Yield: 73 %. Rf 0.8 (cyclohexane/EtOAc: 7/3). IR (neat) $\nu_{\text{max}}/\text{cm}^{-1}$: 3669, 3324, 2974, 1670, 1088, 1045. ¹H NMR (300 MHz, CDCl₃) δ 6.49-6.42 (m, 4H), 6.35 (t, J = 2.3 Hz, 1H), 5.84 (t, J = 4.6 Hz, 1H), 3.75 (s, 3H), 3.72 (m, 2H), 3.69 (s, 6H), 2.58 (t, J = 7.9 Hz, 2H), 2.32 (m, 2H). ¹³C NMR (75 MHz, CDCl₃) δ 160.5 (2C), 147.2, 143.8, 140.1, 132.7, 128.2, 124.3, 121.2, 116.8, 107.0 (3C), 99.4, 55.7, 55.5 (2C), 23.0, 21.7. MS (APCI, m/z) 312.9 [M + H]⁺. Anal. Calcd for C₁₉H₂₁NO₃: C 73.29, H 6.80, N 4.50 found C 73.04, H 6.62, N 4.40.

4.6.3. 3-Methoxy-8-(3,4,5-trimethoxyphenyl)-5,6-dihydronaphthalen-2-amine (**1l**)

Yield: 72 %. Rf 0.6 (cyclohexane/EtOAc: 5/5). IR (neat) $\nu_{\text{max}}/\text{cm}^{-1}$: 2934, 2251, 2157, 1978, 1578, 1508, 1462, 1410, 1366, 1339, 1285, 1243, 1214, 1158, 1124, 1006, 909, 823, 731. ¹H NMR (300 MHz, CDCl₃) δ 6.68 (s, 1H), 6.55 (s, 2H), 6.49 (s, 1H), 5.94 (t, J = 4.6 Hz, 1H), 3.89 (s, 3H), 3.87 (s, 3H), 3.84 (s, 6H), 2.76 (t, J = 7.7 Hz, 2H), 2.35 (m, 2H), NH₂ not seen. ¹³C NMR (75 MHz, CDCl₃) 153.0 (2C), 146.5, 145.9, 139.7, 137.1, 133.4, 128.0, 127.8, 125.2, 113.6, 110.5, 105.9 (2C), 61.0, 56.3 (2C), 55.8, 28.2, 23.9. MS (APCI, m/z) 342.0 [M + H]⁺. Anal. Calcd for C₂₀H₂₃NO₄: C 70.36, H 6.79, N 4.10 found C 69.88, H 6.39, N 3.89.

4.6.4. 2-Methoxy-5-(3,4,5-trimethoxyphenyl)naphthalen-1-amine (**3c**)

Yield: 46 %. Rf 0.33 (cyclohexane/EtOAc: 7/3). IR (neat) $\nu_{\text{max}}/\text{cm}^{-1}$: 3663, 3324, 2974, 2934, 1672, 1659, 1579, 1088, 1045. ¹H NMR (300 MHz, CDCl₃) δ 7.72 (d, J = 8.5 Hz, 1H), 7.36 (m, 2H), 7.20 (d, J = 7.0 Hz, 1H), 7.12 (d, J = 9.2 Hz, 1H), 6.62 (s, 2H), 4.27 (br s, 2H), 3.89 (s, 3H), 3.87 (s, 3H), 3.79 (s, 6H). ¹³C NMR (75 MHz, CDCl₃) δ 153.1 (2C), 142.6, 140.8, 137.2, 137.0, 129.8, 127.7, 124.6 (2C), 124.4, 120.1, 116.9, 113.4, 107.3 (2C), 61.1, 56.7, 56.3 (2C). MS (APCI, m/z) 362 [M + Na]⁺. Anal. Calcd for C₂₀H₂₁NO₄: C 70.78, H 6.24, N 4.13, found C 70.55, H 6.15, N 4.01.

4.7. General procedure for the preparation of naphthols **1e**, **1h** and **3d**.

A solution of **1a**, **b**, and **3a** (1 mmol), KOH (5 mmol), Pd₂dba₃ (0.1 mmol) and *t*BuXPhos (0.2 mmol) in a mixture of dioxane/H₂O: 1/1 was stirred at 90 °C in a sealed tube. After 1 h, the medium was cooled to room temperature, quenched with NH₄Cl and extracted with EtOAc (3 x 10 mL). The combined organic layers were then dried over MgSO₄, filtered and evaporated to dryness. Purification by flash chromatography afforded compounds **1e**, **1h** and **3d**.

4.7.1. 2-Methoxy-5-(3,4,5-trimethoxyphenyl)-7,8-dihydronaphthalen-1-ol (**1e**)

Yield: 63 %. Rf 0.52 (cyclohexane/EtOAc: 7/3). IR (neat) $\nu_{\text{max}}/\text{cm}^{-1}$: 2941, 2177, 1581, 1489, 1355, 1234, 1126, 905, 726, 652, 610. ¹H NMR (300 MHz, CDCl₃) δ 6.63 (d, J = 8.5 Hz, 1H), 6.59 (d, J = 8.5 Hz, 1H), 6.56 (s, 2H), 5.97 (t, J = 4.6 Hz, 1H), 5.72 (s, 1H), 3.89 (s, 6H), 3.84 (s, 6H), 2.89 (t, J = 7.9 Hz, 2H), 2.38 (m, 2H). ¹³C NMR (75 MHz, CDCl₃) δ 153.0 (2C), 146.0, 142.1, 139.7, 137.0, 129.1, 125.5, 122.4, 117.6, 107.4, 106.1 (2C), 61.1, 56.3 (2C), 56.1, 23.0, 20.4, (1 C missing). MS (APCI, m/z) 343.2 [M + H]⁺. Anal. Calcd for C₂₀H₂₂O₅: C 70.16, H 6.48, found C 70.00, H 6.32.

