



HAL
open science

One-Pot Synthesis of 2-Styrylindoles from Ortho-Substituted Chloroenynes

Guangkuan Zhao, Jérôme Bignon, Hélène Lévaïque, Joëlle Dubois, Mouad Alami, Olivier Provot

► **To cite this version:**

Guangkuan Zhao, Jérôme Bignon, Hélène Lévaïque, Joëlle Dubois, Mouad Alami, et al.. One-Pot Synthesis of 2-Styrylindoles from Ortho-Substituted Chloroenynes. *Journal of Organic Chemistry*, 2018, 83 (24), pp.15323-15332. 10.1021/acs.joc.8b02563 . hal-02394175

HAL Id: hal-02394175

<https://hal.science/hal-02394175>

Submitted on 4 Dec 2019

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

One Pot Synthesis of 2-Styrylindoles from Ortho-Substituted Chloroenynes

Guangkuan Zhao,^a Jérôme Bignon,^b Helène Levaique,^b Joëlle Dubois,^b Mouad Alami^{a*} and Olivier Provot^{a*}

^a Univ. Paris-Sud, BioCIS, CNRS, University Paris-Saclay, Equipe Labellisée Ligue Contre Le Cancer, F-92296 Châtenay-Malabry, France

^bCIBI Platform, Institut de Chimie des Substances Naturelles, UPR 2301, CNRS avenue de la terrasse, F-91198 Gif sur Yvette, France.

olivier.provot@u-psud.fr or mouad.alami@u-psud.fr

KEYWORDS: 2-Styrylindole, palladium, Suzuki, coupling, cyclization.

RECEIVED DATE (to be automatically inserted after your manuscript is accepted if required according to the journal that you are submitting your paper to)

ABSTRACT: A facile one pot synthesis of 2-styrylindoles, through Suzuki-arylation of *ortho*-substituted chloroenynes followed by *N*-cyclization and *N*-demethylation has been developed. A variety of 2-styrylindoles were obtained in good to excellent yields and were evaluated for their anticancer properties.

1. INTRODUCTION

Combretastatin A-4 (CA-4, Fig. 1) is a (*Z*)-stilbene isolated in 1989 by Pettit from the South African willow tree *Combretum caffrum*.¹

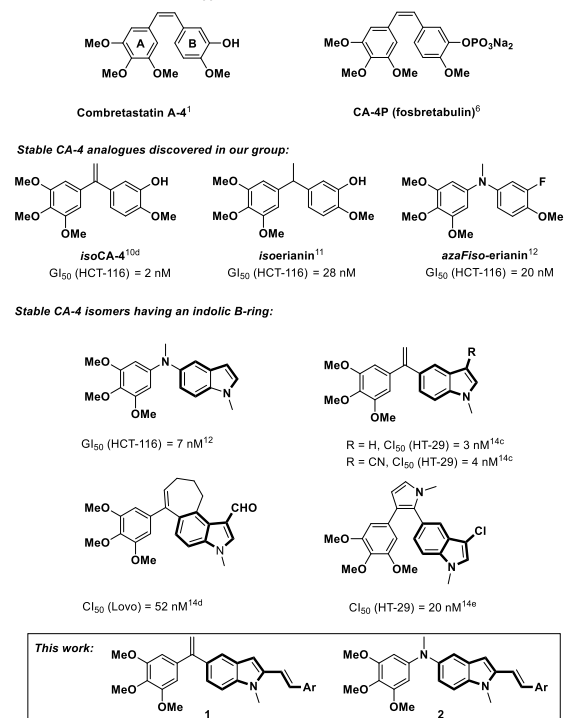


FIGURE 1. CA-4 and structural analogues

This natural compound exhibited strong antitumor properties as for example, a nanomolar level of cytotoxicity against a variety of cancer cell lines including multi-drugs resistant cells.² Moreover at very low doses, CA-4 inhibited tubulin assembly by binding at the colchicine binding-site,³ induced apoptosis⁴ and caused *in vivo* spectacular vascular shutdown in established tumors.⁵ In 2016, CA-4P (fosbretabulin), a phosphate water-soluble prodrug of the natural product has received the status of orphan drug in USA and Europe for the treatment of ovarian cancers, neuroendocrine tumours, certain thyroid cancers and multiform glioma.⁶ Despite these excellent antitumor properties, CA-4 has some drawbacks as a poor water-solubility and a chemical instability due to the isomerization of the *Z*-double bond to its less active *E*-form during storage, administration⁷ and metabolism.⁸ Due to the simplicity of its chemical structure, CA-4 has been extensively studied to find more stable analogues and to establish structure-activity relationships (SARs).⁹ As a part of our research program dedicated to novel stable vascular disrupting agents (VDAs)¹⁰ having a non-isomerizable spacer between A- and B-rings, we found that *isoCA-4*,^{10d} *isoerianin*¹¹ and *azaFiso-erianin*¹² derivatives were as potent as CA-4 with comparable anticancer activities (Fig. 1). Moreover, if the replacement of the 3,4,5-trimethoxyphenyl A-ring of CA-4 has received little attention,¹³ the B-ring of CA-4 has been subject to numerous modifications and can be

replaced for example, by a variety of indole nuclei with no loss of biological properties.¹⁴ For examples, it was recently showed that non-substituted *N*-methylindoles¹² and 3-substituted indoles¹⁴ replaced with a certain success the traditional phenolic B-ring of CA-4. To our knowledge, introduction of styryl substituents on the C-2 position of the indole B-ring and their effects on biological activity was not reported in the CA-4 and *iso*CA-4 series.

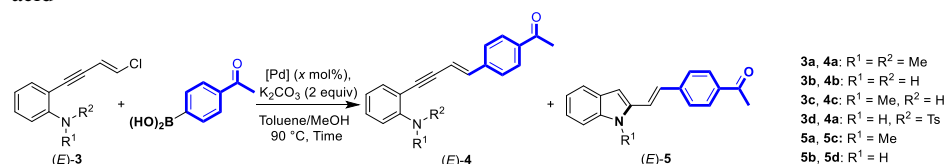
Due to the synthetic and biological interest for 2-alkenylindoles,¹⁵ their preparations have been well studied¹⁶ and often, involve the alkenylation of pre-formed indoles by C-H functionalization¹⁷ or by Suzuki-Miyaura coupling reactions.¹⁸ Otherwise, 2-styrylindoles have also been prepared from 5-*endo-dig*-cyclizations of 2-alkynylanilines having a free NH₂ function by electrochemistry or using various metal catalysts.¹⁹ Herein, we would like to present a novel and rapid access to 2-alkenylindoles from an efficient “one pot” Suzuki arylation–heterocyclization-*N*-demethylation process. *N,N*-Dimethylanilines having on *ortho*-position a conjugated chloroenyne moiety were firstly arylated using different boronic acids in the presence of a catalytic amount of Pd(PPh₃)₄ which was re-used for the

cyclization-step to furnish a small library of 2-styryl indoles after *N*-demethylation. After optimization of this “one pot” three-step process, the cytotoxicity of novel 2-styrylindoles **1** and **2** having a trimethoxyphenyl A-ring will be discussed.

2. RESULTS AND DISCUSSION

The required starting material, (*E*)-2-(4-chlorobut-3-en-1-yn-1-yl)-*N,N*-dimethylaniline **3a**, used as a model substrate, was readily prepared by the Sonogashira coupling of 2-ethynyl-*N,N*-dimethylaniline with (*E*)-1,2-dichloroethylene in 78 %. Since the treatment of chloroenyne **3** with boronic acids in the presence of suitable Pd-catalysts would lead to diarylated enynes²⁰ **4** intermediates, we anticipated that the Pd species might activated the alkyne triple bond of intermediates **4** to provide 2-styrylindoles **5** after *N*-cyclization and ammonium demethylation. To identify suitable conditions for this transformation, we evaluated the Suzuki arylation / cyclization / *N*-demethylation reaction with (*E*)-chloroenyne **3a** in the presence of (4-acetyl) phenylboronic acid and a variety of Pd-catalysts. The result of this study is reported in Table 1.

TABLE 1: Optimization of the tandem Suzuki-Miyaura cyclization reaction between (*E*)-**3** and (4-acetylphenyl) boronic acid^a



Entry	[Pd]	3	<i>x</i>	Time (h)	4	Yield of (<i>E</i>)- 4 (%) ^b	5	Yield of (<i>E</i>)- 5 (%) ^b
1	Pd(PPh ₃) ₄	3a	5	15	4a	46	5a	43
2	Pd(dba) ₂		5	15		nd ^c		nd ^c
3	PdCl ₂ (PhCN) ₂		5	15		nd ^c		nd ^c
4	PdCl ₂ (dppf)		5	15		nd ^c		nd ^c
5	XantPhos Pd G3		5	15		nd ^c		nd ^c
6	Pd(PPh ₃) ₄		8	15		32		55
7	Pd(PPh ₃) ₄		8	30		21		67
8	Pd(PPh₃)₄	8	8	48		0		90
9	Pd(PPh ₃) ₄	3b	8	48	4b	nd ^c	5b	nd ^c
10	Pd(PPh ₃) ₄	3c	8	48	4c	nd ^c	5c	nd ^c
11	Pd(PPh ₃) ₄	3d	8	48	4d	nd ^c	5d	nd ^c

^aConditions: (*E*)-**3** (0.5 mmol), (4-acetyl)boronic acid (0.65 mmol), [Pd] (*x* mmol), K₂CO₃ (2 equiv) and toluene/MeOH (2:1) (9 mL) were heated in a sealed tube at 90 °C for time indicated in Table 1 under an argon atmosphere. ^bYield of isolated product. ^cComplex mixture of compounds.

Initially, we have tested the conditions developed in our laboratory for the coupling of boronic acids with chloroenynes²⁰ using Pd(PPh₃)₄ (5 mol %) as the catalyst, K₂CO₃ (2 equiv) as the base, and toluene/MeOH (2:1) as the solvent combination at 90 °C in a sealed tube (entry 1). After 15 h of stirring and disappearance of chloroenyne (*E*)-**3a**, we isolated the desired indole (*E*)-**5a** together with diarylenyne (*E*)-**4a** in almost similar yields. This promising first result, confirming our initial hypothesis, led us to evaluate other Pd-catalysts to improve the cyclization reaction of the (*E*)-**4a** intermediate. Unfortunately, as depicted in entries 2-5, none of the Pd(0), Pd(II) catalysts as well as the third generation (G3) Buchwald pre-catalyst were able to

transform (*E*)-**3a** into indole (*E*)-**5a** which was not detected in crude mixtures after 15 h of reaction. It is likely that under these conditions, the Suzuki-arylation reaction leading to **4a** did not occur and that (*E*)-**3a** was completely degraded. We then decided to increase the amount of Pd(PPh₃)₄ quantity from 5 to 8 mol %, and we were pleased to observe the formation of indole (*E*)-**5a**, as the main product (90 %) after 48 h of reaction (entry 8). Further screening of solvents, solvent combinations and bases associated to Pd(PPh₃)₄ were less effective for 2-styrylindole (*E*)-**5a** generation. We also examine the efficiency of this process, under our optimized conditions, with arylated chloroenynes **3b-d** (entries 9-11) having on *ortho*-position a free-NH₂ (**3b**), a²

secondary amine (NHMe, **3c**) or a NH-tosylamine (**3d**). In contrast to (*E*)-**3a**, none of chloroenynes **3b-d** were able to provide the desired corresponding indole derivatives which were not detected in the crude complex mixtures. Using 8 mol% of Pd(PPh₃)₄ in the presence of 2 equiv of K₂CO₃ in hot toluene/MeOH mixture, chloroenyne (*E*)-**3a** reacted with various boronic acids to

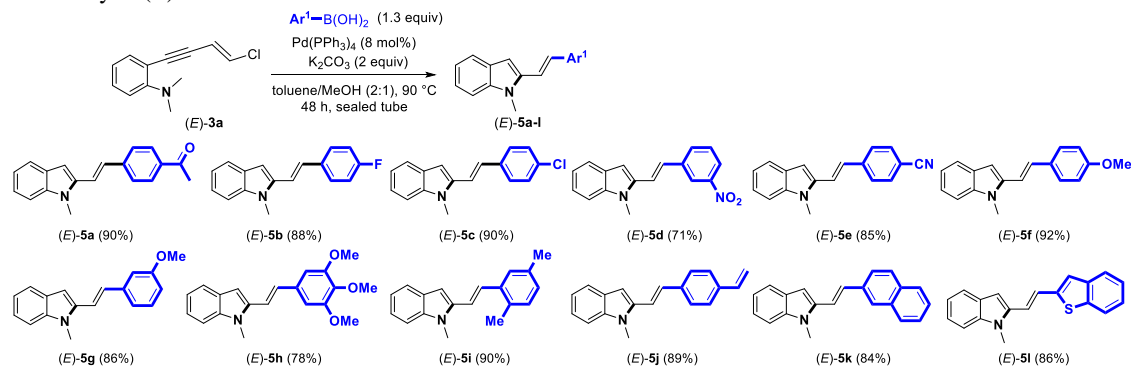
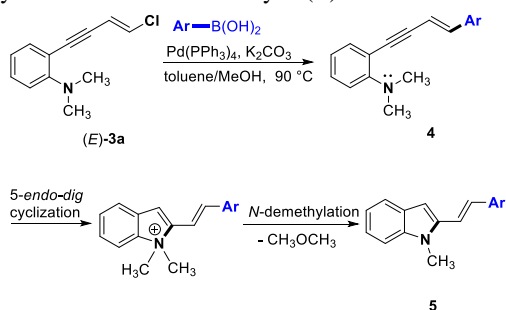


FIGURE 2. Tandem Suzuki-Miyaura cyclization reaction of (*E*)-chloroenyne **3a** using a variety of arylboronic acids.

