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Room-Temperature, Copper-Free, and Amine-Free Sonogashira Reaction in a Green Solvent: Synthesis of Tetraalkynylated Anthracenes and *In Vitro* Assessment of Their Cytotoxic Potentials

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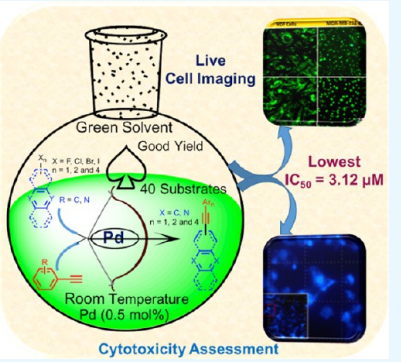
ABSTRACT: The multifold Sonogashira coupling of a class of aryl halides with arylacetylene in the presence of an equivalent of Cs_2CO_3 has been accomplished using a combination of $Pd(CH_3CN)_2Cl_2$ (0.5 mol %) and cataCXium A (1 mol %) under copper-free and amine-free conditions in a readily available green solvent at room temperature. The protocol was used to transform several aryl halides and alkynes to the corresponding coupled products in good to excellent yields. The rate-determining step is likely to involve the oxidative addition of Ar-X. The green protocol provides access to various valuable polycyclic aromatic hydrocarbons (PAHs) with exciting photophysical properties. Among them, six tetraalkynylated anthracenes have been tested for their anticancer properties on the human triple-negative breast cancer (TNBC) cell line MDA-MB-231 and human dermal fibroblasts (HDFs). The 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay was performed to find out the IC_{50} concentration and lethal dose. The compounds being intrinsically fluorescent, their cellular localization was checked by live cell fluorescence imaging. 4′,6-Diamidino-2-phenylindole (DAPI) and propidium iodide (PI) staining was performed to check apoptosis and necrosis, respectively. All of these studies have shown that anthracene and its derivatives can induce cell death via DNA damage and apoptosis.



INTRODUCTION

Organic semiconducting materials based on polyethynylated anthracene[1] have attracted global attention due to their versatile applications in solar cells,[1e,2] organic light-emitting diodes (OLEDs),[1b] organic field-effect transistors (OFETs),[1f,h] devices based on nanowires,[3] sensors,[4] liquid-crystal displays,[5] and organic fluorescence.[1g] The fluorescence efficiency and the electronic properties of the molecules depend on the geometry of the molecules.[1d] The rigid polycyclic aromatic hydrocarbons (PAHs)[1d,6] exhibit high fluorescence efficiency, which can be controlled by the addition of substituents like amino,[7] amino acid ester,[8] aryl,[7] carboxylic acid,[9] and hetero atoms.[1d,7] Addition of polyethynylated units to the PAHs enhances the π-conjugation, which helps to decrease the band gap, lowering the torsional barrier and enhancing the thermal stability, which are favorable for the fabrication of such compounds in optoelectronic devices.[1d] The polyalkynylated unit can be introduced to the PAHs by the Sonogashira reaction. The Sonogashira reaction is vital in organic synthetic chemistry for the synthesis of various organic compounds like natural products,[10] pharmaceutical molecules,[11] biologically active complexes,[12] heterocycles,[13] and organic materials.[1d]

In 1975, Sonogashira, Hagihara, and Tohda reported a cross-coupling reaction by employing $Pd(PPh_3)_2Cl_2$ as the catalyst, CuI as the cocatalyst, and amine as the base, which was later modified using various catalysts, additives, and numerous ligands under different conditions.[1c,d,12,14] Traditionally, in the Sonogashira reaction, Cu(I) coordinates with alkyne to enhance the acidity of the terminal acetylenic proton, assisting in the formation of the acetylide Cu(I), which is involved in the transmetallation step in the catalytic cycle when the alkyne unit is transferred to Pd that subsequently couples with the aryl moiety to form the product via reductive elimination.[1d] However, the presence of copper salts can sometimes have deleterious effects on catalysis,[15] which include but are not limited to participation in the Glasser homocoupling of two terminal alkynes to form dialkynes,[1d,12,15a] inhibition of the activity of the Pd catalyst,[15a] and oxidation of unsaturated Pd(0) species to halide-bridged dinuclear Pd(I) complexes that accelerate polymerization[16] of the alkyne. Rightly, a lot of research emphasis is devoted to the development of copper-

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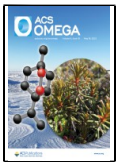


free and preferably amine-free Sonogashira catalytic systems.[12,15,17]

There are reports that demonstrate that Pd and Cu together are no longer required as catalysts for Sonogashira reaction; instead, simply Pd has proven to be adequate when correctly complexed with state-of-the-art ligands in the absence of any amine additives.[12,15a,17c−e,18] In 2003, Buchwald demonstrated a copper-free and amine-free Sonogashira reaction catalyzed by $Pd(CH_3CN)_2Cl_2$ (1 mol %) and X-Phos-type ligand (2 mol %) in the presence of Cs_2CO_3 (2 equiv) in CH_3CN at 70−95 °C.[15a] Lim and coworkers reported a copper-free and amine-free Sonogashira reaction by employing $Pd(CH_3CN)_2Cl_2$ (1 mol %) in combination with Cy*Phine (2 mol %) using Cs_2CO_3 (2 equiv) as the base in CH_3CN at 90 °C for 6 h. Very recently, Mak and coworkers had investigated the reaction mechanism for the same.[17c,18b] It is thus evident that while there are a few studies on copper-free and amine-free Sonogashira systems, reports that accomplish these very important reactions at room temperature are very rare.[12,19]

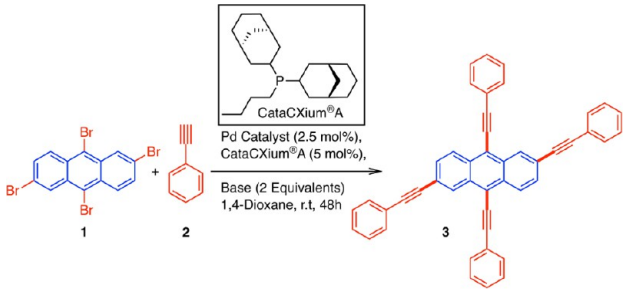
The waste of chemical industries is mainly from solvents, which is about 80−90% of the total mass process.[20] The choice of solvent is very crucial in Pd-catalyzed cross-coupling reactions owing to the stability of the catalyst, selectivity, and rate of the reaction.[21] As per the literature, more than 40% of the reports on Heck−Casser−Sonogashira reactions have been performed in *N*,*N*-dimethylformamide (DMF) solvent, which generates toxic dimethylamine and highly genotoxic nitrosamine.[22] Other solvents like tetrahydrofuran (THF), 1,4-dioxane, dimethoxyethane (DME), dimethyl sulfoxide (DMSO), and trimethylamine (TEA) also have been used in the Sonogashira reaction.[22b] Triethyl amine is a malodorous substance, highly toxic, and exhibits bioaccumulation potential.[23] Exposure to amine vapors for 0.5 h to several hours may cause glaucopsia, blur the vision, and make one see halos around lights.[24] Unfortunately, all other solvents have the same drawbacks like DMF, which are a threat to the environment, the human body, and the ecosystem.[24] Recently, green solvents like dimethylisosorbide, γ-valerolactone, cyrene, *tert*-butyl acetate (^{t}BuOAc), anisole, *N*-octylpyrrolidone (NOP), *N*-cyclohexylpyrrolidone (NCP), *N*-benzylpyrrolidone (NBnP), and *N*-hydroxyethylpyrrolidone (HEP) have been reported in the Sonogashira reaction.[22b−e]

A brief survey of the literature above clearly indicates that development of copper-free and amine-free Sonogashira catalytic systems in green solvents at room temperature is still a challenge that is unaddressed. In particular, 2-methyl tetrahydrofuran (2-MeTHF) that is readily obtained from renewable biomass cellulose, bagasse, corncobs, and agricultural waste[25] has not been explored to date.[22] From the context of PAHs, it would thus be valuable to have a Sonogashira catalytic system that could bring about multifold coupling in a green solvent such as 2-MeTHF at room temperature under copper-free and amine-free conditions. Following our recent success in the multifold Sonogashira reaction employing $Pd(CH_3CN)_2Cl_2$ (2.5 mol %) and cataCXium A (5 mol %) in the presence of copper iodide (5 mol %) and triethyl amine in THF at 90 °C,[1c] in the current work, we report a Sonogashira catalytic system based on $Pd(CH_3CN)_2Cl_2$ (0.5 mol %) and cataCXium A (1 mol %) that operates under copper-free and amine-free conditions in a readily available green solvent such as 2-MeTHF at room temperature. Gratifyingly, this efficient synthetic protocol has been extended with ease to multifold coupling to obtain PAHs based on polyalkynylated arenes. Further, one such PAH based on 2,6,9,10-*tetrakis*((2-methoxyphenyl)ethynyl)anthracene shows preferential cytotoxic activity against breast cancer cell lines.

RESULTS AND DISCUSSION

The optimization of the Sonogashira catalytic system was commenced with 2,6,9,10-tetrabromoanthracene (**1**) and phenylacetylene (**2**) as model substrates with the best-reported conditions at 90 °C[1c] involving $Pd(CH_3CN)_2Cl_2$ (2.5 mol % per halide) and cataCXium A (5 mol % per halide) in a 1:1 mixture of 1,4-dioxane and triethyl amine albeit under copper-free conditions at room temperature (entry 1, Table 1).

Table 1. Optimization of the Pd-Catalyzed Cu-Free and Amine-Free Multifold Sonogashira Coupling at Room Temperature Using Various Bases[a]



entry	base	catalyst	solvent	% yield **3**[b]
1	Et_3N	$Pd(CH_3CN)_2Cl_2$	dioxane	0
2	K_3PO_4	$Pd(CH_3CN)_2Cl_2$	dioxane	52
3	K_2CO_3	$Pd(CH_3CN)_2Cl_2$	dioxane	44
4	Na_2CO_3	$Pd(CH_3CN)_2Cl_2$	dioxane	5
5	$KHCO_3$	$Pd(CH_3CN)_2Cl_2$	dioxane	9
6	$NaHCO_3$	$Pd(CH_3CN)_2Cl_2$	dioxane	trace
7	KOH	$Pd(CH_3CN)_2Cl_2$	dioxane	45
8	NaOH	$Pd(CH_3CN)_2Cl_2$	dioxane	0
9	KO^{t}Bu	$Pd(CH_3CN)_2Cl_2$	dioxane	0
10	NaO^{t}Bu	$Pd(CH_3CN)_2Cl_2$	dioxane	0
11	NaOEt	$Pd(CH_3CN)_2Cl_2$	dioxane	0
12	NaH	$Pd(CH_3CN)_2Cl_2$	dioxane	0
13	Cs_2CO_3	$Pd(CH_3CN)_2Cl_2$	dioxane	98
14[c]	Cs_2CO_3	$Pd(CH_3CN)_2Cl_2$	dioxane	100
15[d]	Cs_2CO_3	$Pd(CH_3CN)_2Cl_2$	dioxane	100

[a]Reaction conditions: 0.101 mmol of **1** and 0.606 mmol of **2** in the presence of the Pd catalyst $Pd(CH_3CN)_2Cl_2$ (2.5 mol % per halide) and cataCXium A (5 mol % per halide) in 1,4-dioxane (5 mL) at room temperature for 48 h. [b]Yield determined from ^{1}H NMR using toluene as the standard. [c]Cs_2CO_3 (1 equiv per halide). [d]Cs_2CO_3 (0.75 equiv per halide).

Unfortunately, these conditions afforded no products even after stirring for 48 h (entry 1, Table 1). This underlines the importance of copper and higher temperatures for these conditions.[1c] With an intention to move away from amines,[23,24] the copper-free Sonogashira reactions at room temperature were repeated with various inorganic bases (entries 2−15, Table 1).

While moderate yields of **3** were obtained with bases such as K_3PO_4 (52%, entry 2, Table 1), K_2CO_3 (44%, entry 3, Table 1), and KOH (45%, entry 7, Table 1), trace or no yield was observed upon use of other bases derived from potassium and sodium (entries 4−6 and 8−12, Table 1). On the other hand, use of 2 equiv of Cs_2CO_3 resulted in very high yields of **3** (ca.

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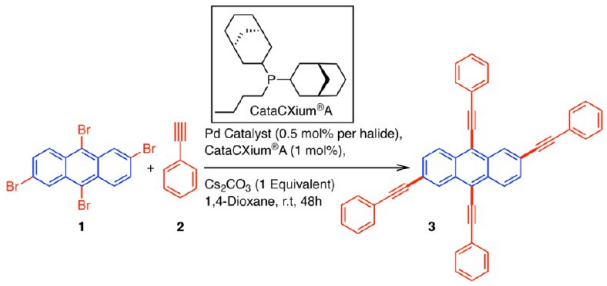
98%, entry 13, Table 1). The yields were unaffected upon lowering the loading of Cs_2CO_3 either to 1 equiv (entry 14, Table 1 and entry 1, Table 2) or to 0.75 equiv (entry 15, Table 1 and entry 2, Table 2).

Table 2. Optimization of the Pd-Catalyzed Cu-Free and Amine-Free Multifold Sonogashira Coupling at Room Temperature under Various Conditions[a]



entry	base	catalyst	solvent	% yield 3[b]
1[c]	Cs_2CO_3	$Pd(CH_3CN)_2Cl_2$	dioxane	100
2[c,d]	Cs_2CO_3	$Pd(CH_3CN)_2Cl_2$	dioxane	100
3[d]	Cs_2CO_3	$Pd(CH_3CN)_2Cl_2$	dioxane	83
4	Cs_2CO_3	$Pd(CH_3CN)_2Cl_2$	dioxane	98
5[e]	Cs_2CO_3	$Pd(CH_3CN)_2Cl_2$	dioxane	80
6	Cs_2CO_3	$Pd(OAc)_2$	dioxane	32
7	Cs_2CO_3	$Pd(dba)_2$	dioxane	87
8	Cs_2CO_3	$Pd(PPh_3)_2Cl_2$	dioxane	36
9	Cs_2CO_3	$Pd(PPh_3)_4$	dioxane	24
10[f]	Cs_2CO_3	$Pd(CH_3CN)_2Cl_2$	dioxane	0
11[f]	Cs_2CO_3	$Pd(OAc)_2$	dioxane	0
12[f]	Cs_2CO_3	$Pd(dba)_2$	dioxane	0
13[f]	Cs_2CO_3	$Pd(PPh_3)_2Cl_2$	dioxane	34
14[f]	Cs_2CO_3	$Pd(PPh_3)_4$	dioxane	3
15	Cs_2CO_3	$Pd(CH_3CN)_2Cl_2$	toluene	0
16	Cs_2CO_3	$Pd(CH_3CN)_2Cl_2$	THF	94
17	Cs_2CO_3	$Pd(CH_3CN)_2Cl_2$	2-MeTHF	98[g]
18[h]	Cs_2CO_3	$Pd(CH_3CN)_2Cl_2$	2-MeTHF	69
19[i]	Cs_2CO_3	$Pd(CH_3CN)_2Cl_2$	2-MeTHF	6
20[j]	Cs_2CO_3	$Pd(CH_3CN)_2Cl_2$	2-MeTHF	32

[a]Reaction conditions: 0.101 mmol of **1** and 0.606 mmol of **2** in the presence of the Pd catalyst (0.5 mol % per halide) and cataCXium A (1 mol % per halide) in 1,4-dioxane (5 mL) at room temperature for 48 h. [b]Yield determined from ^{1}H NMR using toluene as the standard. [c]Pd catalyst (2.5 mol % per halide). [d]Cs_2CO_3 (0.75 equiv per halide). [e]Pd catalyst (0.25 mol % per halide). [f]Without cataCXium A. [g]Average of two runs. [h]Reaction time is 36 h. [i]Cs_2CO_3 (0.5 equiv per halide). [j]Cs_2CO_3 (0.7 equiv per halide).