4.7.2. 5-(3,5-Dimethoxyphenyl)-2-methoxy-7,8-dihydronaphthalen-1-ol (**1h**)

Yield: 62 %. Rf 0.46 (cyclohexane/EtOAc: 7/3). IR (neat) $\nu_{\text{max}}/\text{cm}^{-1}$: 2934, 1590, 1489, 1353, 1276, 1204, 1152, 1095, 1069, 826. ¹H NMR (300 MHz, CDCl₃) δ 6.60 (s, 1H), 6.58 (d, J = 2.3 Hz, 1H), 6.50 (d, J = 2.3 Hz, 2H), 6.44 (t, J =

2.3 Hz, 1H), 5.98 (t, $J = 4.7$ Hz, 1H), 5.71 (s, 1H), 3.88 (s, 3H), 3.79 (s, 6H), 2.88 (t, $J = 8.0$ Hz, 2H), 2.37 (m, 2H). ^{13}C NMR (75 MHz, CDCl_3) δ 160.6 (2C), 145.9, 143.4, 142.1, 140.0, 129.0, 125.7, 122.4, 117.6, 107.4, 107.0 (2C), 99.5, 56.1, 55.5 (2C), 23.0, 20.4. MS (APCI, m/z) 313.2 $[\text{M} + \text{H}]^+$. Anal. Calcd for $\text{C}_{19}\text{H}_{20}\text{O}_4$: C 73.06, H 6.45, found C 72.99, H 6.39.

4.7.3. 2-Methoxy-5-(3,4,5-trimethoxyphenyl)naphthalen-1-ol (**3d**)

Yield: 82 %. Rf 0.39 (cyclohexane/EtOAc: 7/3). IR (neat) $\nu_{\text{max}}/\text{cm}^{-1}$: 2936, 1579, 1500, 1461, 1403, 1340, 1235, 1123, 1073, 1005, 896, 797, 729. ^1H NMR (300 MHz, CDCl_3) δ 8.20 (d, $J = 7.0$ Hz, 1H), 7.53 – 7.44 (m, 2H), 7.31 (dd, $J = 7.0$ Hz, $J = 1.2$ Hz, 1H), 7.22 (d, $J = 9.3$ Hz, 1H), 6.70 (s, 2H), 4.00 (s, 3H), 3.94 (m, 3H), 3.87 (s, 6H), OH not seen. ^{13}C NMR (75 MHz, CDCl_3) δ 153.0 (2C), 141.2, 139.9, 139.8, 137.2, 136.8, 127.8, 125.2, 125.0, 124.5, 121.0, 118.0, 113.1, 107.3 (2C), 61.1, 57.2, 56.3 (2C). MS (APCI, m/z) 341 $[\text{M} + \text{H}]^+$. Anal. Calcd for $\text{C}_{20}\text{H}_{20}\text{O}_5$: C 70.57, H 5.92, found C 70.30, H 5.67.

4.8. General procedure for the synthesis of alkynes **1f**, **1g**, **3e** and **3f**.

A DMF solution of **1a** and **3a** (1 mmol), alkyne (1.2 mmol), $\text{PdCl}_2(\text{PPh}_3)_2$ (0.05 mmol), PPh_3 (0.1 mmol), CuI (0.05 mmol) and Et_2NH (2 mmol) was stirred at 120 °C under microwave irradiation. After 25 min, the medium was cooled down to room temperature, quenched with NH_4Cl and extracted with EtOAc (3 x 10 mL). The combined organic layers were then dried over MgSO_4 , filtered and evaporated to dryness. Purification by flash chromatography afforded compounds **1f**, **1g**, **3e** and **3f**.

4.8.1. 4-(2-Methoxy-5-(3,4,5-trimethoxyphenyl)-7,8-dihydronaphthalen-1-yl)but-3-yn-1-ol (**1f**)

Yield: 41 %. Rf 0.6 (cyclohexane/EtOAc: 4/6). IR (neat) $\nu_{\text{max}}/\text{cm}^{-1}$: 2922, 1590, 1489, 1413, 1353, 1267, 1128, 905, 812, 738. ^1H NMR (300 MHz, CDCl_3) δ 6.97 (d, $J = 8.6$ Hz, 1H), 6.63 (d, $J = 8.6$ Hz, 1H), 6.53 (s, 2H), 5.98 (t, $J = 4.5$ Hz, 1H), 3.89 (s, 3H), 3.87 (s, 3H), 3.84 (m, 8H), 3.02 (t, $J = 7.8$ Hz, 2H), 2.81 (t, $J = 6.0$ Hz, 2H), 2.39 (m, 2H), OH not seen. ^{13}C NMR (75 MHz, CDCl_3) 159.3 (2C), 152.9, 140.6, 139.2, 137.1, 136.5, 128.2, 126.2, 125.3, 111.2 (2C), 107.3, 105.7, 95.1, 77.7, 61.1, 60.9, 56.1, 55.8 (2C), 26.3, 24.4, 23.0. MS (APCI, m/z) 395.6 $[\text{M} + \text{H}]^+$. Anal. Calcd for $\text{C}_{24}\text{H}_{26}\text{O}_5$: C 73.08, H 6.64, found C 72.79, H 6.38.

4.8.2. 3-(2-Methoxy-5-(3,4,5-trimethoxyphenyl)-7,8-dihydronaphthalen-1-yl)prop-2-yn-1-ol (**1g**)

Yield: 25 %. Rf 0.57 (cyclohexane/EtOAc: 4/6). IR (neat) $\nu_{\text{max}}/\text{cm}^{-1}$: 2922, 1590, 1489, 1413, 1353, 1267, 1128, 905, 805, 726, 649. ^1H NMR (300 MHz, CDCl_3) δ 7.00 (d, $J = 8.6$ Hz, 1H), 6.64 (d, $J = 8.6$ Hz, 1H), 6.53 (s, 2H), 5.99 (t, $J = 4.3$ Hz, 1H), 4.61 (s, 2H), 3.89 (s, 3H), 3.87 (s, 3H), 3.84 (s, 6H), 3.04 (t, $J = 7.7$ Hz, 2H), 2.38 – 2.19 (m, 2H). OH not seen. ^{13}C NMR (75 MHz, CDCl_3) 159.3, 152.9 (2C), 141.2, 139.1, 137.1, 136.5, 127.9, 126.7, 125.4, 110.4, 107.4, 105.8 (2C), 95.8, 80.2, 60.9, 56.1 (2C), 55.8, 51.9, 26.2, 22.9. MS (APCI, m/z) 381.8 $[\text{M} + \text{H}]^+$. Anal. Calcd for $\text{C}_{23}\text{H}_{24}\text{O}_5$: C 72.61, H 6.36, found C 72.56, H 6.12.