Substitutions are readily tolerated at all positions of the arylboronic acid substrates to provide the 2-styrylindoles in similar yields (**5f-h**). Introduction of heterocycles on the double bond is also permitted with this protocol since **5l** was obtained in a good yield of 86 % using 2-benzothiophene boronic acid as the nucleophile. The following mechanism depicted in Scheme 1 can be considered.

SCHEME 1. Plausible mechanism for the synthesis of styrylindoles **5** from chloroenyne (*E*)-**3a**.



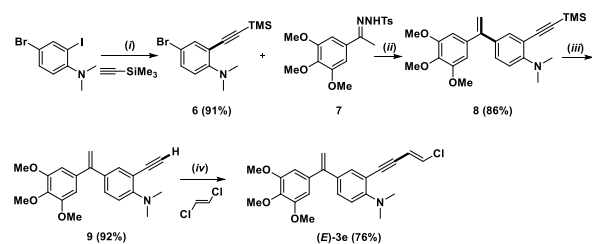
A plausible mechanism is depicted in Scheme 1 involving the formation of an indolinium salt according to a 5-*endo-dig* cyclization of diarylenyne **4**.²¹ Then, a *N*-demethylation step of the indolinium by MeOH leads to styrylindole **5** and dimethylether.²²

Next, as part of our medicinal chemistry project, we next have synthesized *N,N*-dimethylaniline (*E*)-**3e** having a chloroenyne group on *ortho*-position and on *para*-position a 1-(3,4,5-trimethoxyphenyl)vinyl moiety as the future A-ring (Scheme 2).

A Pd-catalyzed reaction of trimethylsilylacetylene with 4-bromo-2-iodo-*N,N*-dimethylaniline afforded trimethyl silylated (TMS)-alkyne **6** according to a Sonogashira coupling reaction (91%).

SCHEME 2. Synthesis of (*E*)-**3e**.^a

generate a number of 2-styrylindoles **5a-l**. As depicted in Figure 2, the reaction exhibits excellent scope: both electron-deficient and electron-rich arylboronic acids reacted efficiently to provide the desired 2-styryl indoles with high to excellent yields for this three-step “one-pot” reaction (from 71 to 92%).



^aConditions: (i) ArI (20 mmol), alkyne (22 mmol), PdCl₂(PPh₃)₂ (5 mol %), CuI (10 mol %), Et₃N, rt. (ii) **7** (12 mmol), **6** (10 mmol), Pd₂dba₃ (5 mol %), Xphos (10 mol %), LiOtBu (2.2 equiv), dioxane, 70 °C. (iii) K₂CO₃, MeOH, rt. (iv) (*E*)-1,2-dichloroethylene (10 equiv), PdCl₂(PPh₃)₂ (5 mol %), CuI (10 mol %), piperidine (2 equiv), Et₂O, rt.

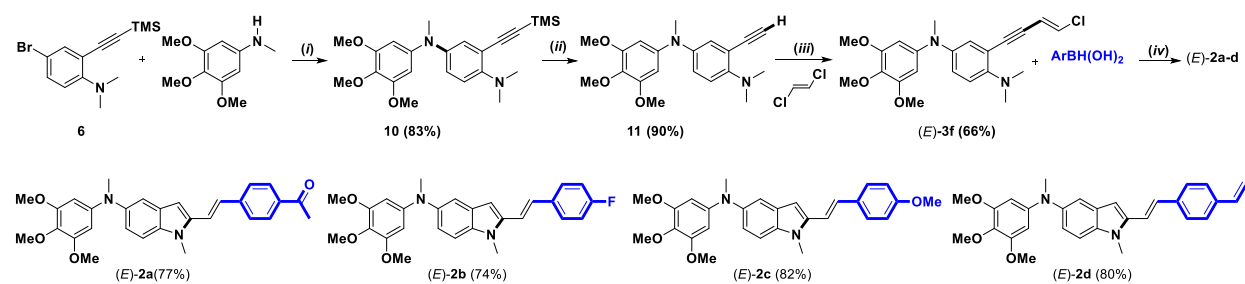
Then, by using a recent methodology developed by Barluenga and co-workers,²³ diarylethylene derivative **8** was synthesized in a good yield of 86% through the palladium coupling reaction of *N*-tosylhydrazone **7** with **6** using Pd₂dba₃ as the catalyst, Xphos as the ligand and LiOtBu as the base in hot dioxane. Under these basic conditions, we were surprised to observe that the TMS group of **8** remained unchanged and was finally deprotected under classical conditions using K₂CO₃ in MeOH to give **9** (92%). A further Sonogashira-Linstrumelle coupling reaction with (*E*)-1,2-dichloroethylene furnished (*E*)-**3e** (76%) as a useful platform to introduce a variety of styryl groups on the C-2 position of novel substituted indole derivatives after Pd-catalyzed arylation-cyclization reactions (Figure 3). By applying our optimized protocol developed for the tandem arylation-cyclization of chloroenyne (*E*)-**3** with boronic acids, we prepared the desired indole derivatives (*E*)-**1a-g** in moderate yields due to difficulties encountered during the purification step.

Next, to synthesize a series of azaisoerianin analogues (*E*)-**2a-d** of biological interest, 3,4,5-trimethoxy-*N*-methylaniline was coupled with alkyne **6** under Pd-catalysis to give tertiary amine **10** (83%). After a desilylation step of the alkyne function of **10**, the resulting terminal alkyne **11** (90%) was then coupled with (*E*)-1,2-dichloroethylene to give (*E*)-**3f** in an³

acceptable yield of 66%. This later was then transformed into the desired indoles **2a-d** using this novel Suzuki-cyclization-*N*-demethylation process with good yields (from 74% to 82%) for the three steps (Scheme 3).

In vitro cytotoxicity of the newly synthesized indole derivatives **1** and **2** was investigated against HCT116, a human colon carcinoma cell line. A colorimetric-based assay was used to determine the drug concentration required to inhibit cell growth by 50% (GI_{50}) after incubation in the culture medium for 72 h. *IsoCA-4* was included as the reference for comparisons. The screening revealed that all newly synthesized indole derivatives **1** and **2** evaluated against HCT cancer cell lines displayed an average level of cytotoxicity when compared with *isoCA-4* (Table 2). The comparison of the GI_{50} values obtained for compounds **1** and **2** clearly revealed that 1,1-diarylethylenes derivatives **1a-g** displayed a promising sub-micromolar level of cytotoxicity ($0.18 \mu\text{M} < GI_{50} < 0.74 \mu\text{M}$) whereas their *N*-Methyl analogues **2a-d** displayed a lower level of cytotoxicity with GI_{50} values ranging from 1.32 to $4.08 \mu\text{M}$. The cytotoxic of promising derivatives **1c** and **1e** having respectively a *p*-methoxy and a *m*-NO₂ group on their aromatic rings displayed encouraging GI_{50} values ($0.26 \mu\text{M}$ for **1c** and $0.18 \mu\text{M}$ for **1e**.) will be furthermore modified in our lab in view of possible improvements of cytotoxicity against a range human cancer cell lines.

SCHEME 3. Synthesis of (*E*)-**2a-d**.



^aConditions: (i) ArBr (1 mmol), 3,4,5-trimethoxy-*N*-methylaniline (1.2 mmol), Pd₂dba₃ (5 mol %), Xphos (10 mol %), NaOtBu (2.2 equiv), toluene, 70 °C. (ii) K₂CO₃, MeOH, rt. (iii) (*E*)-1,2-dichloroethylene (10 equiv), PdCl₂(PPh₃)₂ (5 mol %), CuI (10 mol %), piperidine (5 equiv), Et₂O, rt. (iv) (*E*)-**3f** (0.5 mmol), boronic acid (0.65 mmol), Pd(PPh₃)₄ (8 mol %), K₂CO₃ (2 equiv) were diluted in in toluene/MeOH (2:1) (9 mL) and placed in a sealed tube and heated at 90 °C.

TABLE 2. Cytotoxicity against HCT116 cells^a and ITP of indoles **1a-g** and **2a-d**.

Compound	(<i>E</i>)- 1a	(<i>E</i>)- 1b	(<i>E</i>)- 1c	(<i>E</i>)- 1d	(<i>E</i>)- 1e	(<i>E</i>)- 1f
Cytotoxicity GI_{50}^b [μM]	0.74 ± 0.17	0.43 ± 0.21	0.26 ± 0.02	0.37 ± 0.04	0.18 ± 0.06	0.52 ± 0.07
% of inhibition at 100 μM	21	31	23	37	26	56
Compound	(<i>E</i>)- 1g	(<i>E</i>)- 2a	(<i>E</i>)- 2b	(<i>E</i>)- 2c	(<i>E</i>)- 2d	<i>isoCA-4</i>
Cytotoxicity GI_{50}^b [μM]	0.54 ± 0.03	1.90 ± 0.67	1.32 ± 0.32	1.84 ± 0.27	4.08 ± 0.41	0.002
% of inhibition at 100 μM	40	35	36	83	19	1.0 ± 0.1^c

^aHCT-116 Human colon carcinoma. ^b GI_{50} 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 GI_{50} is the concentration of *isoCA-4* required to inhibit 50% of the rate of microtubule assembly (average of three experiments).

To examine if the cytotoxicity of compounds **1** and **2** was related to an interaction with the microtubule system, indoles **1** and **2** were next evaluated in tubulin assembly

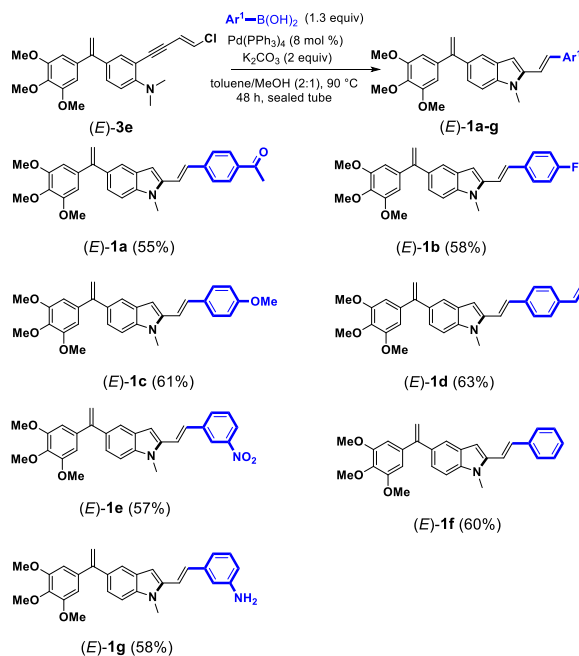


FIGURE 3. Tandem Suzuki-cyclization reaction of (*E*)-chloroenyne **3e** using a variety of arylboronic acids.

assays in parallel with *isoCA-4* (Table 2). However, **1c** and **1e** which displayed the best cytotoxicity level against HCT116 cells inhibited tubulin assembly with⁴

modest GI₅₀ values comparable to the GI₅₀ of all other indole derivatives **1** and **2**. Currently, we are working to improve the cytotoxicity of derivatives **1** through the introduction of more suitable substituents.