In the presence of 0.75 equiv of Cs_2CO_3 when the reaction was performed at a lower loading of $Pd(CH_3CN)_2Cl_2$ (0.5 mol % per halide) and cataCXium A (1 mol % per halide) at room temperature, the yield of **3** decreased to 83% (entry 3, Table 2). However, a combination of an equivalent Cs_2CO_3 and $Pd(CH_3CN)_2Cl_2$ (0.5 mol % per halide) + cataCXium A (1 mol % per halide) resulted in a nearly quantitative yield of product **3** (entry 4, Table 2). Further decrease in the catalyst loading to 0.25 mol % lowered the yield of **3** (entry 5, Table 2). The optimized condition (entry 4, Table 2) was used to screen a series of Pd catalysts. While use of $Pd(dba)_2$ instead of $Pd(CH_3CN)_2Cl_2$ under otherwise similar conditions resulted in a slightly lowered yield of **3** (ca. 87%, entry 7, Table 2), the corresponding yields of **3** upon use of $Pd(OAc)_2$, $Pd(PPh_3)_2Cl_2$, and $Pd(PPh_3)_4$ were poor (entries 6, 8, and 9, Table 2).

The presence of cataCXium A is pivotal for obtaining good yields as is evident from the reactions performed in its absence where no product formation was observed (entries 10−12 and 14, Table 2), with the reaction catalyzed by $Pd(PPh_3)_2Cl_2$ as the only exception where 34% of **3** was observed (entry 13, Table 2). The similar yields obtained in the $Pd(PPh_3)_2Cl_2$-catalyzed reactions in the presence and in the absence of cataCXium A indicate that the latter has no role to play in reactions catalyzed by the former (entry 8 *vs* entry 13, Table 2).

Performing the reaction under the best conditions (entry 4, Table 2) but with toluene as the solvent resulted in no reactivity (entry 15, Table 2). Use of THF led to comparable reactivity (entry 16, Table 2). More importantly, the corresponding reaction in a readily available green solvent 2-MeTHF proceeded smoothly, giving rise to **3** in nearly quantitative yields (entry 17, Table 2). Reducing the reaction time resulted in lower yields of **3** (entry 18, Table 2). Thus, entry 17, Table 2, depicts the best optimized conditions of the current work where the challenging multifold Sonogashira coupling was accomplished using a catalytic system comprising an equivalent Cs_2CO_3 and $Pd(CH_3CN)_2Cl_2$ (0.5 mol %) + cataCXium A (1 mol %) in a green solvent 2-MeTHF at room temperature under copper-free and amine-free conditions.

The applicability of the optimized condition was tested for a series of multifold Sonogashira coupling reactions (Table 3). The twofold Sonogashira coupling of 2,6-dibromopyridine was accomplished with ease to yield the corresponding products **4a** and **4b** in moderate yields (Table 3).

While tetraiodo benzene gave 90% of the corresponding tetraalkynylated product **5a**, the reaction with the corresponding chloro analogue resulted in no reactivity (Table 3), which is in accordance with the C−X (X═Cl and I) bond strengths. This points to the involvement of the oxidative addition of the C−X bond in the rate-determining step (RDS) (see Scheme 1, *vide infra*). Moderate to poor reactivity (**6a** and **6b**, Table 3) was observed in the $Pd(CH_3CN)_2Cl_2$ (0.5 mol %) + cataCXium A (1 mol %)-catalyzed Cu-free and amine-free tetrafold Sonogashira coupling of tetrachloropyrazine at room temperature in 2-MeTHF.

On the other hand, very good yields of Sonogashira coupled products **7a−e** were obtained in the $Pd(CH_3CN)_2Cl_2$ (0.5 mol %) + cataCXium A (1 mol %)-catalyzed twofold coupling of dibromoanthracene at room temperature in 2-Me-THF. The excellent Sonogashira activity of $Pd(CH_3CN)_2Cl_2$ (0.5 mol %) + cataCXium A (1 mol %) toward formation of **3** was extended with equal success to accomplish the synthesis of several of its derivatives (**3a−d** and **3f−g**) albeit with little success in the case of **3e** that originates from a heterocycle-containing acetylene.

With an objective to probe the generic nature of the formulated protocol, the $Pd(CH_3CN)_2Cl_2$ (0.5 mol %) + cataCXium A (1 mol %)-catalyzed Sonogashira coupling in the presence of an equivalent of Cs_2CO_3 in 2-MeTHF at room temperature under copper-free and amine-free conditions was examined for simple substrates involving a onefold coupling. In general, all substrates gave good to excellent yields of products (Table 4). The poor yields of **8d** and **8l** can be attributed to the ability of the substrates to form chelates with Pd. Similar to the case discussed for **5a**, the yield of **8o** was dependent on the halo benzene substrate with the reactivity following the order

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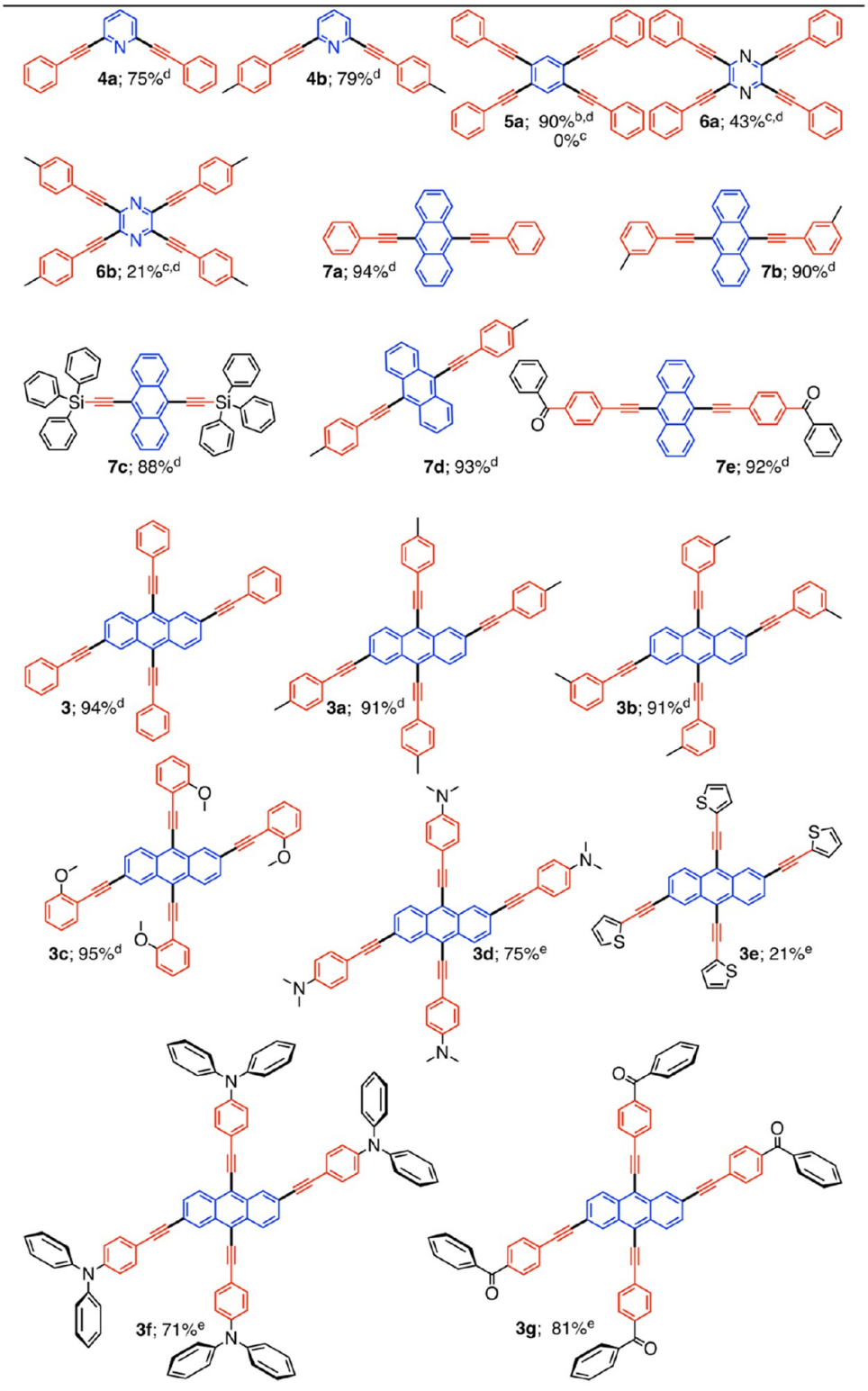
Table 3. $Pd(CH_3CN)_2Cl_2$ (0.5 mol %) + CataCXium A (1 mol %)-Catalyzed Cu-Free and Amine-Free Multifold Sonogashira Coupling at Room Temperature in 2-MeTHF Leading to Various PAHs[a]



[a]Reaction conditions: 0.101 mmol of aryl bromide, 0.606 mmol of arylacetylene (1.5 equiv per halide), 2 mol % $Pd(CH_3CN)_2Cl_2$ (0.5 mol % per halide), 4 mol % cataCXium A (1 mol % per halide), and 0.404 mmol Cs_2CO_3 (1 equiv per halide) in 2-methyltetrahydrofuran (5 mL) at room temperature under argon for 48 h. [b]Aryl iodide used. [c]Aryl chloride used. [d]Isolated yield. [e]Yield calculated from ^1H NMR by using toluene as the standard.

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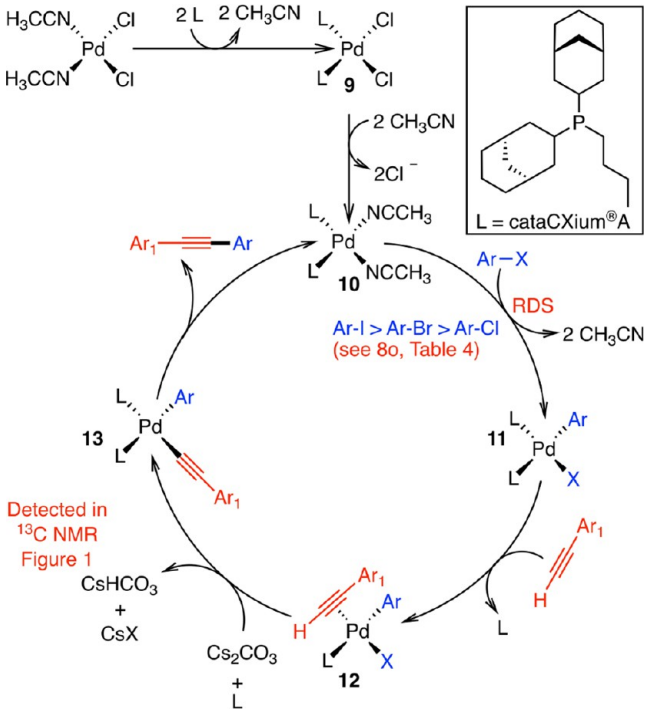
Scheme 1. Plausible Mechanism of $Pd(CH_3CN)_2Cl_2$ and CataCXium A-Catalyzed Cu-Free and Amine-Free Sonogashira Coupling



Ph-I > Ph-Br > Ph-Cl, which is again indicative of the involvement of the oxidative addition of the C−X bond in the rate-determining step (RDS).

In 2016, Mak computed the mechanism for Cu-free Sonogashira reaction at 90 °C using a catalytic system based on $Pd(CH_3CN)_2Cl_2$ and X-Phos-type ligands.[26] In accordance with their proposal and in line with the current observations, the plausible mechanism involved in $Pd(CH_3CN)_2Cl_2$ and cataCXium A-catalyzed Cu-free and amine-free Sonogashira coupling is depicted in Scheme 1. CataCXium A initiates the dissociation of acetonitrile from $Pd(CH_3CN)_2Cl_2$ to give **9**, which is followed by the reduction of Pd(II) in **9** to Pd(0) in **10**. A subsequent oxidative addition of the aryl halide to the Pd(0) center in **10** results in the Pd(II) species **11**. The reactivity of various aryl halides follows the order of C−X (X═Cl, Br, and I) bond strengths and demonstrates the trend Ar-I > Ar-Br > Ar-Cl. Considering the fact that the reaction is facile when an aryl iodide is used and that it slows down in the presence of an aryl chloride, it is likely that the oxidative addition is the RDS. The alkyne then coordinates to the Pd(II) center, giving rise to **12**, from which the Cs_2CO_3 abstracts the proton to give $CsHCO_3$ and the complex **13**. Notably, $CsHCO_3$ was detected by ^{13}C NMR in the reaction after workup in the aqueous fraction (Figure 1). The chemical shift of the bicarbonate carbon is in agreement with the reported value.[27] A final reductive elimination of the alkynylated arene product from **13** leads to the regeneration of the active catalyst **10**.

Anthracenes have been classified as "Group 3—non-classifiable as carcinogenic to human" by the United States Environmental Protection Agency (USEPA).[28] Studies have shown that anthracene derivatives can be used as potential anticancer drugs and chemotherapeutic agents, mainly in breast cancer (BC).[28,29] The most common problem with long-term treatment of cancer is multidrug resistance (MDR), and these anthracene derivatives show promising results in overcoming MDR resistance in cancer treatments.[29a,f] MHY412, a novel anthracene derivative, was successful in arresting BC cells in the sub-G1 phase of the cell cycle via inhibition of cyclin-dependent kinase 2 (CDK2) and the p21 expression in MCF-7/Adr cells.[29a] HL-37, another anthracene derivative, showed potential antitumor activity by inducing apoptosis in MDA-MB-435 and MCF-7 cells via the Ca^{2+}/caspase pathway.[29b] Radiotherapy (RT) and photodynamic therapy (PDT) were performed using anthracene and Ag@anthracene scintillating nanoparticles in colon cancer cell lines. This showed high singlet oxygen species generation ($^1O_2$), which in turn promotes cell death and apoptosis.[28] 7-Methylbenz(a)anthracene and three of its derivatives (7-bromomethyl-12-methylbenz(a)-anthracene,7-bromomethyl-12-methylbenz(a) anthracene, and 4-chloro-7-bromomethylbenz(a)anthracene) have shown anticancer activities against subcutaneous sarcomata in the lung and liver in mice.[30] Rubiasins- anthracene derivatives isolated from the roots and stems of *Rubia cordifilia* have shown chemotherapeutic activity against colon cancer cell lines.[29c] Aromatic azo-derivatives of anthracene have shown potential antitumor effects against BC and adrenal cancer.[29d]

All of these studies have shown that anthracene and its derivatives can induce cell death via DNA damage and inducing apoptosis. They also show selectivity toward rapidly dividing cancer cells.[31] Hence, it would be interesting to study the cytotoxic effects of the anthracenes obtained in the current study. Particular emphasis was laid on studying the cytotoxic effect of the new and less-explored tetraalkynylated anthracene derivatives on cancer cells based on BC cell lines to estimate the minimum inhibitory concentration and simultaneously compare the corresponding results with healthy human dermal fibroblast (HDF) cells.

The cytotoxicity of various tetraalkynylated anthracene derivatives was tested against MDA-MB-231 cell lines and HDF cells as shown in Figures 2 and 3, respectively. All of the tetraalkynylated anthracene derivatives exhibited a concentration-dependent antiproliferative activity. The IC_{50} values of anthracene derivatives (**3**, **3a**−**g**) for both MDA-MB-231 and HDF cells are presented in Table 5. Among all of the considered tetraalkynylated anthracene derivatives, **3c** and **3a** (Figure 2) showed a relatively higher anticancer effect when tested on the MDA-MB-231 cell line. These two compounds exhibited antiproliferative properties even at the lowest concentration (3.12 μM) tested.