4.8.3. 3-(2-Methoxy-5-(3,4,5-trimethoxyphenyl)naphthalen-1-yl)but-3-yn-1-ol (**3e**)

Yield: 52 %. Rf 0.22 (cyclohexane/EtOAc: 6/4). IR (neat) $\nu_{\text{max}}/\text{cm}^{-1}$: 2934, 1580, 1501, 1463, 1409, 1320, 1266, 1236, 1183, 1124, 1060, 1005, 910, 850, 730, 686. ^1H NMR (300 MHz, CDCl_3) δ 8.27 (d, $J = 8.4$ Hz, 1H), 7.90 (d, $J = 9.4$ Hz, 1H), 7.60 – 7.48 (m, 1H), 7.31 (d, $J = 6.8$ Hz, 1H), 7.19 (d, $J = 9.4$ Hz, 1H), 6.66 (s, 2H), 4.01 (s, 3H), 3.98 – 3.89 (m, 5H), 3.87 (s, 6H), 2.92 (t, $J = 6.1$ Hz, 2H), OH not seen. ^{13}C NMR (75 MHz, CDCl_3) 158.7, 152.9 (2C), 140.5, 137.3, 136.2, 134.9, 127.9, 126.8, 126.7, 124.9 (2C), 112.4, 107.3 (2C), 106.5, 96.4, 77.3, 61.2, 60.9, 56.5, 56.2 (2C), 24.6. MS (APCI, m/z) 393.3 $[\text{M} + \text{H}]^+$. Anal. Calcd for $\text{C}_{24}\text{H}_{24}\text{O}_5$: C 73.45, H 6.16, found C 73.34, H 6.02.

4.8.4. 3-(2-Methoxy-5-(3,4,5-trimethoxyphenyl)naphthalen-1-yl)prop-2-yn-1-ol (**3f**)

Yield: 49 %. Rf 0.14 (cyclohexane/EtOAc: 2/8). IR (neat) $\nu_{\text{max}}/\text{cm}^{-1}$: 2922, 1501, 1463, 1413, 1267, 1128, 905, 805, 726, 649. ^1H NMR (300 MHz, CDCl_3) δ 8.35 (d, $J = 8.4$ Hz, 1H), 8.00 (d, $J = 9.4$ Hz, 1H), 7.63 (dd, $J = 8.4$ Hz, $J = 7.0$ Hz, 1H), 7.39 (d, $J = 7.0$ Hz, 1H), 7.26 (d, $J = 9.5$ Hz, 1H), 6.73 (s, 2H), 4.80 (s, 2H), 4.08 (s, 3H), 4.01 (s, 3H), 3.94 (s, 6H), OH not seen. ^{13}C NMR (75 MHz, CDCl_3) 158.1 (2C), 152.1, 139.8, 135.3, 134.2, 127.9, 126.1, 125.9, 124.2,

124.0, 115.5, 106.3 (2C), 96.2, 79.3, 60.2, 55.6, 55.4 (2C), 51.3, two C missing. MS (APCI, m/z) 379.5 [M + H]⁺. Anal. Calcd for C₂₃H₂₂O₅: C 73.00, H 5.86, found C 72.87, H 5.76.

4.9. General procedure for the synthesis of compounds **1j** and **3g**.

A NMP solution of **1a** or **3a** (1 mmol), methyl acrylate (10 mmol), PEPPSI (0.05 mmol) and K₂CO₃ (2 mmol) was stirred at 140 °C in a sealed tube. After 1 h, the medium was cooled down to room temperature, quenched with NH₄Cl and extracted with EtOAc (3 x 10 mL). The combined organic layers were then dried over MgSO₄, filtered, and the solvent was then removed. Purification by flash chromatography afforded compounds **1j** and **3g**.

4.9.1. Methyl-3-(2-methoxy-5-(3,4,5-trimethoxyphenyl)-7,8-dihydronaphthalen-1-yl)acrylate (**1j**)

Yield: 35 %. 0.41 Rf (cyclohexane/EtOAc: 7/3). IR (neat) ν_{\max} / cm⁻¹: 2945, 2500, 1714, 1579, 1504, 1463, 1412, 1352, 1252, 1169, 1124, 1007, 911. ¹H NMR (300 MHz, CDCl₃) δ 7.99 (d, *J* = 16.2 Hz, 1H), 7.05 (d, *J* = 8.6 Hz, 1H), 6.69 (d, *J* = 8.6 Hz, 1H), 6.53 (s, 2H), 6.45 (d, *J* = 16.2 Hz, 1H), 6.01 (t, *J* = 4.1 Hz, 1H), 3.88 (s, 3H), 3.84 (s, 3H), 3.83 (s, 6H), 3.81 (s, 3H), 2.96 (t, *J* = 7.7 Hz, 2H), 2.33 (m, 2H). ¹³C NMR (75 MHz, CDCl₃) 167.9, 157.7, 153.0 (2C), 139.6, 139.1, 138.1, 137.1, 136.7, 128.6, 127.9, 125.1, 123.4, 121.8, 107.8, 105.8 (2C), 60.9, 56.1 (2C), 55.5, 51.6, 25.3, 23.2. MS (APCI, m/z) 411.8 [M + H]⁺. Anal. Calcd for C₂₄H₂₆O₆: C 70.23, H 6.38, found C 70.11, H 6.31.

4.9.2. Methyl-3-(2-methoxy-5-(3,4,5-trimethoxyphenyl)naphthalen-1-yl)acrylate (**3g**)

Yield: 22 %. Rf 0.44 (cyclohexane/EtOAc: 7/3). IR (neat) ν_{\max} / cm⁻¹: 3976, 3412, 2939, 2185, 1713, 1579, 1503, 1464, 1414, 1278, 1171, 1153, 1126, 1063, 1008, 806. ¹H NMR (300 MHz, CDCl₃) δ 8.38 (d, *J* = 16.2 Hz, 1H), 8.20 (d, *J* = 8.9 Hz, 1H), 7.96 (d, *J* = 8.9 Hz, 1H), 7.54 (t, *J* = 7.2 Hz, 1H), 7.33 (d, *J* = 7.2 Hz, 1H), 7.24-7.10 (m, 1H), 6.77 (d, *J* = 16.2 Hz, 1H), 6.66 (s, 2H), 3.99 (s, 3H), 3.94 (s, 3H), 3.87 (s, 9H). ¹³C NMR (75 MHz, CDCl₃) 168.4, 156.5, 153.1 (2C), 141.1, 138.3, 137.4, 136.5, 133.3, 129.9, 127.3, 126.9, 124.9, 123.4, 123.1, 116.9, 112.7, 107.3 (2C), 77.2, 61.1, 56.3 (2C), 51.8. MS (APCI, m/z) 409.7 [M + H]⁺. Anal. Calcd for C₂₄H₂₄O₆: C 70.57, H 5.92, found C 70.21, H 5.68.