3. CONCLUSION

In summary, we have discovered a novel 3-steps Suzuki-Miyaura arylation / cyclization / *N*-demethylation of (*E*)-2-(4-chlorobut-3-en-1-yn-1-yl)-*N,N*-dimethylanilines, giving an efficient and rapid access to 2-styrylindoles with good to excellent yields. Using this strategy, we have rapidly achieved the synthesis of a series of 1,1-diarylethylenes **1** and diarylmethylamines **2** bearing a 3,4,5-trimethoxyphenyl core and various functionalized 2-styrylindoles as *iso*CA-4 and *azaisoerianin* analogues. From the preliminary biological results, indoles **1c** and **1e** were the most promising compounds with nanomolar GI₅₀ values. Structural modifications on the indole nucleus are currently under study in our laboratory and will be published later.

4. EXPERIMENTAL SECTION

General Information and Method. All glasswares were oven-dried at 140 °C and all reactions were conducted under an argon atmosphere. Solvents: cyclohexane, ethyl acetate (EtOAc), for chromatography, were technical grade. The ¹H NMR and ¹³C NMR and ¹⁹F spectra were recorded in CDCl₃, acetone-d₆ or DMSO-d₆ on Bruker Avance 300 spectrometer. The chemical shifts of ¹H are reported in ppm relative to the solvent residual peak in CDCl₃ (δ 7.26), acetone-d₆ (δ 2.05), DMSO-d₆ (δ 2.50) for ¹H NMR. For the ¹³C NMR spectra, the solvent signals of CDCl₃ (δ 77.14), acetone-d₆ (δ 206.26), DMSO-d₆ (δ 39.52) were used as the internal standards. The following abbreviation are used: m (multiplet), s (singlet), d (doublet), t (triplet), dd (doublet of doublet), td (triplet of doublet), ddd (doublet of doublet of doublet). IR spectra were measured on a Bruker Vector 22 spectrophotometer (neat, cm⁻¹). High-resolution mass spectra were recorded on a Bruker Daltonics micrOTOF-Q instrument. Analytical TLC was performed on Merck precoated silica gel 60 F-254 plates. Merck silica gel 60 (230-400 mesh) was used for column chromatography. The plates were visualized by either UV light (254 nm), or by a solution of phosphomolybdic acid in ethanol.

General procedure for the synthesis of (*E*)-chloroenynes **3a**, **3b**, **3e**, **3f**.

To a solution of alkyne (5 mmol) in Et₂O (30 mL) was added successively (*E*)-1,2-dichloroethylene (4 mL, 50 mmol), PdCl₂(PPh₃)₂ (175 mg, 0.25 mmol), piperidine (1 mL, 10 mmol) and CuI (95 mg, 0.5 mmol). After complete disappearance of starting material monitored by TLC, the solution was filtered through a pad of celite using EtOAc. The organic layer was washed successively with sat. NH₄Cl, sat. NaHCO₃ and HCl (1 M) solutions. After drying over MgSO₄ and evaporation *in vacuo*, the crude residue was purified by silica gel column chromatography (0 to 30% AcOEt in cyclohexane) (the crude of **3g** was purified on neutral Al₂O₃).

(*E*)-2-(4-Chlorobut-3-en-1-yn-1-yl)-*N,N*-dimethyl aniline (**3a**)

Brown solid, mp 36.8 – 37.0 °C, yield 78%, 802 mg.

¹H NMR (300 MHz, CDCl₃) δ = 7.52 (dd, *J* = 7.5 Hz, *J* = 1.2 Hz, 1H), 7.28 (td, *J* = 7.5 Hz, *J* = 1.2 Hz, 1H), 6.97 –

6.86 (m, 2H), 6.63 (d, *J* = 13.5 Hz, 1H), 6.25 (d, *J* = 13.5 Hz, 1H), 2.95 (s, 6H). ¹³C{¹H} NMR (75 MHz, CDCl₃) δ = 154.9 (Cq), 134.3 (CH), 129.7 (CH), 129.2 (CH), 120.7 (CH), 117.1 (CH), 114.6 (Cq), 114.4 (CH), 91.5 (Cq), 89.7 (Cq), 43.6 (2 CH₃). IR (neat): 2945, 2197, 1595, 1325, 1049, 1011 cm⁻¹. HRMS (ESI): *m/z* [M+H]⁺ calcd for C₁₂H₁₃N³⁵Cl: 206.0737; found: 206.0735.

(*E*)-2-(4-Chlorobut-3-en-1-yn-1-yl)aniline (**3b**)

Brown oil, yield 79%, 702 mg.

¹H NMR (300 MHz, CDCl₃) δ = 7.16 (d, *J* = 7.5 Hz, 1H), 7.01 (t, *J* = 8.1 Hz, 1H), 6.61 – 6.45 (m, 3H), 6.08 (d, *J* = 13.5 Hz, 1H), 4.01 (br, 2H). ¹³C NMR (75 MHz, CDCl₃) δ = 147.9 (Cq), 132.1 (CH), 130.1 (CH), 129.6 (CH), 118.0 (CH), 114.4 (CH), 113.8 (CH), 107.2 (Cq), 89.6 (Cq), 88.7 (Cq). IR (neat): 3479, 3384, 2194, 1699, 1488, 1314 cm⁻¹. HRMS (ESI): *m/z* [M+H]⁺ calcd for C₁₀H₉N³⁵Cl: 178.0424; found: 178.0424.

(*E*)-2-(4-Chlorobut-3-en-1-yn-1-yl)-*N,N*-dimethyl-4-(1-(3,4,5-trimethoxyphenyl)vinyl)-aniline (**3e**)

Brown oil, yield 76%, 1.51 g.

¹H NMR (300 MHz, acetone-d₆) δ = 7.36 (d, *J* = 2.1 Hz, 1H), 7.26 (dd, *J* = 8.7 Hz, *J* = 2.1 Hz, 1H), 6.91 (d, *J* = 8.7 Hz, 1H), 6.82 (d, *J* = 13.5 Hz, 1H), 6.62 (s, 2H), 6.33 (d, *J* = 13.5 Hz, 1H), 5.38 (s, 1H), 5.35 (s, 1H), 3.79 (s, 6H), 3.77 (s, 3H), 2.97 (s, 6H). ¹³C{¹H} NMR (75 MHz, CDCl₃) δ = 159.1 (Cq), 157.9 (2 Cq), 153.1 (Cq), 142.6 (Cq), 141.7 (Cq), 138.3 (CH), 137.1 (Cq), 135.2 (CH), 134.6 (CH), 121.9 (CH), 119.4 (CH), 118.3 (CH₂), 117.3 (Cq), 110.8 (2 CH), 96.7 (Cq), 94.8 (Cq), 65.2 (CH₃), 61.1 (2 CH₃), 47.9 (2 CH₃). IR (neat): 2937, 2196, 1579, 1502, 1347, 1235 cm⁻¹. HRMS (ESI): *m/z* [M+H]⁺ calcd for C₂₃H₂₅NO₃³⁵Cl: 398.1523; found: 398.1523.

(*E*)-2-(4-Chlorobut-3-en-1-yn-1-yl)-*N*¹,*N*¹,*N*⁴-trimethyl-*N*⁴-(3,4,5-trimethoxyphenyl)-benzene-1,4-diamine (**3f**)

Brown oil, yield 66%, 1.32 g.

¹H NMR (300 MHz, acetone-d₆) δ = 7.09 – 6.90 (m, 3H), 6.83 (d, *J* = 13.5 Hz, 1H), 6.34 (d, *J* = 13.5 Hz, 1H), 6.25 (s, 2H), 3.75 (s, 6H), 3.69 (s, 3H), 3.23 (s, 3H), 2.86 (s, 6H). ¹³C{¹H} NMR (75 MHz, acetone-d₆) δ = 154.8 (2 Cq), 150.8 (Cq), 146.6 (Cq), 143.8 (Cq), 134.2 (Cq), 130.1 (CH), 127.0 (CH), 124.1 (CH), 119.1 (CH), 116.2 (Cq), 115.2 (CH), 98.9 (2 CH), 92.4 (Cq), 89.9 (Cq), 60.6 (CH₃), 56.4 (2 CH₃), 43.9 (2 CH₃), 40.9 (CH₃). IR (neat): 2937, 2197, 1585, 1496, 1235, 1128 cm⁻¹. HRMS (ESI): *m/z* [M+H]⁺ calcd for C₂₂H₂₆N₂O₃³⁵Cl: 401.1632; found: 401.1639.

Procedure for the synthesis of (*E*)-chloroenynes **3c**.

To a solution of **3b** (5 mmol, 888 mg) in DMF (30 mL) was added K₂CO₃ (1.5 equiv) and iodomethane (1.1 equiv). The reaction was stirred at room temperature for 3 h then quenched with water (30 mL). The aqueous layer was extracted with CH₂Cl₂ three times and the combined organic extracts were dried with anhydrous MgSO₄, filtered and concentrated. The crude mixture was purified by silica gel column chromatography (0 to 30% AcOEt in cyclohexane).

(*E*)-2-(4-Chlorobut-3-en-1-yn-1-yl)-*N*-methylaniline (**3c**)

Brown oil, yield 48%, 460 mg.

¹H NMR (300 MHz, CDCl₃) δ = 7.22 – 7.10 (m, 2H), 6.63 – 6.44 (m, 3H), 6.11 (d, *J* = 13.8 Hz, 1H), 4.46 (br, ⁵

1H), 2.80 (s, 3H). ¹³C{1H} NMR (75 MHz, CDCl₃) δ = 149.9 (Cq), 132.2 (CH), 130.5 (CH), 129.5 (CH), 116.4 (CH), 114.0 (CH), 109.2 (CH), 106.7 (Cq), 89.9 (Cq), 88.9 (Cq), 30.3 (CH₃). IR (neat): 3421, 3071, 2191, 1510, 1320 cm⁻¹. HRMS (ESI): m/z [M+H]⁺ calcd for C₁₁H₁₁N³⁵Cl: 192.0580; found: 192.0570.

Procedure for the synthesis of (*E*)-chloroenynes **3d**.

A solution of 4-methylbenzene-1-sulfonyl chloride (1 equiv) in THF (20 mL) was added dropwise over 0.5 h to a solution of **3b** (5 mmol) and pyridine (1.1 equiv) in THF (30 mL) under argon. The solution was stirred at r.t. for 12 h. The resulting mixture was evaporated under vacuum and the residue was purified by silica gel column chromatography (0 to 30% AcOEt in cyclohexane).

(*E*)-*N*-(2-(4-Chlorobut-3-en-1-yn-1-yl)phenyl)-4-methylbenzenesulfonamide (**3d**)

White solid, mp 125.6 – 125.9 °C, yield 63%, 1.05 g.

¹H NMR (300 MHz, CDCl₃) δ = 7.68 (d, *J* = 8.4 Hz, 2H), 7.59 (d, *J* = 8.4 Hz, 1H), 7.33 – 7.22 (m, 4H), 7.10 – 7.01 (m, 2H), 6.63 (d, *J* = 13.8 Hz, 1H), 6.13 (d, *J* = 13.8 Hz, 1H), 2.39 (s, 3H). ¹³C{1H} NMR (75 MHz, CDCl₃) δ = 144.2 (Cq), 137.7 (Cq), 136.2 (Cq), 132.2 (CH), 131.8 (CH), 130.1 (CH), 129.7 (2 CH), 127.3 (2 CH), 124.7 (CH), 120.4 (CH), 114.0 (Cq), 113.0 (CH), 90.9 (Cq), 86.4 (Cq), 21.7 (CH₃). IR (neat): 3074, 1489, 1396, 1159 cm⁻¹. HRMS (ESI): m/z [M+Na]⁺ calcd for C₁₇H₁₄NO₂NaS³⁵Cl: 354.0331; found: 354.0332.

General procedure for the synthesis of 2-styrylindole **5**, **1**, **2**.