In contrast, **3**, **3b**, and **3g** showed the least anticancer effect even at the concentration of 12.5 μM (Figure 2). A gradual increase in the antiproliferative effect was also noticed when the concentration of **3d** and **3b** increased from 6.25 to 100 μM (Figure 2). A similar trend in the antiproliferative effect of all of the considered tetraalkynylated anthracene derivatives (except for **3** and **3g**) with relatively reduced activity was also observed when tested against HDF cells (Figure 3). It is thus evident that the considered tetraalkynylated anthracene derivatives demonstrated an increased cytotoxic effect and selectivity against MDA-MB-231 cells as compared to the HDF cells under the same experimental condition IC_{50} value.

The live cell imaging experiment was conducted to demonstrate the fluorescence properties of tetraalkynylated anthracene derivatives in the living cells. 10 μM concentration was chosen for treatment to further confirm the extent of

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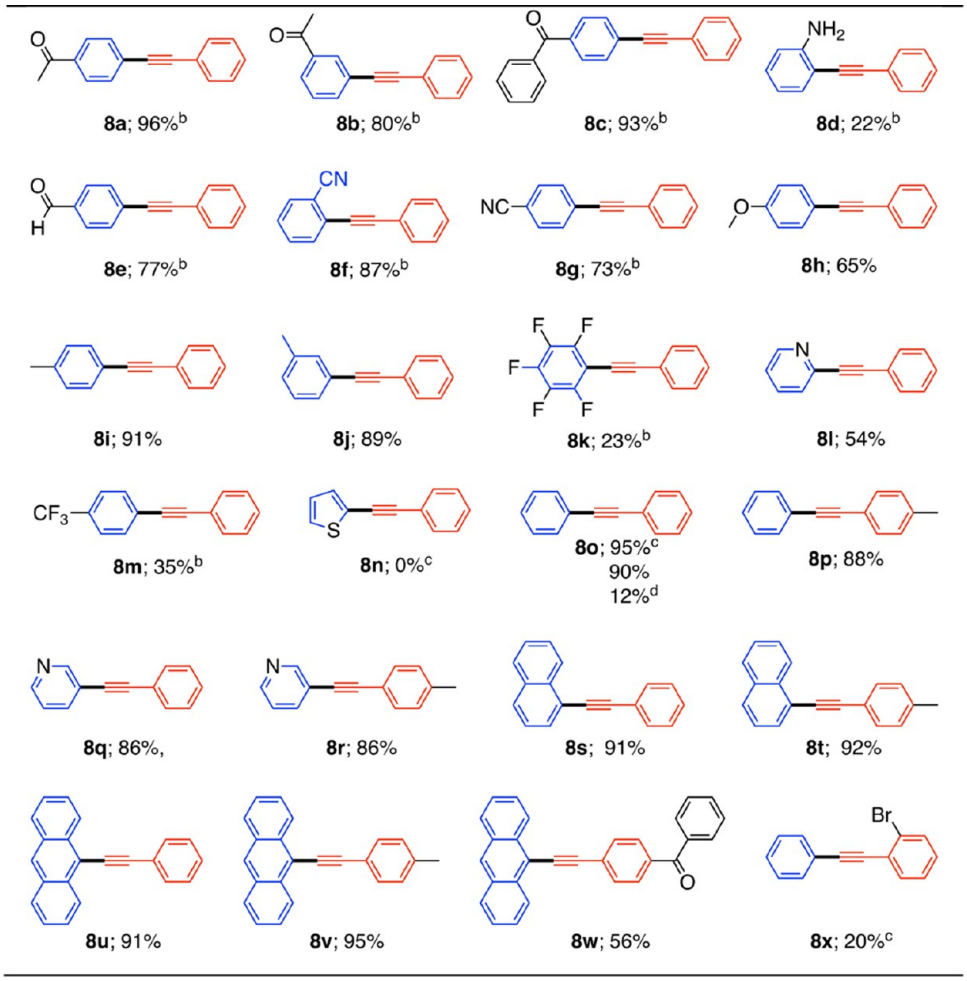
Table 4. $Pd(CH_3CN)_2Cl_2$ (0.5 mol %) + CataCXium A (1 mol %)-Catalyzed Cu-Free and Amine-Free Onefold Sonogashira Coupling at Room Temperature in 2-MeTHF[a]



[a]Reaction conditions: 0.5 mmol of aryl bromide, 1.5 mmol of arylacetylene, 0.5 mol % $Pd(CH_3CN)_2Cl_2$, 1 mol % cataCXium A, 0.5 mmol (1 equiv) Cs_2CO_3 in 2-methyltetrahydrofuran (5 mL) at room temperature under argon for 48 h. All are isolated yields. [b]1 mol % $Pd(CH_3CN)_2Cl_2$ and 2 mol % cataCXium A. [c]Aryl iodide. [d]Aryl chloride.

cellular localization of all of the anthracene derivatives when the same concentration was added to the cells (Figure 4). An intense green fluorescent signal was obtained when both HDF and MDA-MB-231 cells were treated with **3b**, **3c**, and **3d** (Figure 4). On the other hand, in stark contrast to MDA-MB-231 cells treated with **3** and **3a**, the corresponding **3**- and **3a**-treated HDF cells showed a bright-green fluorescence (Figure 4). However, when treated with **3g**, faint live cell fluorescence was observed from both MDA-MB-231 cells and HDF cells (Figure 4). Compound **3** did not show green fluorescence, which indicates that it has not entered the cell. Further, compound **3g** showed no or very faint green fluorescence, indicating less localization inside cells (Figure 4). The possible reason for compound **3g** not showing any localization could be attributed to its molecular structure that prevents its entry inside the cells. The fluorescent signal obtained was mainly confined to the cytoplasm of the cells, indicating cytoplasmic localization.

4′,6-Diamidino-2-phenylindole (DAPI) staining was performed to check if treatment with the tetraalkynylated anthracene derivatives resulted in nuclear fragmentation and apoptosis (Figure 5). The MDA-MB-231 cells (Figure 5) showed increased nuclear fragmentation, nuclear blebbing, and nuclear condensation as compared to HDF cells (Figure 6) under identical treatment conditions. This is commensurable with the results of the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay, which clearly shows that the tetraalkynylated anthracene derivatives display increased cytotoxicity and selectivity against the MDA-MB-231 cell line. DAPI staining in HDF cells shows the presence of numerous healthy rounded cells in each case as compared to MDA-MB-231 cells under the same experimental conditions, supporting the results obtained in the MTT assay (Figure 6). This indicates that the considered compounds affected the nuclear morphology to a higher extent in MDA-MB-231 cells as compared to HDF cells.

Propidium iodide (PI) staining was done to check whether the treatment with the tetraalkynylated anthracene derivatives resulted in membrane disruption. The MDA-MB-231 cells showed increased membrane disintegration (Figure 7) as compared to the HDF cells under the same treatment conditions (Figure 8). This is commensurable with the results of the MTT assay, which shows clearly that the tetraalkynylated anthracene derivatives display increased cytotoxicity and selectivity against the MDA-MB-231 cell line. The results obtained by PI staining clearly make it evident that the

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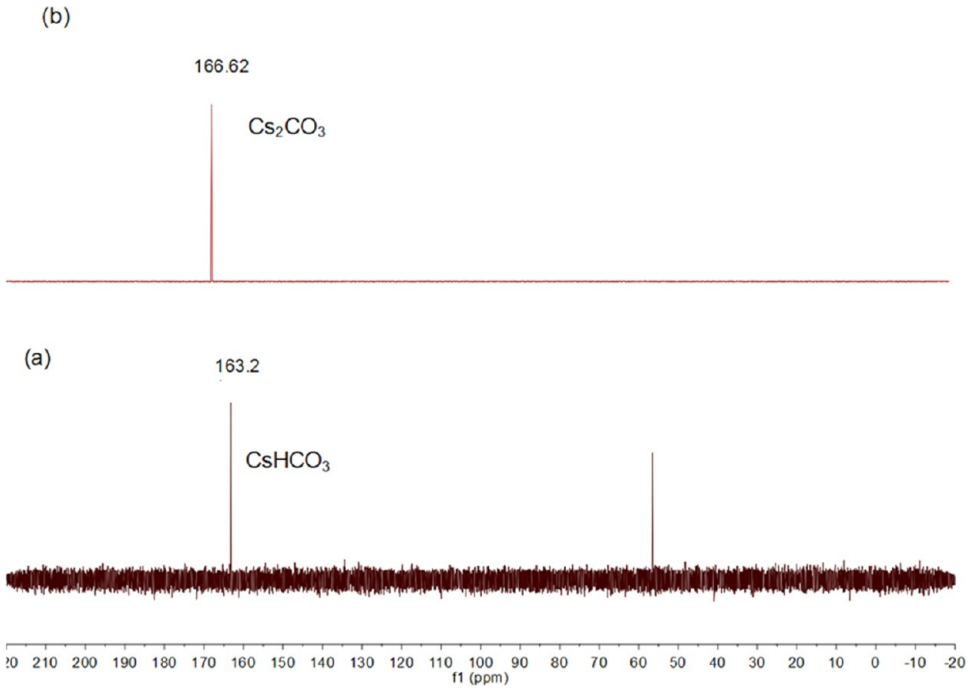

Figure 1. (a) Detection of $CsHCO_3$ in the aqueous fraction by ^{13}C NMR in the $Pd(CH_3CN)_2Cl_2$ and cataCXium A-catalyzed Sonogashira coupling reaction after workup. (b) Carbonate carbon in the ^{13}C NMR of Cs_2CO_3.

tetraalkynylated anthracene derivatives are more cytotoxic against the MDA-MB-231 cell line as compared to HDF cells. They have an inherent selectivity toward the rapidly proliferating cancer cells (Figures 7 and 8).

It is now evident that compound **3c** has the maximum cytotoxic effect as compared to the other compounds and shows more cytotoxicity in MDA-MB-231 cells compared to HDF cells (evident from the IC_{50} value presented in Table 5). However, as discussed previously, an extensive experiment involving multiple cancer cell types and respective normal cells is required to support the claim in the future. It displays extensive cellular localization at 10 μM. Compound **3d** is not cytotoxic at a low concentration of 10 μM in either MDA-MB-231 or HDF cells. Interestingly, it shows beautiful cellular localization at 10 μM (Figure 9). In both compounds, the cytoplasm gets stained while the nucleus remains unstained. Compounds **3c** and **3d** can be potential anticancer agents, which can be further used for bioimaging and diagnostic purposes (to detect cancer cells in a biopsy sample).

CONCLUSIONS

An efficient method for the multifold Sonogashira coupling of a variety of aryl halides with arylacetylene has been formulated using a catalytic system comprising $Pd(CH_3CN)_2Cl_2$ (0.5 mol %) and cataCXium A (1 mol %) in the presence of an equivalent of Cs_2CO_3 at room temperature under copper-free and amine-free conditions in a readily available green solvent. The reaction is tolerant to various substrates, and the coupled products were obtained in good to excellent yields. The reactivity of various aryl halide substrates was in accordance with the C−X (X═Cl, Br, and I) bond strength and followed the order Ar-I > Ar-Br > Ar-Cl. This is indicative of the fact that the oxidative addition of Ar-X is involved in the RDS of the overall catalytic cycle. The generic nature of the protocol was exhibited by accomplishing the Sonogashira coupling not only in a onefold but also in a multifold fashion, thereby obtaining access to various valuable polycyclic aromatic hydrocarbons (PAHs).

The application of one such class of PAHs that involves the tetraalkynylated anthracenes toward the investigation of their cytotoxic potentials was attempted. This led to an exciting set of observations that provided conclusive evidence for the possibility of two of the considered anthracene derivatives as potential candidates for anticancer therapy. Interestingly, the most efficient anthracene derivatives show cytotoxicity even at concentrations as low as 3.12 μM. The anthracene derivatives induced apoptosis via nuclear fragmentation and membrane disruption as inferred from DAPI and PI staining. More pronounced nuclear fragmentation and membrane disruption were noticed in the case of the MDA-MB-231 cells as compared to the HDF cells. This clearly is indicative of the probability of anthracene derivatives being selective toward the TNBC cell line. However, to further confirm the selectivity of the compounds toward a particular cancer type, an extensive biological experiment is required involving multiple cancer cells in a future work. Further, to understand the specificity (if any) toward cancer cells, comparison with respective normal cells would be a valuable finding to strengthen the current study. Gratifyingly, the anthracene derivatives that were not so cytotoxic are still valuable considering their exciting fluorescence properties, which renders them potentially promising fluorescent dyes for bioimaging purposes. The future scope of this study lies in the fact that being strongly fluorescent, these compounds can be used for bioimaging purposes.

EXPERIMENTAL SECTION

Materials and Methods. A constant supply of purified argon using a standard double manifold was used to perform all of the reactions, unless otherwise mentioned. Avra, Sigma-Aldrich, SRL, and Merck Chemicals were the principal suppliers for chemicals such as arylacetylene, aryl halides,

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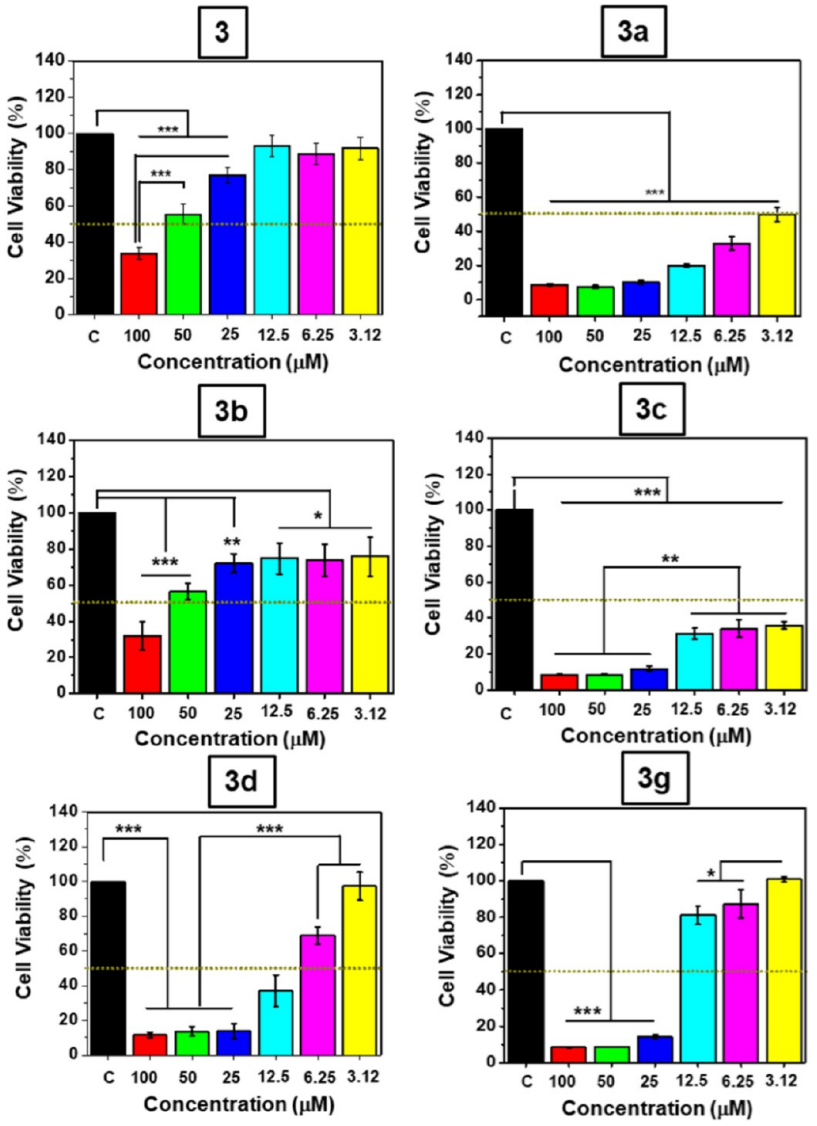

Figure 2. Cytotoxicity assessment of tetraalkynylated anthracene derivatives **3**, **3a**, **3b**, **3c**, **3d**, and **3g** against the MDA-MB-231 cell line. Data represent mean ± SD (n = 3), where ***$p \leq 0.001$, **$p \leq 0.01$, and *$p \leq 0.05$. Dotted lines represent 50% cell viability.

anthracene, bromine, $Pd(CH_3CN)_2Cl_2$, $Pd(PPh_3)_2Cl_2$, $Pd(PPh_3)_4$, $Pd(dba)_2$, $Pd(OAc)_2$, NaOEt, NaOH, KOH, Na^tOBu, K^tOBu, K_2CO_3, Cs_2CO_3, $NaHCO_3$, $KHCO_3$, and K_3PO_4, which were used without additional purification. Along with this, the solvents used in the experiments like 1,4-dioxane, toluene, tetrahydrofuran (THF), and 2-methyl tetrahydrofuran (2-MeTHF) were procured from Merck and were used without purification. All of the reactions were performed under an inert atmosphere and a closed system, unless otherwise mentioned. The reactions were monitored using thin-layer chromatography (TLC) analysis, and column chromatography was done to purify the required product by means of a Merck silica gel (100−200) mesh as the stationary phase.

