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An efficient coupling of *N*-tosylhydrazones with 2-halopyridines: synthesis of 2-α-styrylpyridines endowed with antitumor activity†

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The synthesis of 2-α-styrylpyridines has been carried out by using the coupling of polyoxygenated *N*-tosylhydrazones with various 2-halopyridines. We demonstrated that the use of a catalytic amount of $PdCl_2(MeCN)_2$ in combination with a bidentate ferrocene DPPF or a monodentate alkyl phosphine $^tBu_2MeP\text{-}HBF_4$ constitutes an efficient protocol for this coupling, providing 2-α-styrylpyridines **2** in satisfactory to good yields. Among several polyoxygenated derivatives **2** evaluated, compound **2aa** was found to exhibit excellent antiproliferative and antimitotic activities comparable to that of the reference compound isoCA-4.

Introduction

In recent years, our efforts to discover novel vascular disrupting agents (VDAs)[1] led us to identify isocombretastatin A-4 (isoCA-4) as a lead compound that exhibits potent antineoplastic and antivascular properties[2] (Fig. 1). Since heterocycles are ubiquitous in biologically active compounds,[3] we recently synthesized a series of heterocyclic-based isoCA-4 **1** in which the isoCA-4 B-ring was replaced by an indole nucleus (Fig. 1).[4] In continuation of our structure–activity relationship study of isoCA-4 and in order to obtain compounds with potent activity and improved physiochemical properties, a series of 2-pyridyl-type isoCA-4 of general structure **2** was designed (Fig. 1). Pyridines are among the most prevalent heterocyclic structural units in pharmaceutical targets and is found in important biologically active structures.[3a,5]

Only few reports deal with the preparation of compound **2** and most of them involve traditional cross-coupling reactions of vinylmetal derivatives with 2-halopyridines.[6] To access our target molecules **2**, we envisioned a convergent strategy based on the coupling of *N*-tosylhydrazone derived from a polyoxygenated acetophenone with various 2-halopyridines. Since the pioneering work of Barluenga *et al.*,[7] the palladium-catalyzed reaction of *N*-tosylhydrazones with aryl halides has emerged as an efficient protocol for the construction of C=C double bonds. Despite a number of reports in this area,[8] the use of heteroaryl halides as coupling partners has been largely neglected.[9] To our knowledge, there have been no studies focused on coupling with 2-halogenated pyridines.[10] This may be in part due to the fact that the Pd-catalyzed reactions with these substrates have proven challenging as compared to the analogous couplings of 3- and 4-halopyridine derivatives[11] and thus typically required the use of highly active catalyst systems. Furthermore, although oxidative addition of Pd(0) should be more rapid to 2-bromopyridine than to 3-bromopyridine,[12] the formation of 2,2′-bipyridine as a by-product, which can act as a poison for palladium catalysts,[13] might be the reason for the low reactivity of 2-bromopyridine. From a synthetic viewpoint, the development of a general protocol allowing cross-coupling of 2-halopyridines with *N*-tosylhydrazones derived from acetophenones would be of great interest for the synthesis of 2-α-styrylpyridines **2** in the context of a medicinal chemistry screening program. Herein, we report our success in the

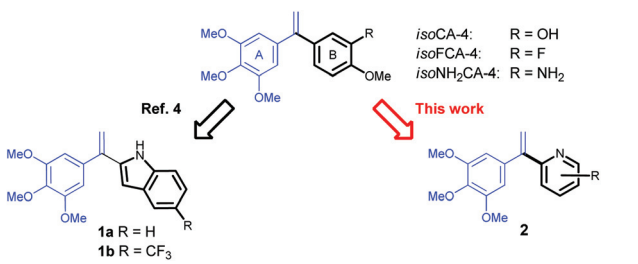

Fig. 1 IsoCA-4, 2-(1-phenylvinyl)indoles **1**, and target structures **2**.