Under argon, chloroenyne (0.5 mmol), the desired boronic acid (1.3 equiv), K₂CO₃ (2 equiv), and Pd(PPh₃)₄ (8 mol%) were mixed in toluene (6 mL) and MeOH (3 mL). The reaction mixture was stirred at 90 °C in 30 mL sealed tube monitored by TLC (48 h). After the mixture were allowed to cool to room temperature and filtrated through a pad of celite washed by CH₂Cl₂. Solvent was removed under reduced pressure and the crude material was purified by silica gel column chromatography (0 to 30% AcOEt in cyclohexane).

(*E*)-1-(4-(2-(1-Methyl-1*H*-indol-2-yl)vinyl)phenyl)ethan-1-one (**5a**)

Yellow solid, mp 188.5 – 188.9 °C, yield 90%, 123.9 mg.

¹H NMR (300 MHz, CDCl₃) δ = 7.99 (d, *J* = 8.4 Hz, 2H), 7.65 – 7.60 (m, 3H), 7.36 – 7.11 (m, 5H), 6.90 (s, 1H), 3.86 (s, 3H), 2.64 (s, 3H). ¹³C{1H} NMR (75 MHz, CDCl₃) δ = 197.5 (Cq), 141.9 (Cq), 138.5 (Cq), 137.8 (Cq), 136.1 (Cq), 129.3 (CH), 129.1 (2 CH), 128.0 (Cq), 126.5 (2 CH), 122.4 (CH), 120.8 (CH), 120.2 (CH), 119.7 (CH), 109.4 (CH), 100.2 (CH), 30.1 (CH₃), 26.7 (CH₃). IR (neat): 3054, 1675, 1597, 1348, 1274 cm⁻¹. HRMS (ESI): m/z [M+H]⁺ calcd for C₁₉H₁₈NO: 276.1388; found: 276.1378.

(*E*)-2-(4-Fluorostyryl)-1-methyl-1*H*-indole (**5b**)

Yellow solid, mp 155.5 – 155.8 °C, yield 88%, 110.6 mg.

¹H NMR (300 MHz, DMSO-*d*₆) δ = 7.77 – 7.71 (m, 2H), 7.54 – 6.99 (m, 8H), 6.86 (s, 1H), 3.85 (s, 3H). ¹³C{1H} NMR (75 MHz, DMSO-*d*₆) δ = 161.7 (d, *J* = 243.5 Hz, Cq), 138.2 (Cq), 137.7 (Cq), 133.6 (d, *J* = 2.0 Hz, Cq), 129.0 (CH), 128.4 (d, *J* = 8.0 Hz, 2 CH), 127.4 (Cq), 121.3 (CH), 119.8 (CH), 119.5 (CH), 117.2 (CH), 115.6 (d, *J* = 21.4 Hz, 2 CH), 109.7 (CH), 98.1 (CH), 29.7

(CH₃). ¹⁹F NMR (188 MHz, DMSO-*d*₆): δ = - 114.1. IR (neat): 1531, 1470, 1349, 1247, 1157 cm⁻¹. HRMS (ESI): m/z [M+H]⁺ calcd for C₁₇H₁₅NF: 252.1189; found: 252.1190.

(*E*)-2-(4-Chlorostyryl)-1-methyl-1*H*-indole (**5c**)

Yellow solid, mp 127.6 – 127.9 °C, yield 90%, 120.5 mg.

¹H NMR (300 MHz, DMSO-*d*₆) δ = 7.72 (d, *J* = 8.4 Hz, 2H), 7.55 – 7.41 (m, 5H), 7.29 (d, *J* = 16.2 Hz, 1H), 7.13 (t, *J* = 7.5 Hz, 1H), 7.02 (t, *J* = 7.5 Hz, 1H), 6.89 (s, 1H), 3.86 (s, 3H). ¹³C{1H} NMR (75 MHz, DMSO-*d*₆) δ = 138.0 (Cq), 137.8 (Cq), 136.0 (Cq), 131.9 (Cq), 128.8 (CH), 128.6 (2 CH), 128.2 (2 CH), 127.4 (Cq), 121.4 (CH), 119.9 (CH), 119.6 (CH), 118.2 (CH), 109.7 (CH), 98.5 (CH), 29.7 (CH₃). IR (neat): 1532, 1443, 1320, 1248 cm⁻¹. HRMS (APCI): m/z [M+H]⁺ calcd for C₁₇H₁₅N³⁵Cl: 268.0888; found: 268.0891.

(*E*)-1-Methyl-2-(3-nitrostyryl)-1*H*-indole (**5d**)

Yellow solid, mp 136.9 – 137.2 °C, yield 71%, 98.8 mg.

¹H NMR (300 MHz, CDCl₃) δ = 8.26 (s, 1H), 7.99 (d, *J* = 8.4 Hz, 1H), 7.67 (d, *J* = 7.5 Hz, 1H), 7.52 (d, *J* = 7.8 Hz, 1H), 7.42 (t, *J* = 7.8 Hz, 1H), 7.23 – 7.01 (m, 5H), 6.77 (s, 1H), 3.73 (s, 3H). ¹³C{1H} NMR (75 MHz, CDCl₃) δ = 148.9 (Cq), 139.0 (Cq), 138.5 (Cq), 137.3 (Cq), 132.3 (CH), 129.7 (CH), 127.9 (Cq), 127.8 (CH), 122.5 (CH), 122.1 (CH), 120.8 (CH), 120.6 (CH), 120.3 (CH), 120.1 (CH), 109.4 (CH), 100.4 (CH), 30.1 (CH₃). IR (neat): 1520, 1463, 1347, 1321 cm⁻¹. HRMS (ESI): m/z [M+H]⁺ calcd for C₁₇H₁₅N₂O₂: 279.1134; found: 279.1125.

(*E*)-4-(2-(1-Methyl-1*H*-indol-2-yl)vinyl)benzotrile (**5e**)

Yellow solid, mp 177.4 – 177.7 °C, yield 85%, 109.8 mg.

¹H NMR (300 MHz, DMSO-*d*₆) δ = 7.95 – 7.77 (m, 4H), 7.66 (d, *J* = 16.2 Hz, 1H), 7.55 (d, *J* = 7.8 Hz, 1H), 7.46 (d, *J* = 8.4 Hz, 1H), 7.38 (d, *J* = 16.2 Hz, 1H), 7.16 (t, *J* = 7.5 Hz, 1H), 7.04 (t, *J* = 7.5 Hz, 1H), 6.98 (s, 1H), 3.88 (s, 3H). ¹³C{1H} NMR (75 MHz, DMSO-*d*₆) δ = 141.8 (Cq), 138.0 (Cq), 137.5 (Cq), 132.5 (2 CH), 128.1 (CH), 127.3 (Cq), 127.1 (2 CH), 121.9 (CH), 121.0 (CH), 120.2 (CH), 119.7 (CH), 119.1 (Cq), 109.9 (CH), 109.3 (Cq), 99.6 (CH), 29.7 (CH₃). IR (neat): 2223, 1599, 1463, 1346, 1322 cm⁻¹. HRMS (ESI): m/z [M+H]⁺ calcd for C₁₈H₁₅N₂: 259.1235; found: 259.1246.

(*E*)-2-(4-Methoxystyryl)-1-methyl-1*H*-indole (**5f**)

Yellow solid, mp 141.4 – 141.8 °C, yield 92%, 121.1 mg.

¹H NMR (300 MHz, CDCl₃) δ = 7.63 (d, *J* = 7.5 Hz, 1H), 7.51 (d, *J* = 8.4 Hz, 2H), 7.34 – 7.12 (m, 4H), 7.05 (d, *J* = 15.9 Hz, 1H), 6.96 (d, *J* = 8.4 Hz, 2H), 6.80 (s, 1H), 3.87 (s, 3H), 3.83 (s, 3H). ¹³C{1H} NMR (75 MHz, CDCl₃) δ = 159.5 (Cq), 138.8 (Cq), 138.1 (Cq), 130.6 (CH), 130.0 (Cq), 128.1 (Cq), 127.7 (2 CH), 121.5 (CH), 120.3 (CH), 119.8 (CH), 114.9 (CH), 114.2 (2 CH), 109.1 (CH), 98.4 (CH), 55.4 (CH₃), 29.9 (CH₃). IR (neat): 1573, 1463, 1395, 1247 cm⁻¹. HRMS (ESI): m/z [M+H]⁺ calcd for C₁₈H₁₈NO: 264.1388; found: 264.1387.

(*E*)-2-(3-Methoxystyryl)-1-methyl-1*H*-indole (**5g**)

Yellow solid, mp 94.1 – 94.5 °C, yield 86%, 102.7 mg.

¹H NMR (300 MHz, CDCl₃) δ = 7.65 (d, *J* = 8.1 Hz, 1H), 7.43 – 7.06 (m, 8H), 6.94 – 6.82 (m, 2H), 3.91 (s, 3H), 3.84 (s, 3H). ¹³C{1H} NMR (75 MHz, CDCl₃) δ = 160.0 (Cq), 138.7 (Cq), 138.4 (Cq), 138.2 (Cq), 130.8 (CH), 129.8 (CH), 128.0 (Cq), 121.9 (CH), 120.5 (CH), 120.0

(CH), 119.2 (CH), 117.5 (CH), 113.4 (CH), 111.9 (CH), 109.2 (CH), 99.2 (CH), 55.4 (CH₃), 30.0 (CH₃). IR (neat): 2936, 1597, 1577, 1433, 1319, 1284, 1157, 1010, 952 cm⁻¹. HRMS (ESI): m/z [M+H]⁺ calcd for C₁₈H₁₈NO: 264.1388; found: 264.1390.

(E)-1-Methyl-2-(3,4,5-trimethoxystyryl)-1H-indole (5h)

Yellow solid, mp 180.2 – 180.3 °C, yield 78%, 126.1 mg.

¹H NMR (300 MHz, DMSO-d₆) δ = 7.63 – 7.30 (m, 3H), 7.23 (d, *J* = 16.2 Hz, 1H), 7.12 (t, *J* = 7.5 Hz, 1H), 7.05 – 6.95 (m, 3H), 6.83 (s, 1H), 3.87 (s, 3H), 3.86 (s, 6H), 3.69 (s, 3H). ¹³C{¹H} NMR (75 MHz, DMSO-d₆) δ = 153.0 (2 Cq), 138.4 (Cq), 137.7 (Cq), 137.4 (Cq), 132.7 (Cq), 130.6 (CH), 127.5 (Cq), 121.2 (CH), 119.8 (CH), 119.5 (CH), 116.6 (CH), 109.6 (CH), 104.1 (2 CH), 97.9 (CH), 60.1 (CH₃), 55.9 (2 CH₃), 29.8 (CH₃). IR (neat): 2925, 1581, 1504, 1465, 1366 cm⁻¹. HRMS (ESI): m/z [M+H]⁺ calcd for C₂₀H₂₂NO₃: 324.1600; found: 324.1600.

(E)-2-(2,5-Dimethylstyryl)-1-methyl-1H-indole (5i)

Yellow solid, mp 121.1 – 121.2 °C, yield 90%, 117.6 mg.

¹H NMR (300 MHz, DMSO-d₆) δ = 7.63 (s, 1H), 7.56 – 7.37 (m, 3H), 7.29 (d, *J* = 15.9 Hz, 1H), 7.16 – 7.08 (m, 2H), 7.05 – 6.99 (m, 2H), 6.90 (s, 1H), 3.86 (s, 3H), 2.37 (s, 3H), 2.33 (s, 3H). ¹³C{¹H} NMR (75 MHz, DMSO-d₆) δ = 138.6 (Cq), 137.7 (Cq), 135.3 (Cq), 135.0 (Cq), 132.4 (Cq), 130.3 (CH), 128.4 (CH), 127.8 (CH), 127.4 (Cq), 125.5 (CH), 121.2 (CH), 119.8 (CH), 119.5 (CH), 117.9 (CH), 109.7 (CH), 98.3 (CH), 29.7 (CH₃), 20.7 (CH₃), 19.0 (CH₃). IR (neat): 2921, 1463, 1319, 1236, 1104, 954 cm⁻¹. HRMS (ESI): m/z [M+H]⁺ calcd for C₁₉H₂₀N: 262.1596; found: 262.1597.