4.10. General procedure for catalytic hydrogenation.

A solution of suitable precursor (50 mg) and Pd/C (5 mg) in MeOH (8 mL) was stirred under a H₂ atmosphere at room temperature. After 4 h, the medium filtered over a pad of Celite and the solvent was removed *in vacuo*. Purification by flash chromatography afforded compounds **2a-e** and **3h**.

4.10.1. 6-Methoxy-1-(3,4,5-trimethoxyphenyl)-1,2,3,4-tetrahydronaphthalene (**2a**)

Yield: 76 %. Rf 0.6 (cyclohexane/EtOAc: 8/2). IR (neat) ν_{\max} / cm⁻¹: 2931, 1589, 1500, 1462, 1417, 1328, 1232, 1124, 1038, 1007, 908, 826, 727, 647. ¹H NMR (300 MHz, CDCl₃) δ 6.80 (d, *J* = 8.3 Hz, 1H), 6.68 – 6.58 (m, 2H), 6.31 (s, 2H), 4.01 – 3.94 (m, 1H), 3.83 (s, 3H), 3.78 (s, 9H), 2.93 – 2.79 (m, 2H), 2.19 – 2.07 (m, 1H), 1.95 – 1.84 (m, 2H), 1.84 – 1.68 (m, 1H). ¹³C NMR (75 MHz, CDCl₃) 157.7, 153.0 (2C), 143.5, 138.7, 136.2, 131.6, 131.2, 113.3, 112.1, 105.8 (2C), 60.9, 56.2 (2C), 55.3, 45.6, 33.6, 30.2, 21.5. MS (APCI, m/z) 329.1 [M + H]⁺. Anal. Calcd for C₂₀H₂₄O₄: C 73.15, H 7.37, found C 72.89, H 7.13.

4.10.2. 2-Methoxy-5-(3,4,5-trimethoxyphenyl)-5,6,7,8-tetrahydronaphthalen-1-amine (**2b**)

Yield: 47 %. Rf 0.49 (cyclohexane/EtOAc: 6/4). IR (neat) ν_{\max} / cm⁻¹: 2933, 1600, 1492, 1458, 1233, 1127. ¹H NMR (400 MHz, CDCl₃) δ 6.60 (d, *J* = 8.2 Hz, 1H), 6.31 (d, *J* = 8.1 Hz, 1H), 6.32 (s, 2H), 3.99 (m, 1H), 3.83 (s, 3H), 3.83 (s, 3H), 3.78 (s, 6H), 2.59 (m, 2H), 2.07 (m, 1H), 1.96 (m, 1H), 1.83-1.81 (m, 2H), NH₂ not seen. The presence of an impurity complicates the NMR spectra and despite our best efforts, we were not able to obtain **2b** with a satisfactory elemental analysis ¹³C NMR (100 MHz, CDCl₃) 153.0 (2C), 145.1, 143.5, 136.2, 133.2, 132.3, 122.8, 119.6, 108.2, 106.0 (2C), 61.0, 56.2 (2C), 55.7, 46.0, 32.7, 24.7, 20.8. MS (APCI, m/z) 344.2 [M + H]⁺.

4.10.3. 2-Methoxy-5-(3,4,5-trimethoxyphenyl)-5,6,7,7-tetrahydronaphthalen-1-ol (**2c**)

Yield: 50 %. Rf 0.66 (cyclohexane/EtOAc: 7/3). IR (neat) ν_{\max} / cm⁻¹: 3518, 2930, 2004, 1589, 1492, 1459, 1280, 1234, 1126, 907, 731, 624. ¹H NMR (300 MHz, CDCl₃) δ 6.63 (d, *J* = 8.5 Hz, 1H), 6.39 (d, *J* = 8.5 Hz, 1H), 6.32 (s, 2H), 5.69 (br s, 1H), 3.96 (m, 1H), 3.86 (s, 3H), 3.84 (s, 3H), 3.79 (s, 6H), 2.96 – 2.65 (m, 2H), 2.17 – 1.73 (m, 4H). ¹³C NMR (75

MHz, CDCl₃) 153.0 (2C), 144.0, 143.4, 142.6, 133.0, 124.3, 120.9, 108.2, 105.9 (2C), 61.0, 56.2 (2C), 56.1, 45.9, 33.0, 23.3, 20.7 (one C missing). MS (APCI, m/z) 345.2 [M + H]⁺. Anal. Calcd for C₂₀H₂₄O₅: C 69.75, H 7.02, found C 69.51, H 6.85.

4.10.4. 4-(2-Methoxy-5-(3,4,5-trimethoxyphenyl)-5,6,7,8-tetrahydronaphthalen-1-yl)butan-1-ol (**2d**)

Yield: 34 %. Rf 0.31 (cyclohexane/EtOAc: 6/4). IR (neat) ν_{\max} / cm⁻¹: 2004, 1589, 1492, 1459, 1280, 1234, 1154, 1126, 1064, 1007, 806, 730, 613. ¹H NMR (300 MHz, CDCl₃) δ 6.71 (d, *J* = 8.4 Hz, 1H), 6.63 (d, *J* = 8.4 Hz, 1H), 6.31 (s, 2H), 4.04 – 3.94 (m, 1H), 3.84 (s, 3H), 3.78 (s, 9H), 3.71 (t, *J* = 6.6 Hz, 1H), 2.82 (t, *J* = 6.6 Hz, 2H), 2.68 (dd, *J* = 12.7 Hz, *J* = 6.4 Hz, 2H), 2.16 – 1.48 (m, 10H). ¹³C NMR (75 MHz, CDCl₃) 155.6, 153.1 (2C), 143.6, 136.5, 136.3, 131.9, 128.5, 128.4, 108.4, 106.1 (2C), 63.0, 60.9, 56.2 (2C), 55.6, 46.4, 33.0, 32.8, 26.8, 25.4, 25.4, 21.5. MS (APCI, m/z) 423.3 [M + Na]⁺. Anal. Calcd for C₂₄H₃₂O₅: C 71.97, H 8.05, found C 71.59, H 7.83.