The purified products were characterized via NMR analysis recorded by a Bruker AVANCE 400, Bruker AVANCE 500, and Bruker AVANCE 600 operating at 400, 500, and 600 MHz for ^1H NMR, at 110 MHz (Bruker AVANCE 400), 126 MHz (Bruker AVANCE 500), and 151 MHz (Bruker AVANCE 600) for $^{13}C\{^1H\}$ NMR, and at 377 MHz (Bruker AVANCE 400) and 471 MHz (Bruker AVANCE 500) for ^{19}F NMR. Peak characterization: s, singlet; d, doublet; t, triplet; and m, multiplet. High-resolution mass spectra (HRMS) and fast atom bombardment (FAB) analysis were acquired using the Agilent technologies model G6564 QTOF and a double focusing magnetic sector mass spectrometer, respectively, in addition to the electron impact (EI) ionization technique (magnetic sector-electric sector double focusing mass analyzer). Fourier transform infrared (FT-IR) measurements were documented using a PerkinElmer IR spectrometer. The melting points were recorded in an open capillary tube with the usage of the Buchi melting point B-540 apparatus.

General Synthetic Protocol for Sonogashira Coupling. A 10 mL Schlenk flask was taken, evacuated, and charged with argon three times. Aryl halide (1 equiv), arylacetylene (1.5 equiv per halide), $Pd(CH_3CN)_2Cl_2$ (0.5 or 1.0 mol % per halide), cataCXium A (1.0 or 2.0 mol % per halide), Cs_2CO_3 (1 equiv per halide), and 2-MeTHF (5 mL) were added and stirred at room temperature for 48 h. The reaction was monitored by TLC analysis. After completion of the reaction, the organic solvent was evaporated under reduced pressure. The reaction mixture was extracted by dichloro-

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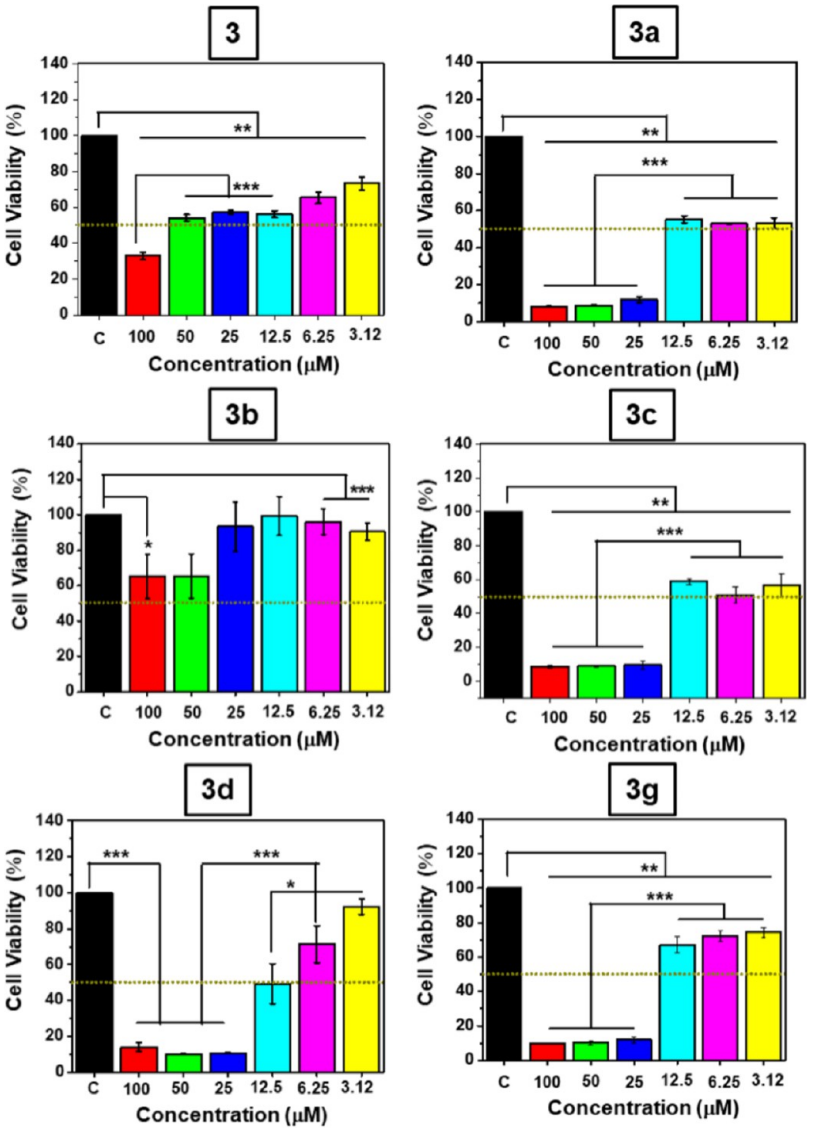

Figure 3. Cytotoxicity assessment of tetraalkynylated anthracene derivatives **3**, **3a**, **3b**, **3c**, **3d**, and **3g** against HDF cells. Data represent mean ± SD (n = 3), where ***$p \leq 0.001$, **$p \leq 0.01$, and *$p \leq 0.05$. Dotted lines represent 50% cell viability.

Table 5. IC_{50} Values of Anthracene Derivatives in MDA-MB-231 and HDF Cells

	IC_{50} (μM)	
compound	MDA-MB-231	HDF
3	50	12.5−50
3a	3.12	3.12−6.25
3b	50	50−100
3c	<3.12	3.12−6.25
3d	12.5	12.5
3g	12.5−25	12.5−25

methane (DCM)/EtOAc and washed with distilled H_2O (20 mL × 3). The organic phase was dried over anhydrous Na_2SO_4 and filtered, and then, the solvent was evaporated under reduced pressure. The yield of the product (wherever applicable) was calculated by recording the ^1H NMR of the crude product using toluene as the external standard. The crude product was purified by silica gel (100−200 mesh) column chromatography using a mixture of DCM/EtOAc and hexane as the eluent prior to determining the isolated yield.

*2,6,9,10-Tetrakis(phenylethynyl)anthracene (**3**).*[1c] Compound (**3**) was synthesized from 2,6,9,10-tetrabromoanthracene (50 mg, 0.101 mmol, 1 equiv), phenylacetylene (62 mg, 0.606 mmol, 1.5 equiv per halide), $Pd(CH_3CN)_2Cl_2$ (0.5 mg, 0.00202 mmol, 0.5 mol % per halide), cataCXium A (1.4 mg, 0.00404 mmol, 1 mol % per halide), and Cs_2CO_3 (131 mg, 0.404 mmol, 1.0 equiv per halide) by using a general synthetic protocol of the Sonogashira reaction. The crude product was passed through 100−200-mesh-size silica by using 50% DCM in hexane as the eluent, and the precipitate was obtained by slow evaporation of the solvent at room temperature. The product (55 mg) was obtained as an orange solid with 94% isolated yield. ^1H NMR (600 MHz, $CDCl_3$) δ 8.81 (s, 2H), 8.61 (d, J = 8.8 Hz, 2H), 7.87−7.76 (m, 4H), 7.69 (d, J = 8.8 Hz, 2H), 7.67−7.61 (m, 4H), 7.47 (dt, J = 12.0, 6.8 Hz, 6H), 7.40 (d, J = 7.1 Hz, 6H). $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 132.0, 132.0, 131.9, 131.7, 130.8, 129.6, 129.1, 128.7, 128.7, 128.5, 127.6, 123.3, 123.2, 122.1, 118.5, 103.2, 91.7, 90.1, 86.0.

*2,6,9,10-Tetrakis(p-tolylethynyl)anthracene (**3a**).*[1c] Compound (**3a**) was synthesized from 2,6,9,10-tetrabromoanthracene (50 mg, 0.101 mmol, 1 equiv), *p*-ethynyltoluene (70 mg,

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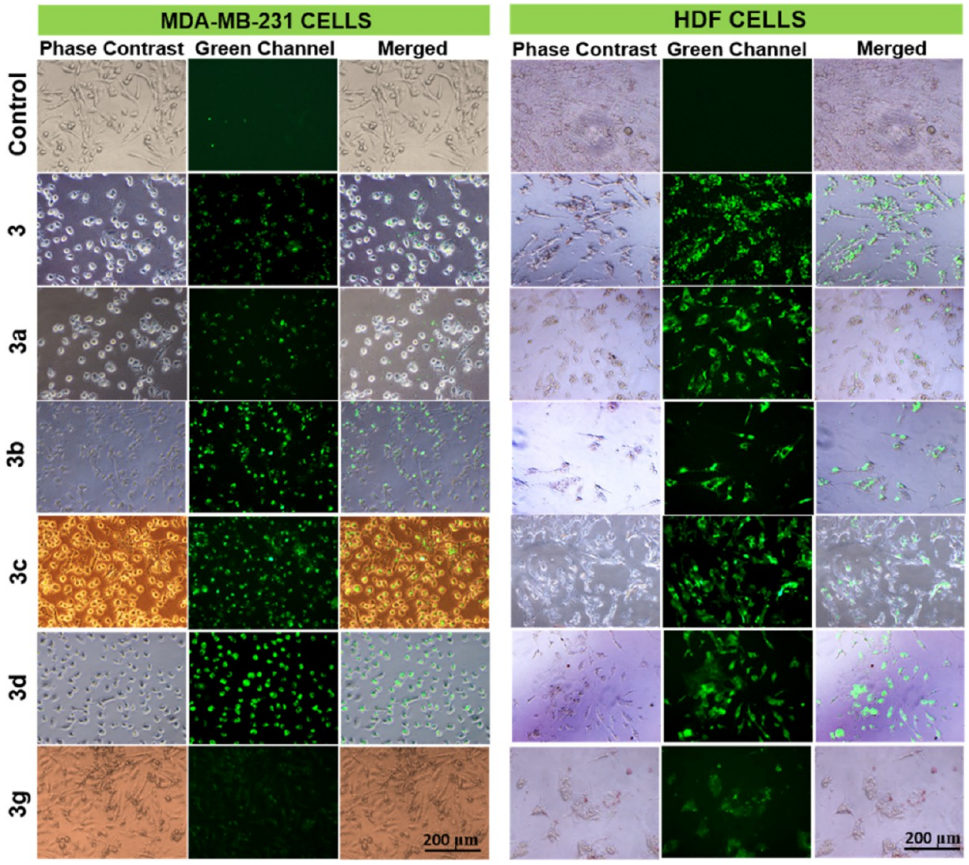

Figure 4. Fluorescence imaging of tetraalkynylated anthracene derivatives in living cells. Images presenting tetraalkynylated anthracene derivative-treated phase contrast microscopic images, fluorescent images of tetraalkynylated anthracene derivative-treated cells in the green channel, and merged images showing cellular localization of the tetraalkynylated anthracene derivatives.

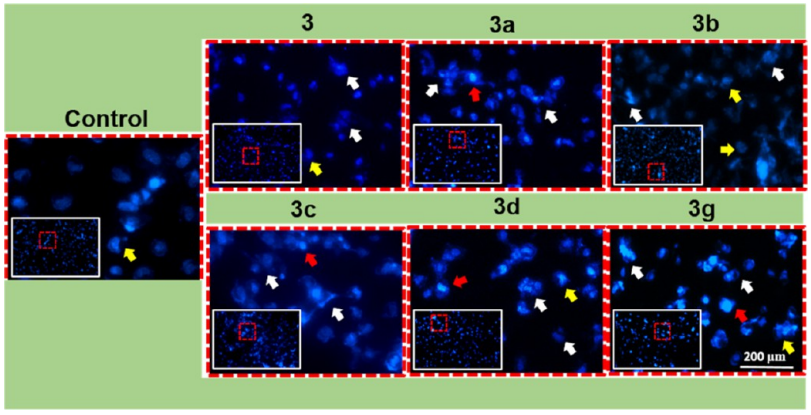

Figure 5. DAPI-stained cells after treatment with the tetraalkynylated anthracene derivatives **3**, **3a**, **3b**, **3c**, **3d**, and **3g** against the MDA-MB-231 cell line. The white arrows represent nuclear fragmentation, the yellow arrows represent nuclear blebbing, and the red arrows represent nuclear condensation.

0.606 mmol, 1.5 equiv per halide), $Pd(CH_3CN)_2Cl_2$ (0.5 mg, 0.00202 mmol, 0.5 mol % per halide), cataCXium A (1.4 mg, 0.00404 mmol, 1.0 mol % per halide), and Cs_2CO_3 (131 mg, 0.404 mmol, 1.0 equiv per halide) by using the general synthetic protocol of the Sonogashira reaction. The crude product was passed through 100−200-mesh-size silica by using 50% DCM in hexane as the eluent, and the precipitate was obtained by slow evaporation of the solvent at room temperature. The product (58 mg) was obtained as an orange solid with 91% isolated yield. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.79 (d, J = 1.6 Hz, 2H), 8.60 (d, J = 8.8 Hz, 2H), 7.70 (d, J = 7.8 Hz, 4H), 7.67 (dd, J = 8.8, 1.6 Hz, 2H), 7.53 (d, J = 8.0 Hz, 4H), 7.28 (d, J = 7.7 Hz, 4H), 7.20 (d, J = 7.7 Hz, 4H), 2.45 (s, 6H), 2.40 (s, 6H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 139.3, 138.8, 132.0, 131.8, 131.8, 131.6, 130.7, 129.5, 129.3, 127.6, 122.1, 120.3, 120.2, 118.4, 103.3, 91.8, 89.6, 85.5, 21.8, 21.7.