(E)-1-Methyl-2-(4-vinylstyryl)-1H-indole (5j)

Yellow solid, mp 157.6 – 157.8 °C, yield 89%, 115.4 mg.

¹H NMR (300 MHz, CDCl₃) δ = 7.50 (d, *J* = 7.8 Hz, 1H), 7.39 (d, *J* = 8.1 Hz, 2H), 7.32 (d, *J* = 8.1 Hz, 2H), 7.21 – 6.99 (m, 5H), 6.72 (s, 1H), 6.63 (dd, *J* = 17.4 Hz, *J* = 10.8 Hz, 1H), 5.69 (d, *J* = 17.6 Hz, 1H), 5.18 (d, *J* = 10.8 Hz, 1H), 3.70 (s, 3H). ¹³C{¹H} NMR (75 MHz, CDCl₃) δ = 138.5 (Cq), 138.3 (Cq), 137.2 (Cq), 136.8 (Cq), 136.5 (CH), 130.5 (CH), 128.1 (Cq), 126.7 (4 CH), 121.9 (CH), 120.5 (CH), 120.0 (CH), 117.0 (CH), 114.0 (CH₂), 109.2 (CH), 99.2 (CH), 30.0 (CH₃). IR (neat): 1530, 1462, 1346, 1320, 907 cm⁻¹. HRMS (ESI): m/z [M+H]⁺ calcd for C₁₉H₁₈N: 260.1439; found: 260.1445.

(E)-1-Methyl-2-(2-(naphthalen-2-yl)vinyl)-1H-indole (5k)

Yellow solid, mp 198.3 – 198.5 °C, yield 84%, 119.0 mg.

¹H NMR (300 MHz, DMSO-d₆) δ = 8.20 – 7.80 (m, 5H), 7.63 – 7.43 (m, 6H), 7.14 (t, *J* = 7.5 Hz, 1H), 7.03 (t, *J* = 7.5 Hz, 1H), 6.94 (s, 1H), 3.90 (s, 3H). ¹³C{¹H} NMR (75 MHz, DMSO-d₆) δ = 138.3 (Cq), 137.8 (Cq), 134.6 (Cq), 133.3 (Cq), 132.6 (Cq), 130.2 (CH), 128.1 (CH), 127.8 (CH), 127.6 (CH), 127.5 (Cq), 126.5 (CH), 126.4 (CH), 126.0 (CH), 123.7 (CH), 121.4 (CH), 119.9 (CH), 119.6 (CH), 117.8 (CH), 109.7 (CH), 98.4 (CH), 29.7 (CH₃). IR (neat): 2923, 1463, 1342, 1320 cm⁻¹. HRMS (ESI): m/z [M+H]⁺ calcd for C₂₁H₁₈N: 284.1439; found: 284.1438.

(E)-2-(2-(Benzo[b]thiophen-2-yl)vinyl)-1-methyl-1H-indole (5l)

Yellow solid, mp 203.7 – 203.8 °C, yield 86%, 124.4 mg.

¹H NMR (300 MHz, DMSO-d₆) δ = 7.96 – 7.78 (m, 2H), 7.64 – 7.34 (m, 6H), 7.21 – 7.11 (m, 2H), 7.03 (t, *J* = 7.2 Hz, 1H), 6.96 (s, 1H), 3.86 (s, 3H). ¹³C{¹H} NMR (75 MHz, DMSO-d₆) δ = 142.3 (Cq), 139.9 (Cq), 138.2 (Cq), 137.9 (Cq), 137.2 (Cq), 127.4 (Cq), 125.0 (CH), 124.8 (CH), 123.8 (CH), 123.7 (CH), 123.6 (CH), 122.3 (CH), 121.7 (CH), 120.0 (CH), 119.7 (CH), 119.0 (CH), 109.8 (CH), 99.4 (CH), 29.7 (CH₃). IR (neat): 2928, 1531, 1469, 1347, 1154 cm⁻¹. HRMS (ESI): m/z [M+H]⁺ calcd for C₁₉H₁₆NS: 290.1003; found: 290.1003.

(E)-1-(4-(2-(1-Methyl-5-(1-(3,4,5-trimethoxyphenyl)vinyl)-1H-indol-2-yl)vinyl)phenyl)-ethan-1-one (1a)

Yellow solid, mp 170.1 – 170.5 °C, yield 55%, 128.6 mg.

¹H NMR (300 MHz, CDCl₃) δ = 7.90 (d, *J* = 8.2 Hz, 2H), 7.55 – 7.52 (m, 3H), 7.25 – 7.10 (m, 4H), 6.78 (s, 1H), 6.55 (s, 2H), 5.38 (s, 1H), 5.31 (s, 1H), 3.82 (s, 3H), 3.79 (s, 3H), 3.73 (s, 6H), 2.55 (s, 3H). ¹³C{¹H} NMR (75 MHz, CDCl₃) δ = 197.5 (Cq), 152.9 (2 Cq), 151.0 (Cq), 141.8 (Cq), 138.4 (Cq), 138.3 (Cq), 138.2 (Cq), 137.9 (Cq), 136.2 (Cq), 133.7 (Cq), 129.5 (CH), 129.1 (2 CH), 127.8 (Cq), 126.5 (2 CH), 123.4 (CH), 120.7 (CH), 119.6 (CH), 112.7 (CH₂), 109.0 (CH), 105.9 (2 CH), 100.5 (CH), 61.1 (CH₃), 56.3 (2 CH₃), 30.3 (CH₃), 26.7 (CH₃). IR (neat): 2936, 1678, 1598, 1579, 1504, 1392 cm⁻¹. HRMS (ESI): m/z [M+H]⁺ calcd for C₃₀H₃₀NO₄: 468.2175; found: 468.2192.

(E)-2-(4-Fluorostyryl)-1-methyl-5-(1-(3,4,5-trimethoxyphenyl)vinyl)-1H-indole (1b)

Yellow solid, mp 151.6 – 151.8 °C, yield 58%, 128.6 mg.

¹H NMR (300 MHz, acetone-d₆) δ = 7.74 – 7.69 (m, 2H), 7.54 (s, 1H), 7.44 – 7.26 (m, 3H), 7.26 – 7.06 (m, 3H), 6.86 (s, 1H), 6.67 (s, 2H), 5.42 (s, 1H), 5.40 (s, 1H), 3.92 (s, 3H), 3.78 (s, 3H), 3.77 (s, 6H). ¹³C{¹H} NMR (75 MHz, acetone-d₆) δ = 163.2 (d, *J* = 244.1 Hz, Cq), 154.0 (2 Cq), 152.2 (Cq), 140.0 (Cq), 139.1 (Cq), 139.0 (Cq), 138.9 (Cq), 134.8 (d, *J* = 3.2 Hz, Cq), 134.0 (Cq), 130.3 (CH), 129.2 (d, *J* = 7.9 Hz, 2 CH), 128.9 (Cq), 123.2 (CH), 120.8 (CH), 118.0 (CH), 116.3 (d, *J* = 21.7 Hz, 2 CH), 112.5 (CH₂), 109.9 (CH), 106.9 (2 CH), 99.8 (CH), 60.6 (CH₃), 56.4 (2 CH₃), 30.2 (CH₃). ¹⁹F NMR (188 MHz, acetone-d₆): δ = -113.558. IR (neat): 2937, 1631, 1505, 1462, 1391, 1277, 1260, 1235 cm⁻¹. HRMS (ESI): m/z [M+H]⁺ calcd for C₂₈H₂₇NO₃F: 444.1975; found: 444.1973.

(E)-2-(4-Methoxystyryl)-1-methyl-5-(1-(3,4,5-trimethoxyphenyl)vinyl)-1H-indole (1c)

Yellow solid, mp 159.7 – 159.9 °C, yield 61%, 136.7 mg.

¹H NMR (300 MHz, CDCl₃) δ = 7.61 (s, 1H), 7.50 (d, *J* = 8.4 Hz, 2H), 7.30 – 7.14 (m, 3H), 7.10 – 6.89 (m, 3H), 6.77 (s, 1H), 6.67 (s, 2H), 5.48 (s, 1H), 5.41 (s, 1H), 3.93 (s, 3H), 3.87 – 3.83 (m, 12H). ¹³C{¹H} NMR (75 MHz, CDCl₃) δ = 159.7 (Cq), 152.9 (2 Cq), 151.2 (Cq), 139.6 (Cq), 138.4 (Cq), 138.0 (Cq), 137.8 (Cq), 133.3 (Cq), 130.9 (CH), 130.0 (Cq), 128.0 (Cq), 127.8 (2 CH), 122.5 (CH), 120.3 (CH), 114.8 (CH), 114.3 (2 CH), 112.5 (CH₂), 108.7 (CH), 105.9 (2 CH), 98.7 (CH), 61.0 (CH₃), 56.2 (2 CH₃), 55.4 (CH₃), 30.1 (CH₃). IR (neat): 2935, 1766, 1604, 1578, 1508, 1464, 1348, 1252 cm⁻¹. HRMS (ESI): m/z [M+H]⁺ calcd for C₂₉H₃₀NO₄: 456.2175; found: 456.2189.

(E)-1-Methyl-5-(1-(3,4,5-trimethoxyphenyl)vinyl)-2-(4-vinylstyryl)-1H-indole (1d)

Yellow solid, mp 139.4 – 139.8 °C, yield 63%, 142.2 mg. ¹H NMR (300 MHz, acetone-d₆) δ = 7.64 (d, *J* = 8.1 Hz, 2H), 7.56 – 7.26 (m, 6H), 7.19 (dd, *J* = 8.4 Hz, *J* = 1.5 Hz, 1H), 6.88 (s, 1H), 6.78 (dd, *J* = 17.7 Hz, *J* = 11.1 Hz, 1H), 6.68 (s, 2H), 5.85 (d, *J* = 17.7 Hz, 1H), 5.41 (d, *J* = 4.8 Hz, 2H), 5.26 (d, *J* = 11.1 Hz, 1H), 3.91 (s, 3H), 3.78 (s, 3H), 3.77 (s, 6H). ¹³C{¹H} NMR (75 MHz, acetone-d₆) δ = 154.0 (2 Cq), 152.2 (Cq), 140.1 (Cq), 139.1 (Cq), 139.0 (Cq), 138.9 (Cq), 137.9 (2 Cq), 137.4 (CH), 134.0 (Cq), 131.1 (CH), 128.9 (Cq), 127.6 (2 CH), 127.4 (2 CH), 123.3 (CH), 120.8 (CH), 118.0 (CH), 114.1 (CH₂), 112.5 (CH₂), 109.9 (CH), 106.9 (2 CH), 99.9 (CH), 60.6 (CH₃), 56.4 (2 CH₃), 30.2 (CH₃). IR (neat): 2935, 1579, 1504, 1463, 1449, 1348 cm⁻¹. HRMS (ESI): *m/z* [M+H]⁺ calcd for C₃₀H₃₀NO₃: 452.2226; found: 452.2223.

(E)-1-Methyl-2-(3-nitrostyryl)-5-(1-(3,4,5-trimethoxyphenyl)vinyl)-1H-indole (1e)

Yellow solid, mp 191.9 – 192.1 °C, yield 57%, 134.1 mg. ¹H NMR (300 MHz, CDCl₃) δ = 8.32 (s, 1H), 8.04 (d, *J* = 8.1 Hz, 1H), 7.72 (d, *J* = 8.1 Hz, 1H), 7.58 – 7.42 (m, 2H), 7.28 – 7.08 (m, 4H), 6.78 (s, 1H), 6.55 (s, 2H), 5.38 (s, 1H), 5.32 (s, 1H), 3.82 (s, 3H), 3.80 (s, 3H), 3.73 (s, 6H). ¹³C{¹H} NMR (75 MHz, CDCl₃) δ = 152.9 (2 Cq), 151.0 (Cq), 148.9 (Cq), 139.0 (Cq), 138.4 (Cq), 138.2 (Cq), 137.9 (2 Cq), 133.7 (Cq), 132.5 (CH), 129.8 (CH), 128.1 (CH), 127.7 (Cq), 123.5 (CH), 122.3 (CH), 120.7 (CH), 120.6 (CH), 119.9 (CH), 112.7 (CH₂), 109.0 (CH), 105.9 (2 CH), 100.7 (CH), 61.1 (CH₃), 56.3 (2 CH₃), 30.3 (CH₃). IR (neat): 2936, 1630, 1578, 1529, 1504, 1465, 1349 cm⁻¹. HRMS (ESI): *m/z* [M+H]⁺ calcd for C₂₈H₂₇N₂O₅: 471.1920; found: 471.1924.