4.10.5. 1-(3,5-Dimethoxyphenyl)-6-methoxy-1,2,3,4-tetrahydronaphthalene (**2e**)

Yield: 72 %. Rf 0.25 (cyclohexane/EtOAc: 8/2). IR (neat) ν_{\max} / cm⁻¹: 2939, 2835, 2049, 2000, 1595, 1501, 1462, 1427, 1323, 1254, 1204, 1154, 1064, 832, 697. ¹H NMR (300 MHz, CDCl₃) δ 6.80 (d, *J* = 8.3 Hz, 1H), 6.68 – 6.54 (m, 2H), 6.31 (t, *J* = 2.3 Hz, 1H), 6.26 (d, *J* = 2.2 Hz, 2H), 3.99 (t, *J* = 6.7 Hz, 1H), 3.78 (s, 3H), 3.75 (s, 6H), 2.96 – 2.71 (m, 2H), 2.20 – 2.03 (m, 1H), 1.95 – 1.79 (m, 2H), 1.79 – 1.65 (m, 1H). ¹³C NMR (75 MHz, CDCl₃) 160.5 (2C), 157.6, 150.2, 138.6, 131.4, 131.3, 113.2, 112.1, 107.1 (2C), 97.6, 55.2 (2C), 55.2, 45.2, 33.1, 30.1, 21.0. MS (APCI, m/z) 299.1 [M + H]⁺. Anal. Calcd for C₁₉H₂₂O₃: C 76.48, H 7.43, found C 76.09, H 7.23.

4.10.6. 3-(2-Methoxy-5-(3,4,5-trimethoxyphenyl)naphthalen-1-yl)propan-1-ol (**3h**)

Yield: 82 %. Rf 0.2 (cyclohexane/EtOAc: 3/7). IR (neat) ν_{\max} / cm⁻¹: 2932, 2035, 1582, 1501, 1462, 1415, 1332, 1257, 1126, 1040, 1007, 806, 730, 613. ¹H NMR (300 MHz, CDCl₃) δ 8.01 (d, *J* = 8.6 Hz, 1H), 7.85 (d, *J* = 9.4 Hz, 1H), 7.53 (dd, *J* = 8.6 Hz, *J* = 7.0 Hz, 1H), 7.31 (d, *J* = 6.9 Hz, 1H), 7.24 (d, *J* = 10.4 Hz, 1H), 6.68 (s, 2H), 3.98 (s, 3H), 3.95 (s, 3H), 3.87 (s, 6H), 3.59 (t, *J* = 5.8 Hz, 2H), 3.27 (t, *J* = 7.0 Hz, 2H), 1.98 (m, 2H), OH not seen. ¹³C NMR (75 MHz, CDCl₃) 154.2, 152.9 (2C), 140.9, 136.7, 133.3, 127.7, 126.2, 125.9, 124.3, 122.8, 122.5 (2C), 112.9, 107.2 (2C), 61.6, 60.9, 56.7, 56.2 (2C), 32.2, 20.6. MS (APCI, m/z) 383.8 [M + H]⁺. Anal. Calcd for C₂₃H₂₆O₅: C 72.23, H 6.85, found C 72.00, H 6.58.

4.11. Biology

4.11.1. Cell Culture and Proliferation Assay.

Cancer cell lines were obtained from the American type Culture Collection (Rockville, MD) and were cultured according to the supplier's instructions. Briefly MDA-MB-231 and H1299 cells were grown in Dulbecco minimal essential medium (DMEM) containing 4.5 g/L glucose supplemented with 10% FCS and 1% glutamine. Human K562 leukemia and HCT116 colorectal carcinoma cells were grown in RPMI 1640 containing 10% FCS and 1% glutamine. Cell lines were maintained at 37 °C in a humidified atmosphere containing 5% CO₂. Cell viability was assessed using Promega CellTiter-Blue TM reagent according to the manufacturer's instructions. Cells were seeded in 96-well plates (5 × 10³ cells/well) containing 50 μ L growth medium. After 24 h of culture, the cells were supplemented with 50 μ L of the tested compound dissolved in DMSO (less than 0.1% in each preparation). After 72 h of incubation, 20 μ L of resazurin was added for 2 h before recording fluorescence (λ_{ex} = 560 nm, λ_{em} = 590 nm) using a Victor microtiter plate fluorimeter (Perkin-Elmer, USA). The GI₅₀ corresponds to the concentration of the tested compound that caused a decrease of 50% in fluorescence of drug treated cells compared with untreated cells. Experiments were performed in triplicate. The GI₅₀ values for all compounds were compared to the GI₅₀ of CA4, *iso*CA-4 and *iso*erianin and measured the same day under the same conditions.

4.11.2. Tubulin Binding Assay

Sheep brain tubulin was purified according to the method of Shelanski[41] by two cycles of assembly-disassembly and then dissolved in the assembly buffer containing 0.1 M MES, 0.5 mM MgCl₂, 1 mM EGTA, and 1 mM GTP, pH 6.6

(the concentration of tubulin was about 2-3 mg/mL). Tubulin assembly was monitored by fluorescence according to reported procedure[50] using DAPI as fluorescent molecule. Assays were realized on 96-well plates prepared with Biomek NKMC and Biomek 3000 from Beckman Coulter and read at 37°C on Wallac Victor fluorimeter from Perkin Elmer. The IC₅₀ value of each compound was determined as the concentration which decreased the maximum assembly rate of tubulin by 50% compared to the rate in the absence of compound. The IC₅₀ values for all compounds were compared to the IC₅₀ of CA4, *iso*CA-4 and *isoerianin* and measured the same day under the same conditions.

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Legends to Figures, Schemes and Tables

Figure 1 Representative tubulin binding agents and general structure of the synthesized analogues **1-3**.