*2,6,9,10-Tetrakis(m-tolylethynyl)anthracene (**3b**).* Compound (**3b**) was synthesized from 2,6,9,10-tetrabromoanthracene (50 mg, 0.101 mmol, 1 equiv), *m*-ethynyltoluene (70 mg,

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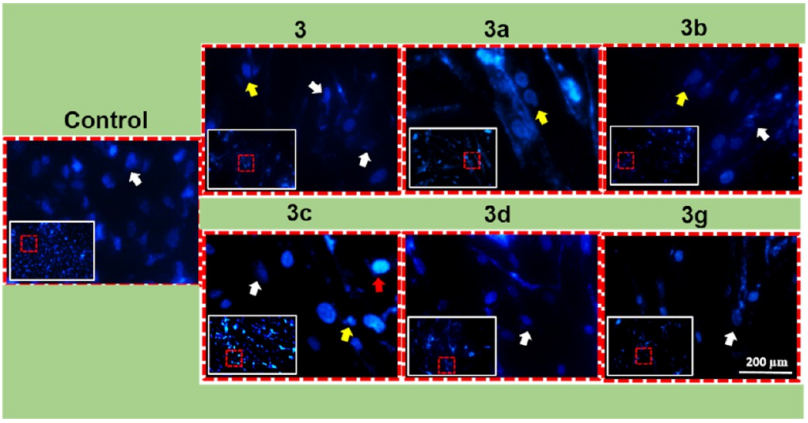

Figure 6. DAPI-stained cells after treatment with the tetraalkynylated anthracene derivatives: **3, 3a, 3b, 3c, 3d**, and **3g** against HDF cells. The white arrows represent nuclear fragmentation, the yellow arrows represent nuclear blebbing, and the red arrows represent nuclear condensation.

0.606 mmol, 1.5 equiv per halide), $Pd(CH_3CN)_2Cl_2$ (0.5 mg, 0.00202 mmol, 0.5 mol % per halide), cataCXium A (1.4 mg, 0.00404 mmol, 1.0 mol % per halide), and Cs_2CO_3 (131 mg, 0.404 mmol, 1.0 equiv per halide) by using the general synthetic protocol of the Sonogashira reaction. The crude product was passed through a 100−200-mesh-size silica by using 50% DCM in hexane as the eluent, and the precipitate was obtained by slow evaporation of the solvent at room temperature. The product (58 mg) was obtained as a red solid with 91% isolated yield. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.82 (s, 2H), 8.63 (d, J = 8.8 Hz, 2H), 7.69 (dd, J = 8.9, 1.6 Hz, 2H), 7.66−7.60 (m, 4H), 7.48 (s, 2H), 7.45 (d, J = 7.7 Hz, 2H), 7.37 (t, J = 7.6 Hz, 2H), 7.31−7.26 (m, 4H), 7.19 (d, J = 7.7 Hz, 2H), 2.46 (s, 6H), 2.39 (s, 6H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 138.5, 138.2, 132.5, 132.5, 132.0, 131.7, 130.8, 130.0, 129.6, 129.6, 129.1, 129.0, 128.6, 128.4, 127.6, 123.1, 123.0, 122.1, 118.5, 103.4, 91.9, 89.9, 85.7, 21.5, 21.4. FT-IR (KBr, cm^{-1}) 3057 (aromatic, C−H str), 3023 (aromatic, C−H str), 2951 (aromatic, C−H str), 2918 (aromatic, C−H str), 2853 (-CH_3, C−H str), 2190 (C≡C str), 1613 (aromatic, C═C str), 1598 (aromatic, C═C str), 1576 (aromatic, C═C str), 1484 (aromatic, C═C str). HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{50}H_{35}$ 635.2739, found 635.2706. Mp = 222−224 °C.

*2,6,9,10-Tetrakis((2-methoxyphenyl)ethynyl)anthracene (**3c**).*[1c] Compound (**3c**) was synthesized from 2,6,9,10-tetrabromoanthracene (50 mg, 0.101 mmol, 1 equiv), *o*-ethynylanisole (80 mg, 0.606 mmol, 1.5 equiv per halide), $Pd(CH_3CN)_2Cl_2$ (0.5 mg, 0.00202 mmol, 0.5 mol % per halide), cataCXium A (1.4 mg, 0.00404 mmol, 1.0 mol % per halide), and Cs_2CO_3 (131 mg, 0.404 mmol, 1.0 equiv per halide) by using the general synthetic protocol of the Sonogashira reaction. The crude product was passed through a 100−200-mesh-size silica by using 50% DCM in hexane as the eluent, and the precipitate was obtained by slow evaporation of the solvent at room temperature. The product (67 mg) was obtained as a red solid with 95% isolated yield. ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.10 (s, 2H), 8.74 (d, J = 8.8 Hz, 2H), 7.74 (d, J = 7.6 Hz, 4H), 7.60 (dd, J = 7.5, 1.8 Hz, 2H), 7.43−7.30 (m, 4H), 7.09−6.87 (m, 8H), 4.11 (s, 6H), 3.97 (s, 6H).^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 160.7, 160.2, 133.8, 133.0, 132.2, 131.5, 131.3, 130.3, 130.1, 129.5, 127.6, 122.1, 120.7, 120.7, 118.8, 112.9, 112.6, 110.9, 110.7, 99.8, 94.6, 91.0, 87.6, 56.0, 55.9.

*4,4′,4″,4‴-(Anthracene-2,6,9,10-tetrayltetrakis(ethyne-2,1-diyl))tetrakis(N,N-dimethylaniline) (**3d**).*[1c] Compound (**3d**) was synthesized from 2,6,9,10-tetrabromoanthracene (50 mg, 0.101 mmol, 1 equiv), *p*-ethynyl-*N*,*N*-dimethylaniline (88 mg, 0.606 mmol, 1.5 equiv per halide), $Pd(CH_3CN)_2Cl_2$ (0.5 mg, 0.00202 mmol, 0.5 mol % per halide), cataCXium A (1.4 mg, 0.00404 mmol, 1.0 mol % per halide), and Cs_2CO_3 (131 mg, 0.404 mmol, 1.0 equiv per halide) by using the general synthetic protocol of the Sonogashira reaction. The crude product was purified by column chromatography by using 60% DCM in hexane as the eluent. Yield 75%; brown solid; calculated by ^{1}H NMR. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.78 (s, 2H), 8.60 (d, J = 8.8 Hz, 2H), 7.68 (d, J = 8.7 Hz, 4H), 7.64 (d, J = 8.1 Hz, 2H), 7.52 (d, J = 8.7 Hz, 4H), 6.78 (d, J = 8.9 Hz, 4H), 6.70 (d, J = 8.8 Hz, 4H), 3.06 (s, 12H), 3.02 (s, 12H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 150.5, 150.3, 133.1, 133.1, 131.8, 131.3, 130.2, 129.2, 127.5, 122.1, 118.1, 112.1, 112.0, 110.3, 110.2, 104.3, 92.7, 88.7, 84.8, 40.4, 40.3.

*2,2′,2″,2‴-(Anthracene-2,6,9,10-tetrayltetrakis(ethyne-2,1-diyl))tetrathiophene (**3e**).*[1c] Compound (**3e**) was synthesized from 2,6,9,10-tetrabromoanthracene (50 mg, 0.101 mmol, 1 equiv), *o*-ethynylthiophene (66 mg, 0.606 mmol, 1.5 equiv per halide), $Pd(CH_3CN)_2Cl_2$ (0.5 mg, 0.00202 mmol, 0.5 mol % per halide), cataCXium A (1.4 mg, 0.00404 mmol, 1.0 mol % per halide), and Cs_2CO_3 (131 mg, 0.404 mmol, 1.0 equiv per halide) by using the general synthetic protocol of the Sonogashira reaction. The crude product was purified by column chromatography by using 40% DCM in hexane as the eluent. Yield 21%; yellow powder; calculated by ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.73 (d, J = 1.5 Hz, 2H), 8.55 (d, J = 8.9 Hz, 2H), 7.68 (dd, J = 8.9, 1.7 Hz, 2H), 7.56 (d, J = 3.7 Hz, 2H), 7.45 (d, J = 5.1 Hz, 2H), 7.40 (d, J = 3.6 Hz, 2H), 7.36 (d, J = 5.1 Hz, 2H), 7.15 (dd, J = 5.2, 3.5 Hz, 2H), 7.06 (dd, J = 5.2, 3.5 Hz, 2H).^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 132.9, 132.6, 131.8, 131.6, 130.6, 129.4, 128.5, 127.9, 127.6, 127.6, 127.4, 123.2, 123.0, 121.9 118.3, 96.5, 93.8, 89.8, 85.2.

*4,4′,4″,4‴-(Anthracene-2,6,9,10-tetrayltetrakis(ethyne-2,1-diyl))tetrakis(N,N-diphenylaniline) (**3f**).*[1c] Compound (**3f**) was synthesized from 2,6,9,10-tetrabromoanthracene (50 mg, 0.101 mmol, 1 equiv), *p*-ethynyl-*N*,*N*-diphenylaniline (163 mg, 0.606 mmol, 1.5 equiv per halide), $Pd(CH_3CN)_2Cl_2$ (0.5 mg, 0.00202 mmol, 0.5 mol % per halide), cataCXium A (1.4 mg, 0.00404 mmol, 1.0 mol % per halide), and Cs_2CO_3 (131 mg, 0.404 mmol, 1.0 equiv per halide) by using the general

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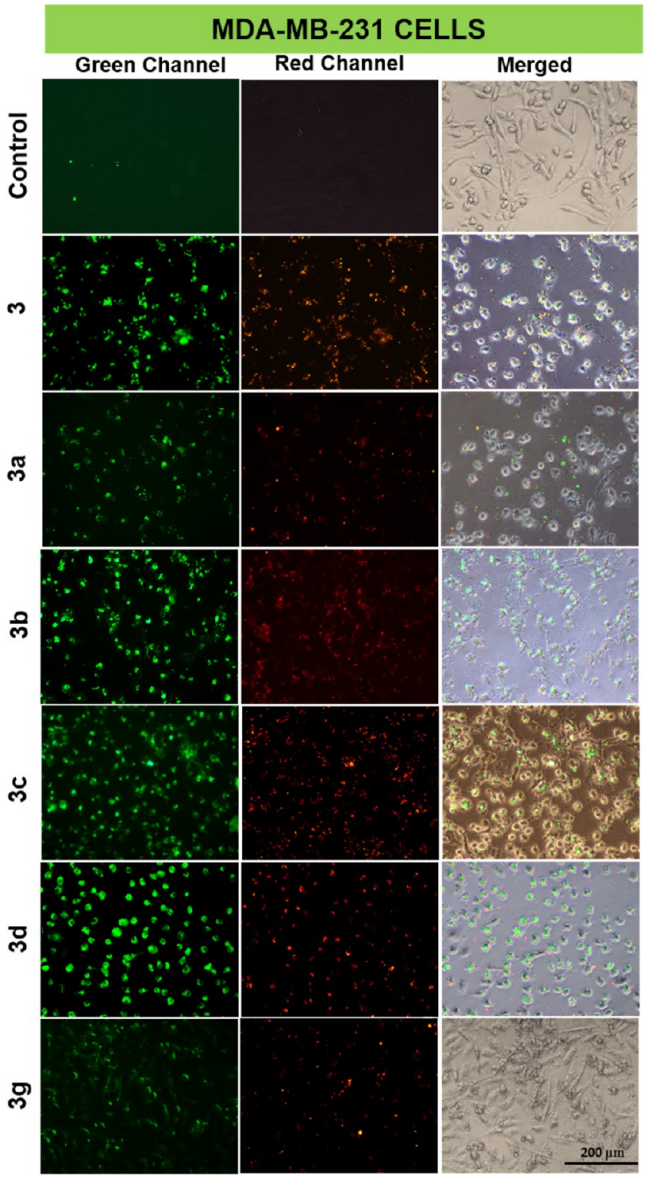

Figure 7. PI-stained cells after treatment with the tetraalkynylated anthracene derivatives: **3, 3a, 3b, 3c, 3d**, and **3g** against the MDA-MB-231 cell line. Images presenting fluorescent images of compound-treated cells in the green channel, fluorescent images of compound-treated cells in the red channel after PI staining, and merged images showing the presence of the red PI stain where membrane disruption has occurred due to cellular localization of the compounds inside the cells.

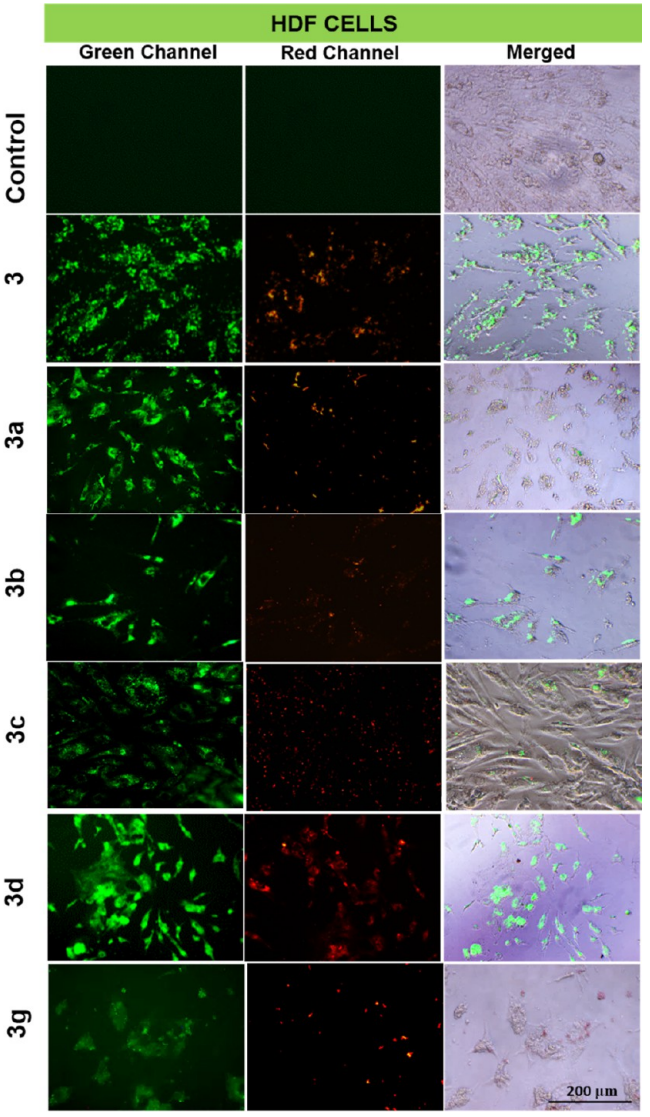

Figure 8. PI-stained cells after treatment with the tetraalkynylated anthracene derivatives: **3, 3a, 3b, 3c, 3d**, and **3g** against HDF cells. Images presenting fluorescent images of compound-treated cells in the green channel, fluorescent images of compound-treated cells in the red channel after PI staining, and merged images showing the presence of the red PI stain where membrane disruption has occurred due to cellular localization of the compounds inside the cells.

synthetic protocol of the Sonogashira reaction. The crude product was purified by column chromatography by using 70% DCM in hexane as the eluent. Yield 71%; maroon solid; calculated by ^{1}H NMR. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.76 (s, 2H), 8.58 (d, J = 8.9 Hz, 2H), 7.71−7.60 (m, 6H), 7.46 (d, J = 8.7 Hz, 4H), 7.37−7.25 (m, 16H), 7.21−6.98 (m, 32H).^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 148.6, 148.2, 147.3, 147.2, 132.9, 132.8, 131.9, 131.5, 130.5, 129.6, 129.5, 129.4, 127.6, 125.3, 125.2, 123.9, 123.7, 122.3, 122.1, 118.2, 116.0, 115.9, 103.6, 92.0, 89.7, 85.6.