(E)-1-Methyl-2-styryl-5-(1-(3,4,5-trimethoxyphenyl)vinyl)-1H-indole (1f)

Yellow solid, mp 121.0 – 121.3 °C, yield 60%, 127.6 mg. ¹H NMR (300 MHz, acetone-d₆) δ = 7.67 (d, *J* = 7.2 Hz, 2H), 7.54 – 7.29 (m, 7H), 7.19 (d, *J* = 8.7 Hz, 1H), 6.88 (s, 1H), 6.67 (s, 2H), 5.41 (s, 1H), 5.39 (s, 1H), 3.93 (s, 3H), 3.78 (s, 9H). ¹³C{¹H} NMR (75 MHz, acetone-d₆) δ = 153.1 (2 Cq), 151.3 (Cq), 139.2 (Cq), 138.2 (Cq), 138.1 (Cq), 138.0 (Cq), 137.4 (Cq), 133.1 (Cq), 130.6 (CH), 128.7 (2 CH), 128.0 (Cq), 127.7 (CH), 126.5 (2 CH), 122.3 (CH), 119.9 (CH), 117.1 (CH), 111.6 (CH₂), 108.9 (CH), 106.0 (2 CH), 98.9 (CH), 59.7 (CH₃), 55.5 (2 CH₃), 29.3 (CH₃). IR (neat): 1579, 1503, 1463, 1449, 1411, 1348, 1236 cm⁻¹. HRMS (ESI): *m/z* [M+H]⁺ calcd for C₂₈H₂₈NO₃: 426.2069; found: 426.2065.

(E)-3-(2-(1-Methyl-5-(1-(3,4,5-trimethoxyphenyl)vinyl)-1H-indol-2-yl)vinyl)aniline (1g)

Yellow solid, mp 95.6 – 95.8 °C, yield 58%, 127.8 mg. ¹H NMR (300 MHz, acetone-d₆) δ = 7.52 (s, 1H), 7.39 – 7.05 (m, 5H), 6.96 – 6.83 (m, 3H), 6.71 – 6.58 (m, 3H), 5.41 (s, 1H), 5.39 (s, 1H), 4.68 (br, 2H), 3.90 (s, 3H), 3.78 (s, 9H). ¹³C{¹H} NMR (75 MHz, acetone-d₆) δ = 153.1 (2 Cq), 151.3 (Cq), 148.7 (Cq), 139.4 (Cq), 139.1 (Cq), 138.2 (Cq), 138.0 (Cq), 137.9 (Cq), 133.0 (Cq), 131.6 (CH), 129.2 (CH), 128.0 (Cq), 122.1 (CH), 119.8 (CH), 116.2 (CH), 115.5 (CH), 114.2 (CH), 112.2 (CH), 111.5 (CH₂), 108.9 (CH), 106.0 (2 CH), 98.6 (CH), 59.7 (CH₃), 55.5 (2 CH₃), one CH₃ peak was buried in the solvent signals. IR (neat): 3450, 2396, 1599, 1579, 1503,

1463, 1412, 1348 cm⁻¹. HRMS (ESI): *m/z* [M+H]⁺ calcd for C₂₈H₂₉N₂O₃: 441.2178; found: 441.2180.

(E)-1-(4-(2-(1-Methyl-5-(methyl(3,4,5-trimethoxyphenyl)amino)-1H-indol-2-yl)vinyl)phenyl)ethan-1-one (2a)

Yellow solid, mp 212.8 – 213.0 °C, yield 77%, 181.2 mg. ¹H NMR (300 MHz, CDCl₃) δ = 7.99 (d, *J* = 8.4 Hz, 2H), 7.62 (d, *J* = 8.4 Hz, 2H), 7.39 (d, *J* = 1.8 Hz, 1H), 7.33 – 7.20 (m, 3H), 7.07 (dd, *J* = 8.4 Hz, *J* = 1.8 Hz, 1H), 6.85 (s, 1H), 6.08 (s, 2H), 3.87 (s, 3H), 3.82 (s, 3H), 3.76 (s, 6H), 3.35 (s, 3H), 2.64 (s, 3H). ¹³C{¹H} NMR (75 MHz, CDCl₃) δ = 197.5 (Cq), 153.6 (2 Cq), 147.2 (Cq), 143.3 (Cq), 142.5 (Cq), 141.8 (Cq), 138.5 (Cq), 136.2 (Cq), 135.9 (Cq), 129.4 (CH), 129.1 (2 CH), 128.7 (Cq), 126.5 (2 CH), 121.2 (CH), 119.6 (CH), 116.3 (CH), 110.2 (CH), 100.0 (CH), 94.2 (2 CH), 61.2 (CH₃), 56.2 (2 CH₃), 41.5 (CH₃), 30.3 (CH₃), 26.7 (CH₃). IR (neat): 2958, 1678, 1598, 1507, 1307, 1263 cm⁻¹. HRMS (ESI): *m/z* [M+H]⁺ calcd for C₂₉H₃₁N₂O₄: 471.2284; found: 471.2286.

(E)-2-(4-Fluorostyryl)-N,1-dimethyl-N-(3,4,5-trimethoxyphenyl)-1H-indol-5-amine (2b)

Yellow solid, mp 180.1 – 180.4 °C, yield 74%, 165.2 mg. ¹H NMR (300 MHz, acetone-d₆) δ = 7.76 – 7.70 (m, 2H), 7.46 – 7.28 (m, 4H), 7.21 – 7.14 (m, 2H), 7.00 (d, *J* = 8.7 Hz, 1H), 6.84 (s, 1H), 6.09 (s, 2H), 3.92 (s, 3H), 3.69 (s, 6H), 3.66 (s, 3H), 3.31 (s, 3H). ¹³C{¹H} NMR (75 MHz, acetone-d₆) δ = 163.2 (d, *J* = 244.6 Hz, Cq), 154.6 (2 Cq), 148.1 (Cq), 143.2 (Cq), 139.9 (Cq), 136.6 (Cq), 134.9 (d, *J* = 3.2 Hz, Cq), 132.2 (Cq), 130.1 (CH), 129.7 (Cq), 129.2 (d, *J* = 7.8 Hz, 2 CH), 121.1 (CH), 118.1 (CH), 116.6 (d, *J* = 22.8 Hz, 2 CH), 116.2 (CH), 111.0 (CH), 99.4 (CH), 95.2 (2 CH), 60.6 (CH₃), 56.3 (2 CH₃), 41.6 (CH₃), one CH₃ peak was buried in the solvent signals. ¹⁹F NMR (188 MHz, acetone-d₆): δ = -115.708. IR (neat): 2934, 1603, 1583, 1506, 1258, 1233 cm⁻¹. HRMS (ESI): *m/z* [M+H]⁺ calcd for C₂₇H₂₈N₂O₃F: 447.2084; found: 447.2085.

(E)-2-(4-Methoxystyryl)-N,1-dimethyl-N-(3,4,5-trimethoxyphenyl)-1H-indol-5-amine (2c)

Yellow solid, mp 110.1 – 110.3 °C, yield 82%, 188.0 mg. ¹H NMR (300 MHz, acetone-d₆) δ = 7.61 (d, *J* = 8.7 Hz, 2H), 7.42 – 7.23 (m, 4H), 7.07 – 6.86 (m, 3H), 6.78 (s, 1H), 6.09 (s, 2H), 3.89 (s, 3H), 3.84 (s, 3H), 3.68 (s, 6H), 3.66 (s, 3H), 3.30 (s, 3H). ¹³C{¹H} NMR (75 MHz, acetone-d₆) δ = 160.6 (Cq), 154.5 (2 Cq), 148.1 (Cq), 143.1 (Cq), 140.5 (Cq), 136.6 (Cq), 132.1 (Cq), 131.2 (CH), 131.0 (Cq), 129.8 (Cq), 128.7 (2 CH), 120.9 (CH), 116.8 (CH), 115.8 (CH), 115.0 (2 CH), 110.9 (CH), 98.7 (CH), 95.1 (2 CH), 60.6 (CH₃), 56.2 (2 CH₃), 55.6 (CH₃), 41.6 (CH₃), one CH₃ peak was buried in the solvent signals. IR (neat): 2958, 1604, 1582, 1507, 1483, 1465, 1247 cm⁻¹. HRMS (ESI): *m/z* [M+H]⁺ calcd for C₂₈H₃₁N₂O₄: 459.2284; found: 459.2291.

(E)-N,1-Dimethyl-N-(3,4,5-trimethoxyphenyl)-2-(4-vinylstyryl)-1H-indol-5-amine (2d)

Yellow solid, mp 133.2 – 133.6 °C, yield 80%, 181.8 mg. ¹H NMR (300 MHz, acetone-d₆) δ = 7.64 (d, *J* = 8.4 Hz, 2H), 7.56 – 7.24 (m, 6H), 6.99 (dd, *J* = 8.7 Hz, *J* = 2.1 Hz, 1H), 6.93 – 6.62 (m, 2H), 6.10 (s, 2H), 5.85 (d, *J* = 18.3 Hz, 1H), 5.26 (d, *J* = 10.8 Hz, 1H), 3.91 (s, 3H), 3.69 (s, 6H), 3.67 (s, 3H), 3.31 (s, 3H). ¹³C{¹H} NMR

(75 MHz, acetone-d₆) δ = 154.6 (2 Cq), 148.1 (Cq), 143.2 (Cq), 140.1 (Cq), 138.0 (Cq), 137.9 (Cq), 137.4 (CH), 136.7 (Cq), 132.2 (Cq), 130.9 (CH), 129.8 (Cq), 127.6 (2 CH), 127.4 (2 CH), 121.2 (CH), 118.1 (CH), 116.8 (CH), 114.1 (CH₂), 111.0 (CH), 99.5 (CH), 95.3 (2 CH), 60.6 (CH₃), 56.3 (2 CH₃), 41.6 (CH₃), 30.2 (CH₃). IR (neat): 2935, 1603, 1582, 1506, 1482, 1465, 1450, 1258 cm⁻¹. HRMS (ESI): *m/z* [M+H]⁺ calcd for C₂₉H₃₁N₂O₃: 455.2335; found: 455.2336.

Procedure for the synthesis of 4-bromo-*N,N*-dimethyl-2-((trimethylsilyl)ethynyl)aniline **6**.

To a stirred mixture of 4-bromo-2-iodo-*N,N*-dimethylaniline (20 mmol), PdCl₂(PPh₃)₂ (0.05 equiv) and CuI (0.1 equiv) in Et₃N (50 mL), trimethylsilylacetylene (1.1 equiv, 3.3 mL) was added dropwise at 0 °C. The mixture was then stirred at room temperature. When the starting material was disappeared (TLC monitoring), the mixture was passed through a pad of Celite to remove the insoluble materials. The filtrate was concentrated in vacuo and the residue was purified by silica gel column chromatography (0 to 10% AcOEt in cyclohexane).

4-bromo-*N,N*-dimethyl-2-((trimethylsilyl)ethynyl)aniline (**6**)

Colorless oil, yield 91%, 5.33 g.

¹H NMR (300 MHz, CDCl₃) δ = 7.29 (d, *J* = 2.4 Hz, 1H), 7.06 (dd, *J* = 9.0 Hz, *J* = 2.5 Hz, 1H), 6.48 (d, *J* = 9.0 Hz, 1H), 2.70 (s, 6H), 0.03 (s, 9H). ¹³C{¹H} NMR (75 MHz, CDCl₃) δ = 154.2 (Cq), 137.0 (CH), 132.3 (CH), 118.3 (CH), 116.4 (Cq), 111.8 (Cq), 103.2 (Cq), 101.2 (Cq), 43.3 (2 CH₃), 0 (3 CH₃). IR (neat): 2958, 2838, 2151, 1488, 1386, 838 cm⁻¹. HRMS (ESI): *m/z* [M+H]⁺ calcd for C₁₃H₁₉N⁷⁹BrSi: 296.0470; found: 296.0469.