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†Electronic supplementary information (ESI) available: Copies of ^1H and ^{13}C NMR spectra, are provided. See DOI: 10.1039/c3ob40263k

development of such a protocol. The potencies of newly synthesized polyoxygenated compounds **2** were evaluated for their capacity to inhibit cancer cellular growth and to act as potential antimitotic agents.

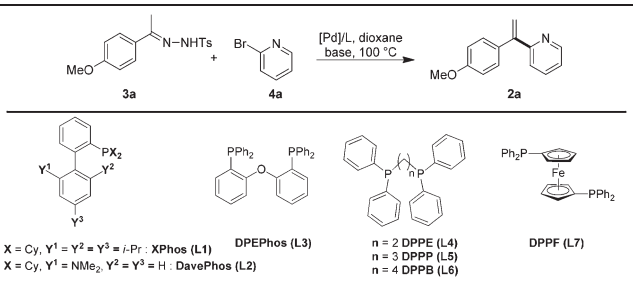
Chemistry

At the outset, we examined the reaction of **3a** (1.5 equiv.) with **4a** (1 equiv.) using the protocol described recently by Prabhu *et al.*[10] ($PdCl_2(PPh_3)_2$/LiO^tBu/dioxane) without the addition of an external ligand and in a sealed tube. Under these conditions, in our hands, we were unable to obtain the desired product **2a** with an isolated yield higher than 30% despite several attempts (entry 1, Table 1). Difficulties in obtaining **2a** in good yield led us to explore alternative protocols for the coupling of **3a** with **4a**. Achieving the reactions under the standard protocol (Pd_2dba_3/XPhos, LiO^tBu) developed by Barluenga[7] or using our previously reported conditions ($PdCl_2(MeCN)_2$/dppp, Cs_2CO_3)[9c] were also inefficient and resulted in the concomitant formation of the expected product **2a** in unsatisfactory yields (15–22%, Table 1, entries 3 and 4) together with two other by-products: (i) the Bamford–Stevens alkene,[14] derived from the evolution of the diazo compound generated from the hydrazone **3a**,[15] and (ii) sulfone which resulted *via* nitrogen loss of sulfonylhydrazone **3a**. To promote the formation of **2a**, we decided to reinvestigate this challenging coupling reaction. $PdCl_2(MeCN)_2$ was fixed as the palladium source; then, an extensive screening of various reaction parameters was conducted.[16] Among various bases examined, LiO^tBu increased the yield of **2a** to 42% (entry 5). Screening with respect to the ligand revealed that the nature of phosphine plays an important role in the outcome of this transformation (entries 8–13). After several attempts, we found that the combination of $PdCl_2(MeCN)_2$ with bidentate ferrocene DPPF (L7) or monodentate alkyl phosphine $^tBu_2$MeP-HBF_4 gave the best results (84–82%, entries 10 and 13). Finally, the screening reactions with respect to the solvent revealed that the use of dioxane is superior to all other choices.[16] A control experiment showed that in the absence of palladium, no product **2a** could be detected. Performing the reaction without a ligand was also inefficient, since **2a** was isolated in a low yield (<20%).[16]

Next, we investigated the scope and limitation of the catalytic process between various *N*-tosylhydrazones **3** and an array of substituted 2-halopyridines **4**; the results are summarized in Table 2. We were pleased to find that this catalytic protocol tolerated both electron-donating and -withdrawing pyridine ring substitutions, and in most cases the desired 1-aryl-1′-(2-pyridyl)ethylenes **2b–g** were obtained in satisfactory to good yields (entries 1–6). This catalyst system proved also to be effective for the cross-coupling of hydrazone **3a** with a range of challenging 2-halopyridines including *ortho*-substituted and electronically deactivated substrates (entries 3–6), as well as component **4e** having a free amino group (entry 4). As illustrated in Table 2, a series of hydrazones **3b–e** can even be coupled with several 2-halopyridines, and all gave the cross-coupling products in good yields (entries 8–18). Thus, coupling with polyoxygenated hydrazone **3b** furnished olefins **2i–n**, which share structural similarity with isoCA-4 (entries 8–13). The site-selectivity of this catalytic system was also briefly explored with dihalogenated pyridine derivatives **4j–m**. As expected, the reaction occurred at the more reactive carbon–halogen bond of the halopyridine substrates giving rise to monocoupling products **2m–p** in satisfactory to good yields (entries 12–15). It is noteworthy that the remaining bromine atom on the heteroaromatic ring could enjoy further metal-catalyzed functionalization processes (*vide infra*). As might be anticipated, extending this reaction to 4-chloro-substituted hydrazone **3c** gave selectively the corresponding 4-chloro-substituted olefin **2q** in a good 80% yield (entry 16). The reaction also worked well with *N*-tosylhydrazones derived from 6-methoxytetralone and cyclooctanone affording the desired products **2r** and **2s** in 60% and 87% yields, respectively (entries 17 and 18).