*((Anthracene-2,6,9,10-tetrayltetrakis(ethyne-2,1-diyl))-tetrakis(benzene-4,1-diyl))tetrakis(phenylmethanone) (**3g**).*[1c] Compound (**3g**) was synthesized from 2,6,9,10-tetrabromoanthracene (50 mg, 0.101 mmol, 1 equiv), (*p*-ethynylphenyl)(phenyl)methanone (125 mg, 0.606 mmol, 1.5 equiv per halide), $Pd(CH_3CN)_2Cl_2$ (0.5 mg, 0.00202 mmol, 0.5 mol % per halide), cataCXium A (1.4 mg, 0.00404 mmol, 1.0 mol % per halide), and Cs_2CO_3 (131 mg, 0.404 mmol, 1.0 equiv per halide) by using the general synthetic protocol of the Sonogashira reaction. The crude product was purified by column chromatography by using 90% DCM in hexane as the eluent. Yield 81%; maroon solid; calculated by ^{1}H NMR. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.87 (s, 2H), 8.67 (d, J = 8.9 Hz, 2H), 7.94 (s, 8H), 7.89−7.73 (m, 18H), 7.63 (q, J = 7.2 Hz, 4H), 7.53 (q, J = 7.4 Hz, 8H).^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 195.9, 195.8, 137.5, 137.3, 137.3, 137.2, 132.7, 132.6, 132.0, 131.9, 131.6, 131.6, 131.0, 130.3, 130.2, 130.0, 130.0, 129.7, 128.4, 128.4, 127.6, 127.1, 127.0, 121.9, 118.5, 102.6, 92.7, 91.3, 88.5.

*2,6-Bis(phenylethynyl)pyridine (**4a**).*[32] Compound (**4a**) was synthesized from 2,6-dibromopyridine (100 mg, 0.42

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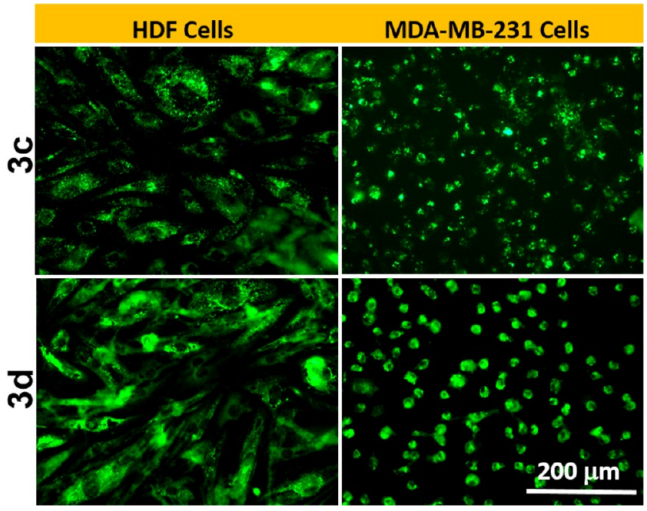

Figure 9. HDF cells and MDA-MB-231 cells stained with compounds **3c** and **3d**, showing an intense green fluorescence, which can be potential fluorescent dyes for bioimaging purposes.

mmol, 1 equiv), phenylacetylene (129 mg, 1.26 mmol, 1.5 equiv per halide), $Pd(CH_3CN)_2Cl_2$ (1.1 mg, 0.00422 mmol, 0.5 mol % per halide), cataCXium A (3 mg, 0.00844 mmol, 1.0 mol % per halide), and Cs_2CO_3 (274 mg, 0.844 mmol, 1.0 equiv per halide) by using the general synthetic protocol of the Sonogashira reaction. The crude product was purified by column chromatography by using 30% DCM in hexane as the eluent. The product (88 mg) was obtained as a white-color solid with 75% isolated yield. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.69 (t, J = 7.8 Hz, 1H), 7.61 (d, J = 5.0 Hz, 4H), 7.48 (d, J = 7.8 Hz, 2H), 7.37 (d, J = 5.9 Hz, 6H). $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 143.9, 136.6, 132.2, 129.2, 128.5, 126.3, 122.2, 89.9, 88.3.

*2,6-Bis(p-tolylethynyl)pyridine (**4b**).*[33] Compound (**4b**) was synthesized from 2,6-dibromopyridine (100 mg, 0.42 mmol, 1 equiv), *p*-ethynyltoluene (146 mg, 1.26 mmol, 1.5 equiv per halide), $Pd(CH_3CN)_2Cl_2$ (1.09 mg, 0.00422 mmol, 1.0 mol %), cataCXium A (3 mg, 0.00844 mmol, 2.0 mol %), and Cs_2CO_3 (274 mg, 0.844 mmol, 1.0 equiv per halide) by using the general synthetic protocol of the Sonogashira reaction. The crude product was purified by column chromatography by using 30% DCM in hexane as the eluent. The product (102 mg) was obtained as a white-color solid with 79% isolated yield. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.66 (t, J = 7.8 Hz, 1H), 7.50 (d, J = 7.8 Hz, 4H), 7.45 (d, J = 7.8 Hz, 2H), 7.17 (d, J = 7.8 Hz, 4H), 2.38 (s, 6H). $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 144.0, 139.5, 136.5, 132.1, 129.3, 126.1, 119.2, 90.2, 87.9, 21.7.

*1,2,4,5-Tetrakis(phenylethynyl)benzene (**5a**).*[34] Compound (**5a**) was synthesized from 1,2,4,5-tetraiodobenzene (100 mg, 0.17 mmol, 1 equiv), phenylacetylene (105 mg, 1.03 mmol, 1.5 equiv per halide), $Pd(CH_3CN)_2Cl_2$ (0.9 mg, 0.0034 mmol, 0.5 mol % per halide), cataCXium A (2.5 mg, 0.0070 mmol 1.0 mol % per halide), and Cs_2CO_3 (228 mg, 0.7 mmol, 1 equiv per halide) by using the general synthetic protocol of the Sonogashira reaction. The crude product was purified by column chromatography by using hexane as the eluent. The product (73 mg) was obtained as a white solid with 90% isolated yield. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.77 (s, 2H), 7.62−7.54 (m, 8H), 7.37 (d, J = 2.8 Hz, 12H). $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 135.0, 131.9, 128.9, 128.6, 125.5, 123.1, 95.6, 87.6.

*2,3,5,6-Tetrakis(phenylethynyl)pyrazine (**6a**).*[35] Compound (**6a**) was synthesized from tetrachloropyrazine (100 mg, 0.46 mmol, 1 equiv), phenylacetylene (281 mg, 2.76 mmol, 1.5 equiv per halide), $Pd(CH_3CN)_2Cl_2$ (2.4 mg, 0.00918 mmol, 0.5 mol % per halide), cataCXium A (6.6 mg, 0.01836 mmol 1.0 mol % per halide), and Cs_2CO_3 (598 mg, 1.836 mmol, 1 equiv per halide) by using the general synthetic protocol of the Sonogashira reaction. The crude product was purified by column chromatography by using 30% DCM in hexane as the eluent. The product (95 mg) was obtained as an orange solid with 43% isolated yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (dd, J = 7.9, 1.8 Hz, 8H), 7.50−7.33 (m, 12H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 139.2, 132.4, 130.0, 128.7, 121.8, 97.9, 86.2.

*2,3,5,6-Tetrakis(p-tolylethynyl)pyrazine (**6b**).*[35] Compound (**6b**) was synthesized from tetrachloropyrazine (100 mg, 0.46 mmol, 1 equiv), *p*-ethynyltoluene (281 mg, 2.76 mmol, 1.5 equiv per halide), $Pd(CH_3CN)_2Cl_2$ (2.4 mg, 0.00918 mmol, 0.5 mol % per halide), and cataCXium A (6.6 mg, 0.01836 mmol 1.0 mol % per halide) by using the general synthetic protocol of the Sonogashira reaction. The crude product was purified by column chromatography by using hexane as the eluent. The product (52 mg) was obtained as a white solid with 21% isolated yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, J = 7.9 Hz, 8H), 7.20 (d, J = 7.8 Hz, 7H), 2.40 (s, 12H). $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 140.4, 139.1, 132.3, 129.5, 118.8, 98.1, 85.9, 21.8.

*9,10-Bis(phenylethynyl)anthracene (**7a**).*[36] Compound (**7a**) was synthesized from 9,10-dibromoanthracene (100 mg, 0.30 mmol, 1 equiv), phenylacetylene (92 mg, 0.9 mmol, 1.5 equiv per halide), $Pd(CH_3CN)_2Cl_2$ (0.8 mg, 0.003 mmol, 0.5 mol % per halide), cataCXium A (2.1 mg, 0.006 mmol, 1.0 mol % per halide), and Cs_2CO_3 (193 mg, 0.6 mmol, 1.0 equiv per halide) by using the general synthetic protocol of the Sonogashira reaction. The crude product was purified by column chromatography by using hexane as the eluent. The product (107 mg) was obtained as a brown-color solid with 94% isolated yield. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.70 (dd, J = 6.6, 3.3 Hz, 4H), 7.82−7.75 (m, 4H), 7.65 (dd, J = 6.7, 3.2 Hz, 4H), 7.53−7.39 (m, 6H). $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 132.2, 131.8, 128.8, 128.7, 127.4, 126.9, 123.5, 118.6, 102.5, 86.6.

*9,10-Bis(m-tolylethynyl)anthracene (**7b**).* Compound (**7b**) was synthesized from 9,10-dibromoanthracene (100 mg, 0.30 mmol, 1 equiv), *m*-ethynyltoluene (104 mg, 0.90 mmol, 1.5 equiv per halide), $Pd(CH_3CN)_2Cl_2$ (0.8 mg, 0.003 mmol, 0.5 mol % per halide), cataCXium A (2.1 mg, 0.006 mmol, 1.0 mol % per halide), and Cs_2CO_3 (193 mg, 0.6 mmol, 1.0 equiv per halide) by using the general synthetic protocol of the Sonogashira reaction. The crude product was purified by column chromatography by using hexane as the eluent. The product (110 mg) was obtained as an orange-color solid with 90% isolated yield. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.70 (dd, J = 6.6, 3.3 Hz, 4H), 7.65 (dd, J = 6.7, 3.2 Hz, 4H), 7.62−7.55 (m, 4H), 7.35 (t, J = 7.6 Hz, 2H), 7.26−7.22 (m, 2H), 2.45 (s, 6H). $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 138.4, 132.3, 132.2, 129.7, 128.9, 128.6, 127.4, 126.9, 123.3, 118.6, 102.7, 86.3, 21.4. FT-IR (KBr, cm^{-1}) 3055 (aromatic, C−H str), 2950 (aromatic, C−H str), 2916 (aromatic, C−H str), 2845 (-CH_3 C−H str) 2190 (C≡C str), 1598 (aromatic, C=C str), 1575 (aromatic, C=C str), 1486 (aromatic, C=C str). HRMS

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(ESI) m/z $[M + H]^+$ calcd for $C_{32}H_{23}$ 407.1800, found 407.1789. Mp = 182−184 °C.

*9,10-Bis((triphenylsilyl)ethynyl)anthracene (**7c**).* Compound (**7c**) was synthesized from 9,10-dibromoanthracene (100 mg, 0.30 mmol, 1 equiv), ethynyltriphenylsilane (256 mg, 0.90 mmol, 1.5 equiv per halide), $Pd(CH_3CN)_2Cl_2$ (0.8 mg, 0.003 mmol, 0.5 mol % per halide), cataCXium A (2.1 mg, 0.006 mmol, 1.0 mol % per halide), and Cs_2CO_3 (193 mg, 0.6 mmol, 1.0 equiv per halide) by using the general synthetic protocol of the Sonogashira reaction. The crude product was purified by column chromatography by using hexane as the eluent. The product (194 mg) was obtained as a brown-color solid with 88% isolated yield. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.65 (dd, J = 6.7, 3.3 Hz, 4H), 7.93−7.78 (m, 12H), 7.59 (dd, J = 6.8, 3.3 Hz, 4H), 7.46 (dt, J = 14.3, 7.0 Hz, 18H). $^{13}C\{^1H\}$ NMR(151 MHz, $CDCl_3$) δ 135.8, 133.5, 132.8, 130.2, 128.3, 127.4, 118.6, 106.1, 103.4. FT-IR (KBr, cm^{-1}) 3067 (aromatic, C−H str), 3049 (aromatic, C−H str), 2916 (aromatic, C−H str), 2955 (aromatic, C−H str), 2916 (aromatic, C−H str), 2127 (C≡C str), 1427 (aromatic, C=C str), 1374 (aromatic, C=C str). HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{54}H_{39}Si_2$ 743.2590, found 743.2575. Mp = 249−251 °C.

*9,10-Bis(p-tolylethynyl)anthracene (**7d**).*[37] Compound (**7d**) was synthesized from 9,10-dibromoanthracene (100 mg, 0.30 mmol, 1 equiv), *p*-ethynyltoluene (104 mg, 0.90 mmol, 1.5 equiv per halide), $Pd(CH_3CN)_2Cl_2$ (0.8 mg, 0.003 mmol, 0.5 mol % per halide), cataCXium A (2.1 mg, 0.006 mmol, 1.0 mol % per halide), and Cs_2CO_3 (193 mg, 0.6 mmol, 1.0 equiv per halide) by using the general synthetic protocol of the Sonogashira reaction. The crude product was purified by column chromatography by using hexane as the eluent. The product (113 mg) was obtained as a brown-color solid with 93% isolated yield. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.69 (dd, J = 6.7, 3.3 Hz, 4H), 7.67 (d, J = 7.7 Hz, 4H), 7.63 (dd, J = 6.8, 3.2 Hz, 4H), 7.27 (d, J = 8.1 Hz, 4H), 2.44 (s, 6H). $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 139.0, 132.2, 131.7, 129.4, 127.4, 126.8, 120.5, 118.6, 102.7, 86.0, 21.7.

*((Anthracene-9,10-diylbis(ethyne-2,1-diyl))bis(4,1-phenylene))bis(phenylmethanone) (**7e**).* Compound (**7e**) was synthesized from 9,10-dibromoanthracene (50 mg, 0.15 mmol, 1 equiv), (*p*-ethynylphenyl)(phenyl)methanone (92 mg, 0.45 mmol, 1.5 equiv per halide), $Pd(CH_3CN)_2Cl_2$ (0.4 mg, 0.0015 mmol, 0.5 mol % per halide), cataCXium A (1.0 mg, 0.006 mmol, 1.0 mol % per halide), and Cs_2CO_3 (193 mg, 0.003 mmol, 1.0 equiv per halide) by using the general synthetic protocol of the Sonogashira reaction. The crude product was purified by column chromatography by using 60% DCM in hexane as the eluent. The product (80 mg) was obtained as an orange-color solid with 92% isolated yield. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.71 (ddd, J = 6.7, 3.3, 1.7 Hz, 4H), 7.91 (q, J = 7.4, 6.7 Hz, 8H), 7.85 (d, J = 8.1 Hz, 4H), 7.72−7.67 (m, 4H), 7.64 (t, J = 7.3 Hz, 2H), 7.53 (t, J = 7.6 Hz, 4H). $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 196.0, 137.5, 137.3, 132.8, 132.3, 131.6, 130.4, 130.1, 128.5, 127.6, 127.3, 127.3, 118.6, 102.0, 89.5. FT-IR (KBr, cm^{-1}) 3055 (aromatic, C−H str), 3045 (aromatic, C−H str), 2196 (C≡C str), 1650 (C=O str), 1596 (aromatic, C=C str). HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{44}H_{27}O_2$ 587.2011, found 587.2004. Mp = 249−251 °C.

*1-(4-(Phenylethynyl)phenyl)ethan-1-one (**8a**).*[38] Compound (**8a**) was synthesized from *p*-bromoacetophenone (100 mg, 0.5 mmol, 1 equiv), phenylacetylene (77 mg, 0.75 mmol, 1.5 equiv per halide), $Pd(CH_3CN)_2Cl_2$ (1.3 mg, 0.005 mmol, 1.0 mol %), cataCXium A (3.6 mg, 0.010 mmol, 2.0 mol %), and Cs_2CO_3 (162 mg, 0.5 mmol, 1.0 equiv) by using the general synthetic protocol of the Sonogashira reaction. The crude product was purified by column chromatography by using 2% ethyl acetate in hexane as the eluent. The product (106 mg) was obtained as a white solid with 96% isolated yield. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.94 (d, J = 8.4 Hz, 2H), 7.61 (d, J = 8.4 Hz, 2H), 7.55 (d, J = 3.9 Hz, 2H), 7.37 (d, J = 3.3 Hz, 3H), 2.62 (s, 3H).$^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 197.5, 136.3, 131.8, 131.8, 128.9, 128.5, 128.4, 128.3, 122.7, 92.8, 88.7, 26.7.