Scheme 1 Synthesis of compounds **1-3**.

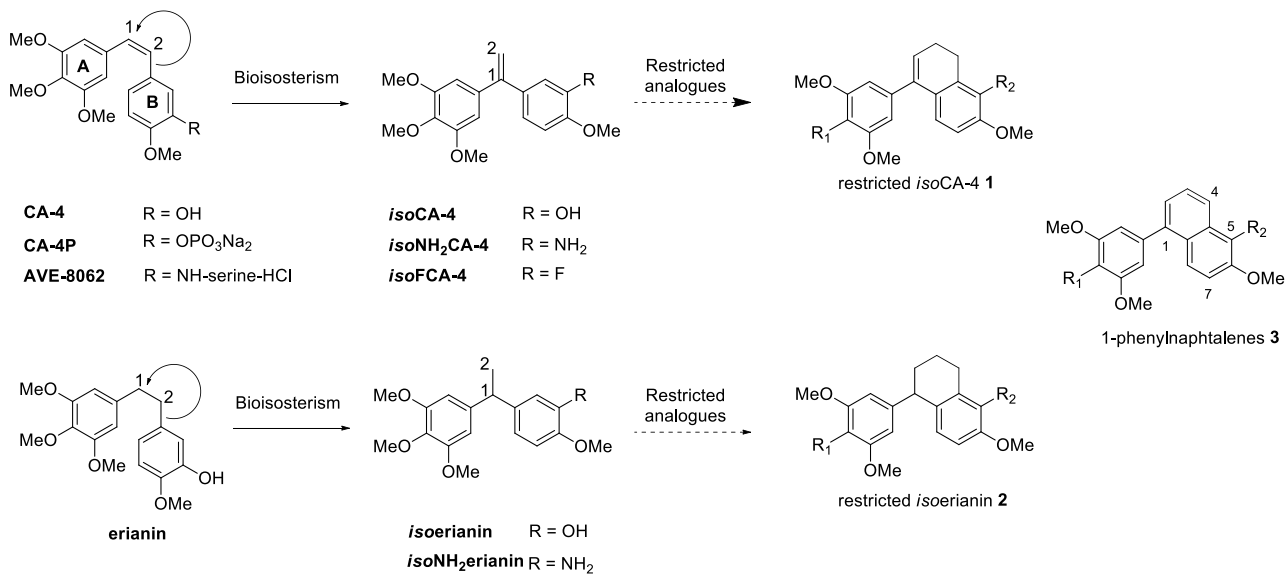
Scheme 2 Synthesis of compounds **1k,l**.

Table 1 Cytotoxicity of compounds **1-3** against HCT 116 cells.^a

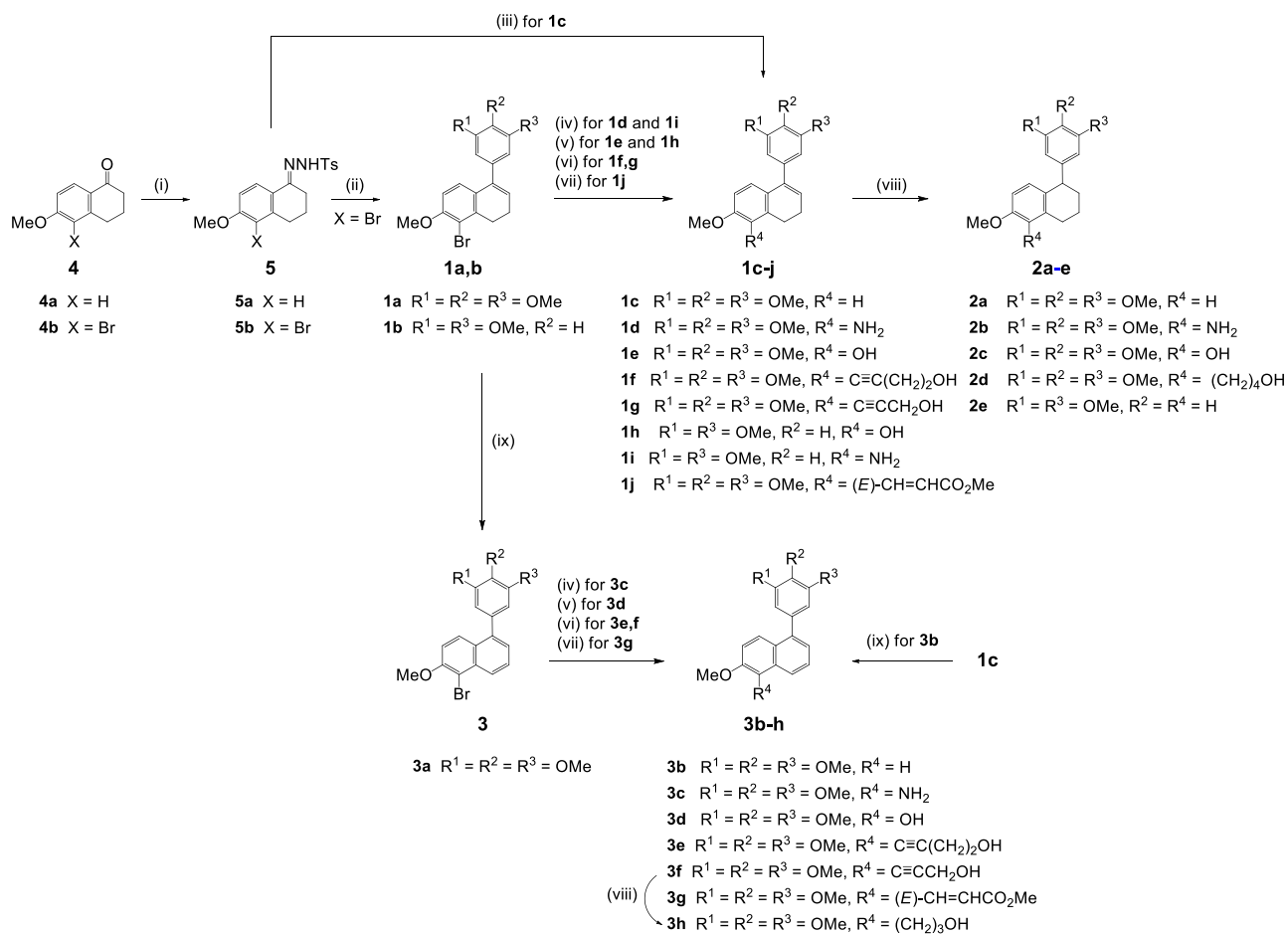
Table 2. Cytotoxicities of selected compounds against different human cancer cell lines and inhibition of tubulin polymerization (ITP).