Procedure for the synthesis of **8**.

A 50 mL flask was charged with aryl halide **6** (10 mmol), Xphos (10 mol%), Pd₂dba₃ (5 mol%), LiOtBu (2.2 equiv), the tosylhydrazone **7** (1.2 equiv) and dioxane (25 mL). The system was stirred at 70° with monitored by TLC analysis. When the reaction was completed, the crude reaction mixture was allowed to cool to room temperature and filtered through celite washed by CH₂Cl₂. The solvents were evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (0 to 20% AcOEt in cyclohexane).

N,N-Dimethyl-4-(1-(3,4,5-trimethoxyphenyl)vinyl)-2-((trimethylsilyl)ethynyl)aniline (**8**)

Brown oil, yield 86%, 3.52 g.

¹H NMR (300 MHz, CDCl₃) δ = 7.47 (d, *J* = 1.8 Hz, 1H), 7.17 (dd, *J* = 8.7 Hz, *J* = 1.8 Hz, 1H), 6.79 (d, *J* = 8.4 Hz, 1H), 6.55 (s, 2H), 5.36 (s, 1H), 5.30 (s, 1H), 3.88 (s, 3H), 3.81 (s, 6H), 2.99 (s, 6H), 0.26 (s, 9H). ¹³C{¹H} NMR (75 MHz, CDCl₃) δ = 154.8 (Cq), 153.0 (2 Cq), 149.1 (Cq), 137.9 (Cq), 137.4 (Cq), 134.6 (CH), 132.9 (Cq), 129.6 (CH), 116.3 (CH), 114.8 (Cq), 113.9 (Cq), 112.6 (CH₂), 105.8 (2 CH), 104.7 (Cq), 61.0 (CH₃), 56.3 (2 CH₃), 43.3 (2 CH₃), 0.1 (3 CH₃). IR (neat): 2999, 2957, 2835, 2786, 2148, 1598, 1503, 1465, 1347 842 cm⁻¹. HRMS (ESI): *m/z* [M+H]⁺ calcd for C₂₄H₃₂NO₃Si: 410.2151; found: 410.2149.

Procedure for the synthesis of **10**.

Aryl bromine **6** (1 mmol) (note: the yield will drastically decrease when increasing the quantity of starting

material), Xphos (10 mol%), Pd₂dba₃ (5 mol%), NaOtBu (2.2 equiv), 3,4,5-trimethoxy-*N*-methylaniline (1.2 equiv) were mixed in 8 mL of toluene. The system was stirred at 70° in a 30 mL sealed tube with monitored by TLC analysis. When the reaction was completed, the crude reaction mixture was allowed to cool to room temperature and filtered through celite washed by CH₂Cl₂. The solvents were evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (0 to 20% AcOEt in cyclohexane).

*N*¹,*N*¹,*N*⁴-Trimethyl-*N*⁴-(3,4,5-trimethoxyphenyl)-2-((trimethylsilyl)ethynyl)benzene-1,4-diamine (**10**)

Brown oil, yield 83%, 342.5 mg.

¹H NMR (300 MHz, acetone-d₆) δ = 7.06 – 6.87 (m, 3H), 6.21 (s, 2H), 3.73 (s, 6H), 3.67 (s, 3H), 3.21 (s, 3H), 2.88 (s, 6H), 0.22 (s, 9H). ¹³C{¹H} NMR (75 MHz, acetone-d₆) δ = 154.9 (2 Cq), 154.1 (Cq), 151.6 (Cq), 146.9 (Cq), 143.6 (Cq), 128.2 (CH), 124.7 (CH), 119.0 (CH), 116.7 (Cq), 105.9 (Cq), 99.6 (Cq), 98.6 (2 CH), 60.8 (CH₃), 56.5 (2 CH₃), 43.9 (2 CH₃), 41.1 (CH₃), 0.2 (3 CH₃). IR (neat): 2958, 2783, 2149, 1715, 1611, 1496, 1247, 841 cm⁻¹. HRMS (ESI): *m/z* [M+H]⁺ calcd for C₂₃H₃₃N₂O₃Si: 413.2260; found: 413.2266.

Procedure for the Synthesis of terminal alkyne **9**, **11**.

To an oven dried 100 mL round-bottomed flask was added 2-((trimethylsilyl)ethynyl)aniline (5 mmol), MeOH (30 mL), and oven dried K₂CO₃ (1 equiv). The flask was stirred under argon atmosphere at room temperature. When TLC show the disappearance of starting material, H₂O (30 mL) was added to the flask. After extracted with CH₂Cl₂ (3 × 30 mL), the organic layer was dried over anhydrous MgSO₄, and concentrated in vacuo. The crude oil was then purified by column chromatography on silica gel (0 to 20% AcOEt in cyclohexane).

2-Ethynyl-*N,N*-dimethyl-4-(1-(3,4,5-trimethoxyphenyl)vinyl)aniline (**9**)

Brown oil, yield 92%, 1.55 g.

¹H NMR (300 MHz, CDCl₃) δ = 7.41 (d, *J* = 2.1 Hz, 1H), 7.18 – 7.14 (m, 1H), 6.79 (d, *J* = 8.7 Hz, 1H), 6.47 (s, 2H), 5.30 (s, 1H), 5.24 (s, 1H), 3.81 (s, 3H), 3.75 (s, 6H), 3.32 (s, 1H), 2.90 (s, 6H). ¹³C{¹H} NMR (75 MHz, CDCl₃) δ = 155.2 (Cq), 153.0 (2 Cq), 149.0 (Cq), 137.3 (Cq), 134.8 (CH), 133.4 (Cq), 129.7 (CH), 116.7 (CH), 113.7 (Cq), 112.9 (CH₂), 112.8 (Cq), 105.8 (2 CH), 83.1 (Cq), 82.5 (CH), 61.0 (CH₃), 56.3 (2 CH₃), 43.6 (2 CH₃). IR (neat): 3276, 2957, 2836, 1599, 1579, 1464, 1451, 1347, 1266 cm⁻¹. HRMS (ESI): *m/z* [M+H]⁺ calcd for C₂₁H₂₄NO₃: 338.1756; found: 338.1755.

2-Ethynyl-*N*¹,*N*¹,*N*⁴-trimethyl-*N*⁴-(3,4,5-trimethoxyphenyl)benzene-1,4-diamine (**11**)

Brown oil, yield 90%, 1.53 g.

¹H NMR (300 MHz, CDCl₃) δ = 7.15 (d, *J* = 2.7 Hz, 1H), 6.96 (dd, *J* = 8.7 Hz, *J* = 2.7 Hz, 1H), 6.87 (d, *J* = 8.7 Hz, 1H), 6.15 (s, 2H), 3.81 (s, 3H), 3.77 (s, 6H), 3.38 (s, 1H), 3.23 (s, 3H), 2.89 (s, 6H). ¹³C{¹H} NMR (75 MHz, CDCl₃) δ = 153.7 (2 Cq), 150.6 (Cq), 145.7 (Cq), 142.9 (Cq), 132.8 (Cq), 127.5 (CH), 123.3 (CH), 118.3 (CH), 115.8 (Cq), 97.5 (2 CH), 82.7 (Cq), 82.3 (CH), 61.1 (CH₃), 56.2 (2 CH₃), 44.2 (2 CH₃), 40.8 (CH₃). IR (neat): 2937, 2826, 1612, 1495, 1450, 1309, 1236 cm⁻¹. HRMS (ESI): *m/z* [M+H]⁺ calcd for C₂₀H₂₅N₂O₃: 341.1865; found: 341.1870.

Supporting Information:

Supporting Information contains copies of ^1H , ^{13}C and ^{19}F NMR spectra of new compounds.

Acknowledgment.

Authors acknowledge support of this project by CNRS, University Paris Sud, and by La Ligue Nationale Contre le Cancer through an Equipe Labellisée 2014 grant. Guangkuan Zhao thanks the CSC (Chinese Scholarship Council) for its Ph.D. funding. Our laboratory BioCIS-UMR 8076 is a member of the Laboratory of Excellence LERMIT supported by a grant from the Agence Nationale de la Recherche, (ANR-10-LABX-33).

REFERENCES

- (1) Pettit, G. R.; Singh, S. B.; Hamel, E.; Lin, C. M.; Alberts, D. S.; Garcia-Kendall, D. Isolation and structure of the strong cell growth and tubulin inhibitor combretastatin A-4. *Experientia* **1989**, *45*, 209-210.
- (2) Pettit, G. R.; Rhodes, M. R.; Herald, D. L.; Hamel, E.; Schmidt, J. M.; Pettit, R. K. Antineoplastic agents. 445. Synthesis and evaluation of structural modifications of (Z)- and (E)-combretastatin A-4. *J. Med. Chem.* **2005**, *48*, 4087-4099.
- (3) Lin, C. M.; Singh, S. B.; Chu, P. S.; Dempcy, R. O.; Schmidt, J. M.; Pettit, G. R.; Hamel, E. Interactions of tubulin with potent natural and synthetic analogs of the antimetabolic agent combretastatin: A structure-activity study. *Mol. Pharmacol* **1988**, *34*, 200-208.
- (4) Mendez-Callejas, G. M.; Leone, S.; Tanzarella, C.; Antocchia, A. Combretastatin A-4 induces p53 mitochondrial-relocalisation independent-apoptosis in non-small lung cancer cells. *Cell. Biol. Int.* **2014**, *38*, 296-308.
- (5) Su, J.; Laursen, B. E.; Eskildsen-Helmond, Y.; Horsman, M. R.; Simonsen, U. The vascular-disrupting agent, combretastatin-A4-phosphate, enhances neurogenic vasoconstriction in rat small arteries. *Eur. J. Pharmacol.* **2012**, *695*, 104-111.
- (6) <http://investor.mateon.com/>
- (7) Ohsumi, K.; Hatanaka, T.; Fujita, K.; Nakagawa, R.; Fukuda, Y.; Nihei, Y.; Suga, Y.; Morinaga, Y.; Akiyama, Y.; Tsuji, T. Syntheses and antitumor activity of cis-restricted combretastatins: 5-membered heterocyclic analogues. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 3153-3158.
- (8) Aprile, S.; Del Grosso, E.; Tron, G. C.; Grosa, G. In vitro metabolism study of combretastatin A-4 in rat and human liver microsomes. *Drug Metab. Dispos.* **2007**, *35*, 2252-2261.
- (9) For recent reviews and refs therein, see: (a) Seddigi, Z. S.; Malik, M. S.; Saraswati, A. P.; Ahmed, S. A.; Babalghith, A. O.; Lamfon, H. A.; Kamal, A. Recent advances in combretastatin based derivatives and prodrugs as antimetabolic agents. *Med. Chem. Commun.* **2017**, *8*, 1592-1603. (b) Bukhari, S. N. A.; Kumar, G. B.; H. M. Revankar, H. M.; Qin, H. L. Development of combretastatins as potent tubulin polymerization inhibitors. *Bioorg. Chem.* **2017**, *72*, 130-147. (c) Siebert, A.; Gensicka, M.; Cholewinski, G.; Dzierzbicka, K. Synthesis of combretastatin A-4 analogs and their biological activities. *Anticancer Agents Med. Chem.* **2016**, *16*, 942-960.
- (10) (a) Renko, D.; Provot, O.; Rasolofonjatovo, E.; Bignon, J.; Rodrigo, J.; Dubois, J.; Brion, J. D.; Hamze, A.; Alami, M. Rapid synthesis of 4-arylchromenes from ortho-substituted alkynols: a versatile access to restricted isocombretastatin A-4 analogues as antitumor agents. *Eur. J. Med. Chem.* **2015**, *79*, 834-844. (b) Rasolofonjatovo, E.; Provot, O.; Hamze, A.; Rodrigo, J.; Bignon, J.; Wdzieczak-Bakala, J.; Lenoir, C.; Desravines, D.; Dubois, J.; Brion, J. D.; Alami, M. Design, synthesis and anticancer properties of 5-arylbenzoxepins as conformationally restricted isocombretastatin A-4 analogues. *Eur. J. Med. Chem.* **2013**, *62*, 28-39. (c) Hamze, A.; Rasolofonjatovo, E.; Provot, O.; Mousset, C.; Veau, D.; Rodrigo, J.; Bignon, J.; Liu, J. M.; Wdzieczak-Bakala, J.; Thoret, S.; Dubois, J.; Brion, J. D.; Alami, M. B-Ring-modified isocombretastatin A-4 analogues endowed with interesting anticancer activities. *ChemMedChem* **2011**, *6*, 2179-2191. (d) Messaoudi, S.; Tréguier, B.; Hamze, A.; Provot, O.; Peyrat, J. F.; De Losada, J. R.; Liu, J. M.; Bignon, J.; Wdzieczak-Bakala, J.; Thoret, S.; Dubois, J.; Brion, J. D.; Alami, M. Isocombretastatins A versus combretastatins A: The forgotten isoCA-4 isomer as a highly promising cytotoxic and antitubulin agent. *J. Med. Chem.* **2009**, *52*, 4538-4542.
- (11) Messaoudi, S.; Hamze, A.; Provot, O.; Tréguier, B.; De Losada, J. R.; Bignon, J.; Liu, J. M.; Wdzieczak-Bakala, J.; Thoret, S.; Dubois, J.; Brion, J. D.; Alami, M. Discovery of isoeirinin analogues as promising anticancer agents. *ChemMedChem* **2011**, *6*, 488-497.
- (12) Soussi, M. A.; Provot, O.; Bernadat, G.; Bignon, J.; Wdzieczak-Bakala, J.; Desravines, D.; Dubois, J.; Brion, J. D.; Messaoudi, S.; Alami, M. Discovery of azaisoeirinin derivatives as potential antitumor agents. *Eur. J. Med. Chem.* **2014**, *78*, 178-189.
- (13) (a) Soussi, M. A.; Provot, O.; Bernadat, G.; Bignon, J.; Desravines, D.; Dubois, J.; Brion, J. D.; Messaoudi, S.; Alami, M. Isocombretaquinoxalines: Potent cytotoxic agents with antitubulin activity. *ChemMedChem* **2015**, *10*, 1392-1402. (b) Khelifi, I.; Naret, T.; Renko, D.; Hamze, A.; Bernadat, G.; Bignon, J.; Lenoir, C.; Dubois, J.; Brion, J. D.; Provot, O.; Alami, M. Design, synthesis and anticancer properties of isocombretaquinoxalines as potent tubulin assembly inhibitors. *Eur. J. Med. Chem.* **2017**, *127*, 1025-1034.
- (14) (a) Maya, A. B. S.; Pérez-Melero, C.; Mateo, C.; Alonso, D.; Fernández, J. L.; Gajate, C.; Mollinedo, F.; Peláez, R.; Caballero, E.; Medarde, M. Further naphthylcombretastatins. An investigation on the role of the naphthalene moiety. *J. Med. Chem.* **2005**, *48*, 556-568. (b) Mateo, C.; Álvarez, R.; Prez-Melero, C.; Peláez, R.; Medarde, M. Conformationally restricted macrocyclic analogues of combretastatins. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 6316-6320. (c) Álvarez, R.; Puebla, P.; Fernando Díaz, J.; Bento, A. C.; García-Navas, R.; de la Iglesia-Vicente, J.; Mollinedo, F.; Andreu, J. M.; Medarde, M.; Peláez, R. Endowing indole-based tubulin inhibitors with an 10