*1-(3-(Phenylethynyl)phenyl)ethan-1-one (**8b**).*[39] Compound (**8b**) was synthesized from *m*-bromoacetophenone (100 mg, 0.5 mmol, 1 equiv), phenylacetylene (77 mg, 0.75 mmol, 1.5 equiv per halide), $Pd(CH_3CN)_2Cl_2$ (1.3 mg, 0.005 mmol, 1.0 mol %), cataCXium A (3.6 mg, 0.010 mmol, 2.0 mol %), and Cs_2CO_3 (162 mg, 0.5 mmol, 1.0 equiv) by using the general synthetic protocol of the Sonogashira reaction. The crude product was purified by column chromatography by using 2% ethyl acetate in hexane as the eluent. The product (88 mg) was obtained as a brown liquid with 80% isolated yield. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.11 (s, 1H), 7.92 (d, J = 7.9 Hz, 1H), 7.71 (d, J = 7.6 Hz, 1H), 7.55 (d, J = 3.9 Hz, 2H), 7.46 (t, J = 7.7 Hz, 1H), 7.36 (s, 3H), 2.63 (s, 3H). $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 197.5, 137.3, 135.9, 131.8, 131.7, 128.8, 128.7, 128.5, 127.9, 124.0, 122.9, 90.5, 88.4, 26.7.

*Phenyl(4-(phenylethynyl)phenyl)methanone (**8c**).*[40] Compound (**8c**) was synthesized from *p*-bromobenzophenone (100 mg, 0.38 mmol, 1 equiv), phenylacetylene (58 mg, 0.57 mmol, 1.5 equiv per halide), $Pd(CH_3CN)_2Cl_2$ (1 mg, 0.0038 mmol, 1.0 mol %), cataCXium A (2.7 mg, 0.0076 mmol, 2.0 mol %), and Cs_2CO_3 (124 mg, 0.38 mmol, 1.0 equiv) by using the general synthetic protocol of the Sonogashira reaction. The crude product was purified by column chromatography by using 5% ethyl acetate in hexane as the eluent. The product (101 mg) was obtained as an off-white solid with 93% isolated yield. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.80 (d, J = 7.4 Hz, 4H), 7.62 (dd, J = 21.1, 7.7 Hz, 3H), 7.56 (d, J = 3.8 Hz, 2H), 7.50 (t, J = 7.6 Hz, 2H), 7.38 (d, J = 3.8 Hz, 3H). $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 196.1, 137.6, 136.9, 132.6, 131.9, 131.5, 130.2, 130.1, 128.9, 128.6, 128.5, 127.7, 122.8, 92.6, 88.8.

*2-(Phenylethynyl)aniline (**8d**).*[41] Compound (**8d**) was synthesized from *o*-bromoaniline (100 mg, 0.58 mmol, 1 equiv), phenylacetylene (89 mg, 0.87 mmol, 1.5 equiv per halide), $Pd(CH_3CN)_2Cl_2$ (1.5 mg, 1.0 mol %), cataCXium A (4.1 mg, 2.0 mol %), and Cs_2CO_3 (188 mg, 0.58 mmol, 1.0 equiv) by using the general synthetic protocol of the Sonogashira reaction. The crude product was purified by column chromatography by using 30% ethyl acetate in hexane as the eluent. The product (25 mg) was obtained as a brown solid with 22% isolated yield. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.53 (d, J = 6.1 Hz, 2H), 7.36 (dd, J = 14.0, 6.7 Hz, 4H), 7.15 (t, J = 7.2 Hz, 1H), 6.73 (d, J = 7.9 Hz, 2H), 4.28 (s, 2H). $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 147.9, 132.2, 131.6, 129.8, 128.5, 128.3, 123.4, 118.1, 114.4, 108.0, 94.8, 86.0.

*p-(Phenylethynyl)benzaldehyde (**8e**).*[42] Compound (**8e**) was synthesized from *p*-bromobenzaldehyde (100 mg, 0.54 mmol, 1 equiv), phenylacetylene (83 mg, 0.81 mmol, 1.5 equiv per halide), $Pd(CH_3CN)_2Cl_2$ (1.4 mg, 0.0054 mmol, 1.0 mol %), cataCXium A (3.9 mg, 0.0108 mmol, 2.0 mol %), and Cs_2CO_3 (0.81 mmol, 1.0 equiv) by using the general synthetic protocol of the Sonogashira reaction. The crude product was purified by column chromatography by using hexane as the

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eluent. The product (86 mg) was obtained as a brown liquid with 77% isolated yield. ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.02 (s, 1H), 7.87 (d, J = 7.8 Hz, 2H), 7.68 (d, J = 7.8 Hz, 2H), 7.56 (dd, J = 6.6, 3.0 Hz, 2H), 7.43−7.33 (m, 3H). $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 191.6, 135.5, 132.2, 131.9, 129.7, 129.7, 129.1, 128.6, 122.6, 93.6, 88.6.

*o-(Phenylethynyl)benzonitrile (**8f**).*[43] Compound (**8f**) was synthesized from *o*-bromobenzonitrile (100 mg, 0.55 mmol, 1 equiv), phenylacetylene (84 mg, 0.82 mmol, 1.5 equiv per halide), $Pd(CH_3CN)_2Cl_2$ (1.4 mg, 0.0055 mmol, 1.0 mol %), cataCXium A (3.9 mg, 0.011 mmol, 2.0 mol %), and Cs_2CO_3 (178 mg, 0.55 mmol, 1.0 equiv) by using the general synthetic protocol of the Sonogashira reaction. The crude product was purified by column chromatography by using 5% ethyl acetate in hexane as the eluent. The product (97 mg) was obtained as a brown liquid with 87% isolated yield. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.67 (d, J = 7.8 Hz, 1H), 7.62 (s, 3H), 7.57 (t, J = 7.7 Hz, 1H), 7.44−7.36 (m, 4H). $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 132.7, 132.5, 132.2, 132.1, 129.3, 128.5, 128.3, 127.3, 122.1, 117.6, 115.4, 96.1, 85.7.

*p-(Phenylethynyl)benzonitrile (**8g**).*[43] Compound (**8g**) was synthesized from *p*-bromobenzonitrile (100 mg, 0.55 mmol, 1 equiv), phenylacetylene (84 mg, 0.82 mmol, 1.5 equiv per halide), $Pd(CH_3CN)_2Cl_2$ (1.4 mg, 0.0055 mmol, 1.0 mol %), cataCXium A (3.94 mg, 0.011 mmol, 2.0 mol %), and Cs_2CO_3 (178 mg, 0.55 mmol, 1.0 equiv) by using the general synthetic protocol of the Sonogashira reaction. The crude product was purified by column chromatography by using hexane as the eluent. The product (81 mg) was obtained as a white solid with 73% isolated yield. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.64 (d, J = 8.1 Hz, 2H), 7.61 (d, J = 8.0 Hz, 2H), 7.55 (dd, J = 6.4, 2.7 Hz, 2H), 7.38 (d, J = 5.3 Hz, 3H). $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 132.2, 132.2, 131.9, 129.2, 128.6, 128.4, 122.3, 118.6, 111.6, 93.9, 87.8.

*1-Methoxy-4-(phenylethynyl)benzene (**8h**).*[38] Compound (**8h**) was synthesized from *p*-bromoanisole (100 mg, 0.53 mmol, 1 equiv), phenylacetylene (82 mg, 0.80 mmol, 1.5 equiv per halide), $Pd(CH_3CN)_2Cl_2$ (0.7 mg, 0.0027 mmol 0.5 mol %), cataCXium A (1.9 mg, 0.0053 1.0 mol %), and Cs_2CO_3 (173 mg, 0.53 mmol, 1.0 equiv) by using the general synthetic protocol of the Sonogashira reaction. The crude product was purified by column chromatography by using hexane as the eluent. The product (72 mg) was obtained as an off-white solid with 65% isolated yield. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.54−7.50 (m, 2H), 7.50−7.45 (m, 2H), 7.38−7.29 (m, 3H), 6.88 (d, J = 8.8 Hz, 2H), 3.83 (s, 3H). $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 159.7, 133.2, 131.5, 128.4, 128.0, 123.7, 115.5, 114.1, 89.5, 88.2, 55.4.

*1-Methyl-4-(phenylethynyl)benzene (**8i** and **8p**).*[44] Compound (**8i**) was synthesized from *p*-bromotoluene (100 mg, 0.58 mmol, 1 equiv), phenylacetylene (89 mg, 0.87 mmol, 1.5 equiv per halide), $Pd(CH_3CN)_2Cl_2$ (0.8 mg, 0.0029 mmol, 0.5 mol %), cataCXium A (2 mg, 0.0058 mmol, 1.0 mol %), and Cs_2CO_3 (189 mg, 0.58 mmol, 1.0 equiv) by using the general synthetic protocol of the Sonogashira reaction. The crude product was purified by column chromatography by using hexane as the eluent. Compound (**8p**) was synthesized from bromobenzene (100 mg, 0.64 mmol, 1 equiv), *p*-ethynyltoluene (112 mg, 0.96 mmol, 1.5 equivalent), $Pd(CH_3CN)_2Cl_2$ (0.8 mg, 0.0032 mmol, 0.5 mol %), cataCXium A (2.3 mg, 0.0064 mmol, 1.0 mol %), and Cs_2CO_3 (207 mg, 0.64 mmol, 1 equiv) by using the general synthetic protocol of the Sonogashira reaction. The products (**8i** = 102 mg and **8p** = 108 mg) were obtained as white solids with 91% (**8i**) and 88% (**8p**) isolated yields. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.53 (d, J = 5.9 Hz, 2H), 7.43 (d, J = 7.8 Hz, 2H), 7.34 (d, J = 7.1 Hz, 3H), 7.16 (d, J = 7.8 Hz, 2H), 2.37 (s, 3H). $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 138.5, 131.6, 131.6, 129.2, 128.4, 128.2, 123.6, 120.3, 89.6, 88.8, 21.6.

*1-Methyl-3-(phenylethynyl)benzene (**8j**).*[44] Compound (**8j**) was synthesized from *m*-bromotoluene (100 mg, 0.58 mmol, 1 equiv), phenylacetylene (89 mg, 0.87 mmol, 1.5 equiv per halide), $Pd(CH_3CN)_2Cl_2$ (0.8 mg, 0.0029 mmol, 0.5 mol %), cataCXium A (2 mg, 0.0058 mmol, 1.0 mol %), and Cs_2CO_3 (189 mg, 0.58 mmol) by using the general synthetic protocol of the Sonogashira reaction. The crude product was purified by column chromatography by using hexane as the eluent. The products (X = 100 mg) were obtained as a colorless liquid with 89% isolated yield. ^{1}H NMR (600 MHz, $CHCl_3$) δ 7.57−7.50 (m, 2H), 7.40−7.29 (m, 5H), 7.24 (t, J = 7.6 Hz, 1H), 7.15 (d, J = 7.7 Hz, 1H), 2.36 (s, 3H). $^{13}C\{^1H\}$ NMR (151 MHz, CDCl3) δ 138.1, 132.3, 131.7, 129.3, 128.8, 128.4, 128.3, 128.3, 123.5, 123.2, 89.7, 89.1, 21.3.

*1,2,3,4,5-Pentafluoro-6-(phenylethynyl)benzene (**8k**).*[45] Compound (**8k**) was synthesized from pentafluoroiodobenzene (293 mg, 1 mmol, 1 equiv), phenylacetylene (153 mg, 1.5 mmol, 1.5 equiv per halide), $Pd(CH_3CN)_2Cl_2$ (2.6 mg, 0.01 mmol, 1.0 mol %), cataCXium A (7.2 mg, 0.02 mmol, 2.0 mol %), and Cs_2CO_3 (325 mg, 1 mmol, 1.0 equiv) by using the general synthetic protocol of the Sonogashira reaction. The crude product was purified by column chromatography by using hexane as the eluent. The product (61 mg) was obtained as a white solid with 23% isolated yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54 (d, J = 7.3 Hz, 2H), 7.35 (m, 3H). ^{19}F NMR (377 MHz, $CDCl_3$) δ −136.49 (d, J = 14.4 Hz, 2F), −153.74 to −156.76 (m, 1F), −162.89 (dd, J = 21.0, 14.8 Hz, 2F). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 132.6, 129.3, 128.5, 121.9, 81.7, 74.0.

*2-(Phenylethynyl)pyridine (**8l**).*[46] Compound (**8l**) was synthesized from *o*-bromopyridine (100 mg, 0.63 mmol, 1 equiv), phenylacetylene (97 mg, 0.95 mmol, 1.5 equiv per halide), $Pd(CH_3CN)_2Cl_2$ (0.8 mg, 0.032 mmol, 0.5 mol %), cataCXium A (2.3 mg, 0.0063 mmol, 1.0 mol %), and Cs_2CO_3 (205 mg, 0.63 mmol, 1.0 equiv) by using the general synthetic protocol of the Sonogashira reaction. The crude product was purified by column chromatography by using 2% ethyl acetate in hexane as the eluent. The product (61 mg) was obtained as a colorless liquid with 54% isolated yield. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.62 (d, J = 4.9 Hz, 1H), 7.71−7.67 (m, 1H), 7.61 (dd, J = 6.3, 2.7 Hz, 2H), 7.53 (d, J = 7.8 Hz, 1H), 7.37 (d, J = 5.3 Hz, 3H), 7.24 (d, J = 6.4 Hz, 1H). $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 150.0, 143.4, 136.4, 132.2, 129.1, 128.5, 127.3, 122.9, 122.3, 89.7, 88.5.

*1-(Phenylethynyl)-4-(trifluoromethyl)benzene (**8m**).*[38] Compound (**8m**) was synthesized from 1-iodo-4-(trifluoromethyl)benzene (100 mg, 0.37 mmol, 1 equiv), phenylacetylene (56 mg, 0.55 mmol, 1.5 equiv per halide), $Pd(CH_3CN)_2Cl_2$ (0.9 mg, 0.0036 mmol, 1.0 mol %), cataCXium A (2.6 mg, 0.0073 mmol, 2.0 mol %), and Cs_2CO_3 (120 mg, 0.37 mmol, 1.0 equiv) by using the general synthetic protocol of the Sonogashira reaction. The crude product was purified by column chromatography by using hexane as the eluent. The product (31 mg) was obtained as a white solid with 35% isolated yield. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.62 (q, J = 8.3 Hz, 4H), 7.57−7.50 (m, 2H), 7.37 (q, J = 3.1, 2.4 Hz, 3H). $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ

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131.95, 131.89, 130.17, 129.95, 128.98, 128.60, 127.27, 125.43 (d, J = 3.9 Hz), 125.00, 123.19, 122.70, 91.89, 88.10. ^{19}F NMR (471 MHz, $CDCl_3$) δ −62.8.