Table 3. Evaluation of G₂/M arrest in MDA-MB231, K562, HCT116 and H1299 cells exposed to **2c**, **1e** and **3d**.

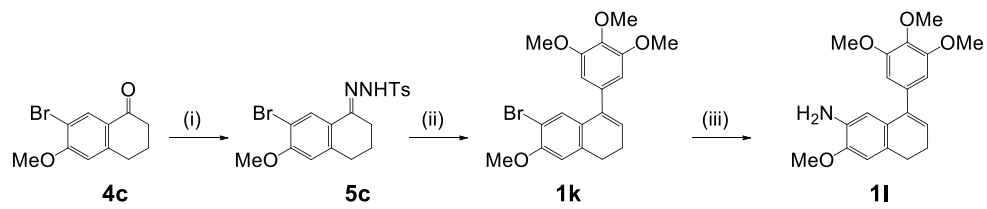
Figure 2. Docked pose of **2c**, **1e** and **3c** overlaid with isoCA-4 and isoerianin in the tubulin binding site.



<Figure 1>



<Scheme 1>



<Scheme 2>

Cpnd				
Cytotoxicity GI ₅₀ ^b [nM]	320 ± 30	950 ± 80	300 ± 30	7 ± 0.8
Cpnd				
Cytotoxicity GI ₅₀ ^b [nM]	85 ± 6	250 ± 22	600 ± 50	70 ± 6
Cpnd				
Cytotoxicity GI ₅₀ ^b [nM]	20 ± 2	700 ± 65	Nc ^c	70 ± 6
Cpnd				
Cytotoxicity GI ₅₀ ^b [nM]	70 ± 6	20 ± 1.5	1700 ± 100	250 ± 28
Cpnd				
Cytotoxicity GI ₅₀ ^b [nM]	800 ± 70	800 ± 60	55 ± 6	250 ± 30
Cpnd				
Cytotoxicity GI ₅₀ ^b [nM]	5500 ± 500	Nc ^c	Nc ^c	Nc ^c
	3 ± 0.2 ^d	28 ± 2	2 ± 0.1 ^d	

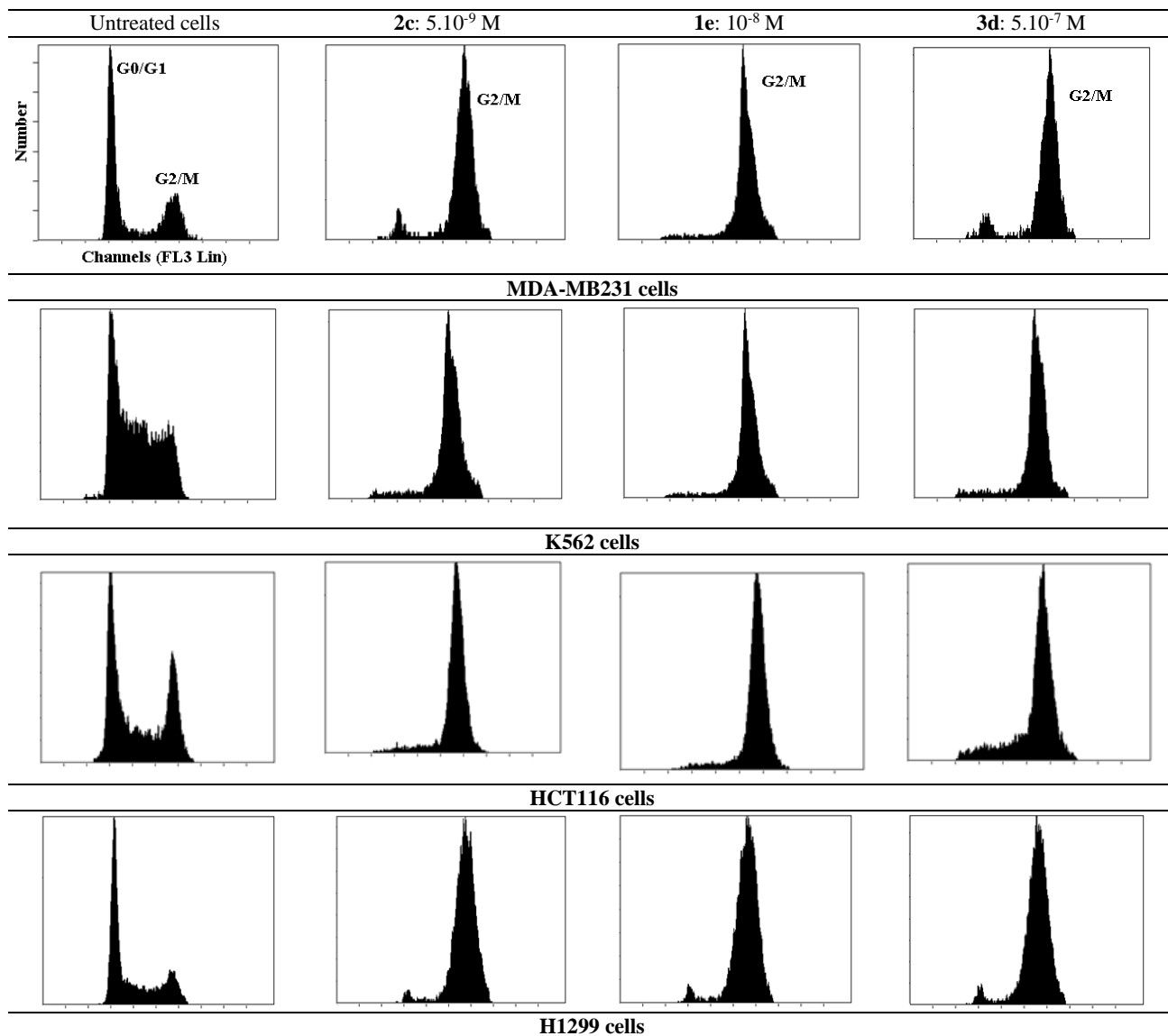
^a HCT116: human colon carcinoma cells. ^b GI₅₀ is the concentration of compound needed to reduce cell growth by 50% following 72 h cell treatment with the tested drug (average of three experiments). ^c GI₅₀ value not calculated owing to the low activity of the compound. ^d The GI₅₀ values for *isoCA-4*, *isoerianin* and *CA-4* were determined in this study.