anchor for derivatization: Highly potent 3-substituted indole phenstatins and isocombretastatins. *J. Med. Chem.* **2013**, *56*, 2813-2827. (d) Yan, J.; Hu, J. H.; An, B. J.; Huang, L.; Li, X. S. Design, synthesis, and biological evaluation of cyclic-indole derivatives as anti-tumor agents via the inhibition of tubulin polymerization. *Eur. J. Med. Chem.* **2017**, *125*, 663-675. (e) Mahal, K.; Biersack, B.; Schrufer, S.; Resch, M.; Ficner, R.; Schobert, R.; Mueller, T. Combretastatin A-4 derived 5-(1-methyl-4-phenylimidazol-5-yl)indoles with superior cytotoxic and anti-vascular effects on chemoresistant cancer cells and tumors. *Eur. J. Med. Chem.* **2016**, *118*, 9-20.

(15) see for examples: (a) Yates, P.; MacLachlan, F. N.; Rae, I. D.; Rosenberger, M.; Szabo, A. G.; Willis, C. R.; Cava, M. P.; Behforouz, M.; Lakshmikantham, M. V.; Zeiger, W. Haplophytine. A novel type of indole alkaloid. *J. Am. Chem. Soc.* **1973**, *95*, 7842-7850. (b) Fuenfschiling, P. C.; Hoehn, P.; Muetz, J. P. An improved manufacturing process for fluvastatin. *Org. Process. Res. Dev.* **2007**, *11*, 13-18. (c) Fernandez, L. S.; Buchanan, M. S.; Carroll, A. R.; Feng, Y. J.; Quinn, R. J.; Avery, V. M. Flindersia A-C: Antimalarial bis-indole alkaloids from flindersia species. *Org. Lett.* **2009**, *11*, 329-332. (d) Chevolut, L.; Chevolut, A. M.; Gajhede, M.; Larsen, C.; Anthoni, U.; Christophersen, C. Chartelline A: A pentahalogenated alkaloid from the marine bryozoan chartella papyracea. *J. Am. Chem. Soc.* **1985**, *107*, 4542-4543. (e) Anthoni, U.; Chevolut, L.; Larsen, C.; Nielsen, P. H.; Christophersen, C. Marine alkaloids. 12. Chartellines, halogenated β -lactam alkaloids from the marine bryozoan chartella papyracea. *J. Org. Chem.* **1987**, *52*, 4709-4712.

(16) For selected examples, see: (a) Fayol, A.; Fang, Y. Q.; Lautens, M. Synthesis of 2-vinyl indoles and derivatives via a Pd-catalyzed tandem coupling reaction. *Org. Lett.* **2006**, *8*, 4203-4206. (b) Rossi, E.; Abbiati, G.; Canevari, V.; Celentano, G.; Magri, E. 2-Trifluoromethanesulfonyloxyindole-1-carboxylic acid ethyl ester: A practical intermediate for the synthesis of 2-carbosubstituted indoles. *Synthesis* **2006**, 299-304. (c) Wang, Y. Z.; Liu, L. Z.; Zhang, L. M. Combining Zn ion catalysis with homogeneous gold catalysis: an efficient annulation approach to *N*-protected indoles. *Chem. Sci.* **2013**, *4*, 739-746. (d) Das, B.; Kundu, P.; Chowdhury, C. Facile synthesis of 2-arylmethylindoles and 2-vinyl indoles through palladium-catalyzed heteroannulations of 2-(2-propynyl)aniline and 2-(2-propynyl)tosylanilide. *Org. Biomol. Chem.* **2014**, *12*, 741-748. (e) Sha, F.; Tao, Y.; Tang, C. Y.; Zhang, F.; Wu, X. Y. Construction of benzo[*c*]carbazoles and their antitumor derivatives through the Diels-Alder reaction of 2-alkenylindoles and arynes. *J. Org. Chem.* **2015**, *80*, 8122-8133. (f) Huang, L. J.; Weng, J.; Wang, S.; Lu, G. Organocatalytic Diels-Alder reaction of 2-vinylindoles with methyleneindolinones: An efficient approach to functionalized carbazolespirooxindoles. *Adv. Synth. Catal.* **2015**, *357*, 993-1003.

(17) (a) Sharma, S.; Han, S.; Kim, M.; Mishra, N. K.; Park, J.; Shin, Y.; Ha, J.; Kwak, J. H.; Jung, Y. H.; Kim, I. S. Rh-catalyzed oxidative C-C bond formation and C-N bond cleavage: Direct access to C2-olefinated free (NH)-indoles and pyrroles. *Org. Biomol. Chem.*

2014, *12*, 1703-1706. (b) Shi, L. J.; Zhong, X.; She, H. D.; Lei, Z. Q.; Li, F. W. Manganese catalyzed C-H functionalization of indoles with alkynes to synthesize bis/trisubstituted indolylalkenes and carbazoles: The acid is the key to control selectivity. *Chem. Commun.* **2015**, *51*, 7136-7139.

(18) (a) Tobisu, M.; Fujihara, H.; Koh, K.; Chatani, N. Synthesis of 2-boryl- and silylindoles by copper-catalyzed borylative and silylative cyclization of 2-alkenylaryl isocyanides. *J. Org. Chem.* **2010**, *75*, 4841-4847. (b) Zhao, Z. D.; Jaworski, A.; Piel, I.; Snieckus, V. Anionic indole *N*-Carbamoyl *N* \rightarrow C translocation. A directed remote metalation route to 2-aryl- and 2-heteroarylindoles. Synthesis of benz[*a*]carbazoles and indeno[1,2-*b*]indoles. *Org. Lett.* **2008**, *10*, 2617-2620.

(19) (a) Arcadi, A.; Bianchi, G.; Inesi, A.; Marinelli, F.; Rossi, L. Electrochemical-mediated cyclization of 2-alkynylanilines: A clean and safe synthesis of indole derivatives. *Eur. J. Org. Chem.* **2008**, 783-787. (b) Cacchi, S.; Carnicelli, V.; Marinelli, F. Palladium-catalyzed cyclization of 2-alkynylanilines to 2-substituted indoles under an acidic two-phase system. *J. Organomet. Chem.* **1994**, *475*, 289-296. (c) Arcadi, A.; Cacchi, S.; Marinelli, F. Palladium-catalyzed coupling of aryl and vinyl triflated or halides with 2-ethynylaniline: An efficient route to functionalized 2-substituted indoles. *Tetrahedron Lett.* **1989**, *30*, 2581-2584. (d) Yu, M. S.; Lopez de Leon, L.; McGuire, M. A.; Botha, G. Synthesis of 2-dienylindole, SB 242784, by a three-component palladium-catalyzed coupling reaction. *Tetrahedron Lett.* **1998**, *39*, 9347-9350. (e) Arcadi, A.; Bianchi, G.; Marinelli, F. Gold(III)-catalyzed annulation of 2-alkynylanilines: A mild and efficient synthesis of indoles and 3-haloindoles. *Synthesis* **2004**, 610-618.

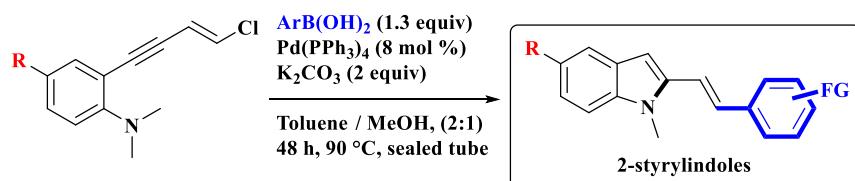
(20) Tikad, A.; Hamze, A.; Provot, O.; Brion, J. D.; Alami, M. Suzuki coupling reactions of (*E*)- and (*Z*)-chloroenynes with boronic acids: Versatile access to functionalized 1,3-enynes. *Eur. J. Org. Chem.* **2010**, 725-731.

(21) Diarylenynes **4** were isolated after 5 h of reaction in yields ranging from 60 to 70% (depending of the boronic acid).

(22) Jacubert, M.; Provot, O.; Peyrat, J. F.; Hamze, A.; Brion, J. D. Alami, M. *p*-Toluenesulfonic acid-promoted selective functionalization of unsymmetrical arylalkynes: a regioselective access to various arylketones and heterocycles. *Tetrahedron* **2010**, *66*, 3775-3787.

(23) (a) Barluenga, J.; Moriel, P.; Valdés, C.; Aznar, F. *N*-tosylhydrazones as reagents for cross-coupling reactions: A route to polysubstituted olefins. *Angew. Chem. Int. Ed.* **2007**, *46*, 5587-5590. (b) Roche, M.; Hamze, A.; Provot, O.; Brion, J. D.; Alami, M. Synthesis of *ortho/ortho'*-substituted 1,1-diarylethylenes through cross-coupling reactions of sterically encumbered hydrazones and aryl halides. *J. Org. Chem.* **2013**, *78*, 445-454.

Table of contents



- 3 steps "one pot" rapid access to functionalized 2-styrylindoles
- 21 examples (55 to 92 %)
- Good to excellent functional group tolerance