*1,2-Diphenylethyne (**8o**).*[47] Compound (**8o**) was synthesized from bromobenzene (100 mg, 0.64 mmol, 1 equiv), phenylacetylene (98 mg, 0.96 mmol, 1.5 equiv per halide), $Pd(CH_3CN)_2Cl_2$ (0.8 mg, 0.0032 mmol, 0.5 mol %), cataCXium A (2.3 mg, 0.0064 mmol, 1.0 mol %), and Cs_2CO_3 (207 mg, 0.64 mmol, 1.0 equiv) by using the general synthetic protocol of the Sonogashira reaction. The crude product was purified by column chromatography by using hexane as the eluent. The product (104 mg) was obtained as a colorless liquid with 91% isolated yield. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.57 (d, J = 7.8 Hz, 4H), 7.38 (d, J = 7.3 Hz, 6H). $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 131.7, 128.4, 123.4, 89.5.

*3-(Phenylethynyl)pyridine (**8q**).*[38] Compound (**8q**) was synthesized from 3-bromopyridine (100 mg, 0.63 mmol, 1.0 equiv), phenylacetylene (97 mg, 0.95 mmol, 1.5 equiv per halide), $Pd(CH_3CN)_2Cl_2$ (0.8 mg, 0.0032 mmol, 0.5 mol %), cataCXium A (2.3 mg, 0.0063 mmol, 1.0 mol %), and Cs_2CO_3 (205 mg, 0.63 mmol, 1.0 equiv) by using the general synthetic protocol of the Sonogashira reaction. The crude product was purified by column chromatography by using 2% ethyl acetate in hexane as the eluent. The product (97 mg) was obtained as a brown-color solid with 86% isolated yield. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.78 (s, 1H), 8.56 (d, J = 4.9 Hz, 1H), 7.86 (d, J = 7.9 Hz, 1H), 7.55 (dd, J = 6.5, 3.0 Hz, 2H), 7.38 (d, J = 3.0 Hz, 3H), 7.33 (dd, J = 7.9, 5.0 Hz, 1H). $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 151.7, 148.0, 139.1, 131.8, 129.0, 128.6, 123.4, 122.5, 120.9, 93.2, 85.7.

*3-(p-Tolylethynyl)pyridine (**8r**).*[48] Compound (**8r**) was synthesized from 3-bromopyridine (100 mg, 0.63 mmol, 1 equiv), *p*-ethynyltoluene (110 mg, 0.94 mmol, 1.5 equiv per halide), $Pd(CH_3CN)_2Cl_2$ (0.8 mg, 0.0032 mmol, 0.5 mol %), cataCXium A (2.3 mg, 0.0063 mmol, 1.0 mol %), and Cs_2CO_3 (205 mg, 0.63 mmol, 1.0 equiv) by using the general synthetic protocol of the Sonogashira reaction. The crude product was purified by column chromatography by using 2% ethyl acetate hexane as the eluent. The product (105 mg) was obtained as a white solid with 86% isolated yield. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.75 (d, J = 2.2 Hz, 1H), 8.53 (dd, J = 4.8, 1.7 Hz, 1H), 7.79 (dt, J = 7.9, 1.9 Hz, 1H), 7.51−7.38 (m, 2H), 7.27 (dd, J = 7.8, 4.8 Hz, 1H), 7.18 (d, J = 7.8 Hz, 2H), 2.38 (s, 3H). $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 152.3, 148.5, 139.2, 138.5, 131.7, 129.3, 123.1, 120.8, 119.5, 93.0, 85.4, 21.7.

*1-(Phenylethynyl)naphthalene (**8s**).*[49] Compound (**8s**) was synthesized from 1-bromonapthalene (100 mg, 0.48 mmol, 1 equiv), phenylacetylene (74 mg, 0.72 mmol, 1.5 equiv per halide), $Pd(CH_3CN)_2Cl_2$ (0.6 mg, 0.0024 mmol, 0.5 mol %), cataCXium A (1.7 mg, 0.0048 mmol, 1.0 mol %), and Cs_2CO_3 (156 mg, 0.48 mmol, 1.0 equiv) by using the general synthetic protocol of the Sonogashira reaction. The crude product was purified by column chromatography by using hexane as the eluent. The product (100 mg) was obtained as a colorless liquid with 91% isolated yield. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.46 (d, J = 8.4 Hz, 1H), 7.87 (dd, J = 14.6, 8.2 Hz, 2H), 7.78 (d, J = 7.1 Hz, 1H), 7.67 (d, J = 6.4 Hz, 2H), 7.64−7.59 (m, 1H), 7.55 (t, J = 7.4 Hz, 1H), 7.47 (t, J = 7.7 Hz, 1H), 7.44−7.35 (m, 3H). $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 133.4, 133.3, 131.8, 130.5, 128.9, 128.5, 128.5, 128.4, 126.9, 126.5, 126.3, 125.4, 123.5, 121.0, 94.4, 87.6.

*1-(p-Tolylethynyl)naphthalene (**8t**).*[49] Compound (**8t**) was synthesized from 1-bromonapthalene (100 mg, 0.48 mmol, 1 equiv), *p*-ethynyltoluene (84 mg, 0.72 mmol, 1.5 equiv per halide), $Pd(CH_3CN)_2Cl_2$ (0.6 mg, 0.0024 mmol, 0.5 mol %), cataCXium A (1.7 mg, 1.0 mol %), and Cs_2CO_3 (156 mg, 0.48 mmol, 1.0 equiv) by using the general synthetic protocol of the Sonogashira reaction. The crude product was purified by column chromatography by using hexane as the eluent. The product (107 mg) was obtained as a white solid with 92% isolated yield. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.46 (d, J = 8.3 Hz, 1H), 7.87 (d, J = 8.1 Hz, 1H), 7.84 (d, J = 8.3 Hz, 1H), 7.76 (d, J = 7.0 Hz, 1H), 7.63−7.57 (m, 1H), 7.54 (dd, J = 13.8, 7.5 Hz, 3H), 7.46 (t, J = 7.7 Hz, 1H), 7.22 (d, J = 7.8 Hz, 2H), 2.41 (s, 3H). $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 138.7, 133.4, 133.3, 131.7, 130.3, 129.3, 128.7, 128.4, 126.8, 126.5, 126.4, 125.4, 121.2, 120.4, 94.6, 87.0, 21.7.

*9-(Phenylethynyl)anthracene (**8u**).*[50] Compound (**8u**) was synthesized from 9-bromoanthracene (100 mg, 0.39 mmol, 1 equiv), phenylacetylene (59 mg, 0.58 mmol, 1.5 equiv per halide), $Pd(CH_3CN)_2Cl_2$ (0.5 mg, 0.0019 mmol, 0.5 mol %), cataCXium A (1.4 mg, 0.0039 mmol, 1.0 mol %), and Cs_2CO_3 (127 mg, 0.39 mmol, 1.0 equiv) by using the general synthetic protocol of the Sonogashira reaction. The crude product was purified by column chromatography by using hexane as the eluent. The product (98 mg) was obtained as a white solid with 91% isolated yield. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.66 (d, J = 8.7 Hz, 2H), 8.45 (s, 1H), 8.03 (d, J = 8.4 Hz, 2H), 7.78 (d, J = 8.5 Hz, 2H), 7.60 (t, J = 7.6 Hz, 2H), 7.56−7.50 (m, 2H), 7.46 (t, J = 7.9 Hz, 2H), 7.42 (d, J = 7.7 Hz, 1H). $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 132.7, 131.8, 131.3, 128.8, 128.6, 128.6, 127.8, 126.9, 126.7, 125.8, 123.7, 117.4, 100.8, 86.4.

*9-(p-Tolylethynyl)anthracene (**8v**).*[51] Compound (**8v**) was synthesized from 9-bromoanthracene (100 mg, 0.39 mmol, 1 equiv), *p*-ethynyltoluene (67 mg, 0.58 mmol, 1.5 equiv per halide), $Pd(CH_3CN)_2Cl_2$ (0.5 mg, 0.0019 mmol, 0.5 mol %), cataCXium A (1.4 mg, 0.0039 mmol, 1.0 mol %), and Cs_2CO_3 (127 mg, 0.39 mmol, 1.0 equiv) by using the general synthetic protocol of the Sonogashira reaction. The crude product was purified by column chromatography by using hexane as the eluent. The product (108 mg) was obtained as a white solid with 95% isolated yield. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.66 (d, J = 8.7 Hz, 2H), 8.43 (s, 1H), 8.02 (d, J = 8.4 Hz, 2H), 7.67 (d, J = 7.7 Hz, 2H), 7.62−7.57 (m, 2H), 7.52 (t, J = 7.5 Hz, 2H), 7.27 (d, J = 5.9 Hz, 2H), 2.43 (s, 3H). $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 138.8, 132.6, 131.7, 131.3, 129.4, 128.8, 127.6, 126.9, 126.6, 125.8, 120.7, 117.7, 101.1, 85.7, 21.7.

*(4-(Anthracen-9-ylethynyl)phenyl)(phenyl)methanone (**8w**).* Compound (**8w**) was synthesized from 9-bromoanthracene (50 mg, 0.19 mmol, 1 equiv), (*p*-ethynylphenyl)-(phenyl)methanone (60 mg, 0.29 mmol, 1.5 equiv per halide), $Pd(CH_3CN)_2Cl_2$ (0.3 mg, 0.00095 mmol, 0.5 mol %), cataCXium A (0.7 mg, 0.0019 mmol, 1.0 mol %), and Cs_2CO_3 (62 mg, 0.19 mmol, 1 equiv) by using the general synthetic protocol of the Sonogashira reaction. The crude product was purified by column chromatography by using 5% DCM in hexane as the eluent. The product (41 mg) was obtained as a green solid with 56% isolated yield. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.65 (d, J = 8.7 Hz, 2H), 8.49 (s, 1H), 8.05 (d, J = 8.4 Hz, 2H), 7.91 (d, J = 8.0 Hz, 2H), 7.90−7.82 (m, 4H), 7.66−7.60 (m, 3H), 7.54 (q, J = 7.6 Hz, 4H). $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 196.1, 137.6, 137.0, 132.9, 132.7, 131.5, 131.3, 130.4, 130.1, 128.9, 128.6, 128.5, 128.0, 127.0, 126.7, 125.9, 116.7, 100.0, 89.6. FT-IR (KBr,

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cm^{-1}) 3052 (aromatic, C−H str), 2923 (aromatic, C−H str), 2853 (aromatic, C−H str), 2198 (C≡C str), 1654 (C═O str) 1594 (aromatic, C═C str), 1445 (aromatic, C═C str). HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{29}H_{19}O$ 383.1436, found 383.1436. Mp = 150−152 °C.

*1-Bromo-2-(phenylethynyl)benzene (**8x**).*[52] Compound (**8x**) was synthesized from iodobenzene (100 mg, 0.49 mmol, 1 equiv), 1-bromo-2-ethynylbenzene (133 mg, 0.73 mmol, 1.5 equiv per halide), $Pd(CH_3CN)_2Cl_2$ (0.6 mg, 0.0024 mmol, 0.5 mol %), cataCXium A (1.76 mg, 0.0049 mmol, 1.0 mol %), and Cs_2CO_3 (0.81 mmol, 1.0 equiv) by using the general synthetic protocol of the Sonogashira reaction. The crude product was purified by column chromatography by using hexane as the eluent. The product (25 mg) was obtained as a brown liquid with 20% isolated yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65−7.53 (m, 4H), 7.39−7.34 (m, 3H), 7.29 (td, J = 7.6, 1.3 Hz, 1H), 7.18 (td, J = 7.7, 1.7 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 133.38, 132.61, 131.85, 129.52, 128.80, 128.53, 127.18, 125.79, 125.57, 123.07, 94.07, 88.16.

Cell Culture and Maintenance. The human triple-negative breast cancer (TNBC) cell line MDA-MB-231 (procured from National Centre for Cell Science NCCS, Pune, India) and the human dermal fibroblast (HDF; procured from Himedia, India) were cultured and maintained separately in high-glucose Dulbecco's modified Eagle's medium (DMEM; Gibco, Life Technologies, United States) supplemented with 10% fetal bovine serum (FBS; Gibco, Life Technologies, United States) and 1% streptomycin−penicillin (Sigma, United States). Cells were seeded in tissue culture flasks (T25; ThermoFisher, United States) and placed at 37 °C in a humidified (85%) incubator (ThermoFisher Scientific, United States) with 5% CO_2. The medium was replenished every alternate day.

Cytotoxicity Assay. The cytotoxicity of chemical compounds **3**, **3a**, **3b**, **3c**, **3d**, and **3g** was tested *in vitro* on the human TNBC cell line MDA-MB-231 and HDF cells by virtue of the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) reduction assay as described in a previous report.[53] Briefly, 1 × 10^4 cells per well were seeded into a 96-well plate and incubated at 37 °C for 24 h in a CO_2 incubator. Post incubation, the used medium was replaced with 200 μL of fresh medium containing different concentrations (3.12, 6.25, 12.5, 25, 50, and 100 μM) of chemical compounds. Treated cells along with the control (phosphate-buffered saline (PBS, pH 7.4) treatment) were then incubated for 72 h in a similar condition as described. Post 72 h, the used medium was replaced with 180 μL of fresh medium and 20 μL of MTT (5 mg/mL) was added to each well followed by incubation at 37 °C for 4 h. Plates were then centrifuged at 1000 rpm for 5 min, and 200 μL of dimethyl sulfoxide (DMSO, Sigma, United States) was added to each well to dissolve the purple pellets (formazan crystals). Absorbance was recorded at 570 nm using a multiplate reader (Multiskan Sky, ThermoFisher, United States).

Live Cell Fluorescence Imaging. The fluorescence of chemical compounds inside the live cells was checked with both MDA-MB-231 and HDF cells. In brief, both types of cells were seeded (1 × 10^4 cells per well) in a 96-well plate separately and incubated at 37 °C for 24 h in a CO_2 incubator. Post incubation, cells were treated with various chemical compounds at a concentration of 10 μM in complete DMEM and incubated for the next 72 h. To observe the fluorescence of live cells, images were taken at 24 h. Cells were thoroughly washed with PBS (pH 7.4), and images were captured using a fluorescence microscope (EVOS FL, Life Technologies, United States).

PI Staining. PI staining was performed in both MDA-MB-231 cells and HDF cells to check if the treatment with the chemical compounds resulted in membrane disintegration and cellular uptake of the dye. The dead cells whose membrane undergoes disintegration take up the PI stain and show bright orange-red fluorescence (λ_{Ex}: 493 nm, and λ_{Em}: 636 nm).

Both types of cells were seeded (1 × 10^4 cells per well) in a 96-well plate separately and incubated at 37 °C for 24 h in a CO_2 incubator. Post incubation, the cells were treated with various chemical compounds at a concentration of 10 μM in complete DMEM and incubated for the next 72 h. Thereafter, cells were thoroughly washed with PBS (pH 7.4), and PI at the concentration of 10 μg/mL was added followed by incubation at 37 °C for 15 min. After incubation, PI was removed and washed thoroughly with PBS. Images were captured using a fluorescence microscope (EVOS FL, Life Technologies, United States).

DAPI Staining. Post treatment of MDA-MB-231 and HDF cells with the compounds for 72 h, the cells were washed thoroughly with PBS and then fixed with 10% NBF for 30 min. Post fixation, NBF was removed and cells were washed with PBS and then stained with DAPI for 15 min. After 15 min of staining, DAPI was removed and washed with PBS to remove excess stain. Images were captured in a fluorescence microscope (NIKON Eclipse Ti2, Japan).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.3c00732.

Characterization details including ^{1}H, ^{13}C{^{1}H}, and ^{19}F NMR spectra; and HRMS spectra (PDF)

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Notes

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■ ABBREVIATIONS

TNBC, triple-negative breast cancer; HDF, human dermal fibroblasts; MTT, 3-(4,5-dimethylthiazolyl-2)-2,5-diphenyltetrazolium bromide; DAPI, 4′,6-diamidino-2-phenylindole; PI, propidium iodide; PAHs, polycyclic aromatic hydrocarbons; RDS, rate-determining step; TLC, thin-layer chromatography

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