<Table 1>

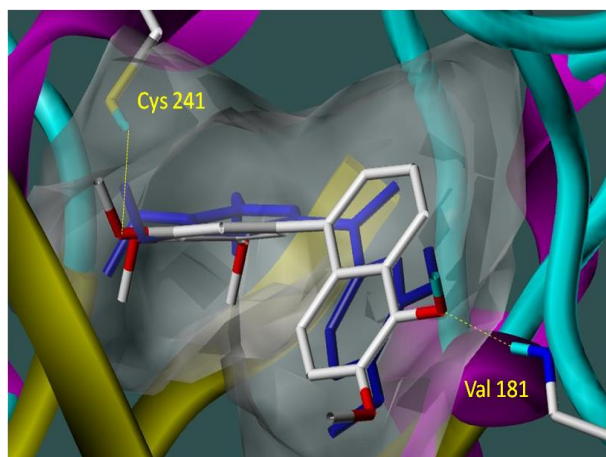
Compound	GI ₅₀ ^a [nM]			Inhibition of tubulin polymerization IC ₅₀ ^b [μM]
	Non-small lung human carcinoma (H1299)	Human breast cancer (MDA-MB231)	Chronic myelogenous leukemia (K562)	
1d	30 ± 2	85 ± 5	180 ± 14	2.1 ± 0.2
1e	32 ± 2.5	20 ± 1.5	15 ± 0.8	1.9 ± 0.2
1h	33 ± 2	20 ± 1	20 ± 1.5	2.0 ± 0.2
1i	32 ± 2	70 ± 6	200 ± 12	3.1 ± 0.5
2a	80 ± 7	100 ± 7	150 ± 10	^c
2b	45 ± 3	70 ± 3	110 ± 9	^c
2c	30 ± 2.5	30 ± 2	55 ± 3	3.0 ± 0.3
3c	90 ± 7	60 ± 4	85 ± 5	2.0 ± 0.3
3d	310 ± 25	500 ± 35	380 ± 25	6.9 ± 0.8
isoCA-4	3 ± 0.4	4 ± .5	5 ± 4	2.2 ± 0.2 ^d
isoerianin	38 ± 3	40 ± 5	20 ± 1.5	3.2 ± 0.3 ^d
CA-4	5 ± 0.4	3 ± 0.3	4 ± 0.3	1.0 ± 0.2 ^d

^a GI₅₀ is the concentration of compound needed to reduce cell growth by 50% following 72 h cell treatment with the tested drug (average of three experiments). ^b TTP, inhibition of tubulin polymerization; IC₅₀ is the concentration of compound required to inhibit 50% of the rate of microtubule assembly (average of three experiments). ^c IC₅₀ value not calculated owing to the low activity of the compound. ^d The GI₅₀ and IC₅₀ values for *isoCA-4*, *isoerianin* and *CA-4* were determined in this study.

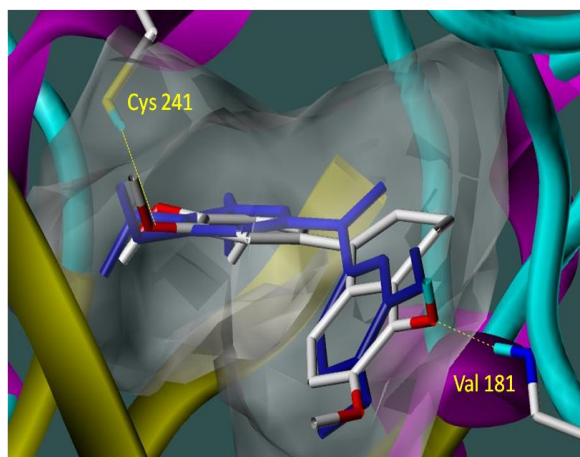
<Table 2>



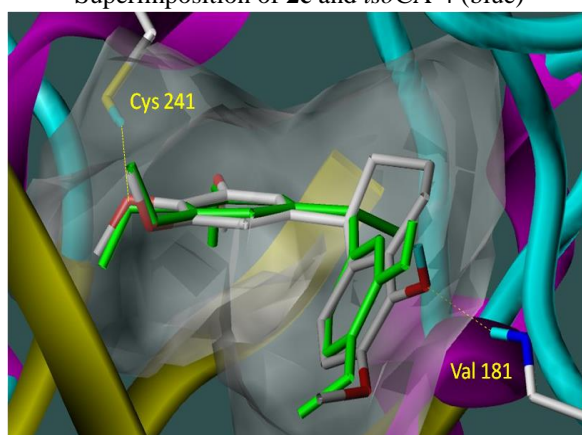
<Table 3>



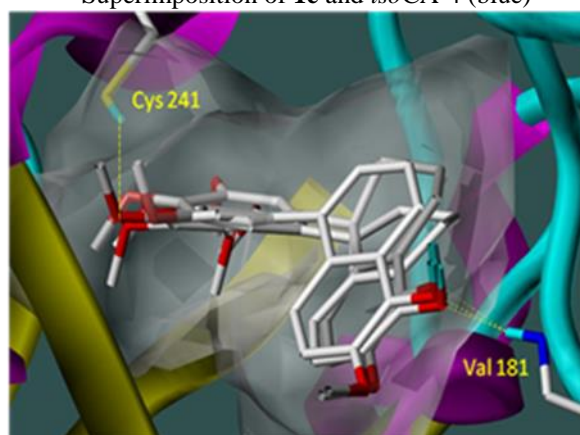
Superimposition of **2c** and *isoCA-4* (blue)



Superimposition of **1e** and *isoCA-4* (blue)



Superimposition of **3d** and *isoerianin* (green)



Superimposition of **1e**, **2c** and **3d**

<Figure 2>