To establish the generality of this protocol, a series of heteroaromatic halides **4n–s** were coupled with hydrazones **3a** or **3b** under our optimized conditions. We found that the protocol is effective not only for 2-halopyridines, but also for a variety of other heterocyclic substrates including 2-bromoquinoline, 2-bromopyrazine, 2-chloro-1-*N*-methylbenzimidazole,

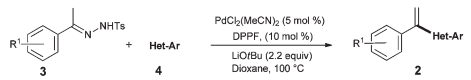
Table 1 Optimization coupling reaction of **3a** with **4a** under various conditions[a]



Entry	[Pd]	Ligand	Base	Yield[b] (%)
1	$PdCl_2(PPh_3)_2$	—	LiO^tBu	30[c,d]
2	$PdCl_2(MeCN)_2$	PPh_3	LiO^tBu	33
3	**Pd_2dba_3**	Xphos	LiO^tBu	15
4	**$PdCl_2(MeCN)_2$**	DPPP	Cs_2CO_3	22
5	$PdCl_2(MeCN)_2$	DPPP	LiO^tBu	42
6	$PdCl_2(MeCN)_2$	DPPP	NaO^tBu	32
7	$PdCl_2(MeCN)_2$	DPPP	KO^tBu	27
8	$PdCl_2(MeCN)_2$	DPPB	LiO^tBu	30
9	$PdCl_2(MeCN)_2$	DPPE	LiO^tBu	28
10	**$PdCl_2(MeCN)_2$**	**DPPF**	**LiO^tBu**	**84**[e]
11	$PdCl_2(MeCN)_2$	DPEPhos	LiO^tBu	32
12	$PdCl_2(MeCN)_2$	DavePhos	LiO^tBu	44
13	**$PdCl_2(MeCN)_2$**	**$^tBu_2$MeP-HBF_4**	**LiO^tBu**	**82**

[a] The reactions were carried out in a sealed tube with **3a** (1.5 mmol), **4a** (1 mmol), [Pd] (5 mol%), ligand (10 mol%), base (2.2 equiv.) at 100 °C in 3.0 mL of solvent. [b] Isolated yield of **2a**. [c] Average yield calculated after three experiments. [d] The same yield was obtained by using 4 equiv. of LiO^tBu. [e] Performing the reaction at atmospheric pressure led to 55% of **2a**.

Table 2 Palladium-catalyzed coupling of *N*-tosylhydrazone **3** with various aryl halides **4**[a]



3 4 2

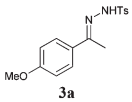
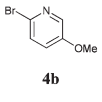
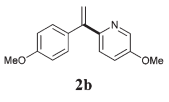
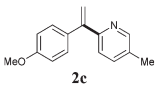
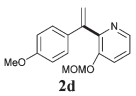
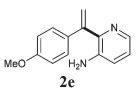
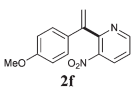
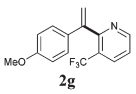
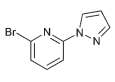
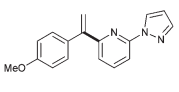
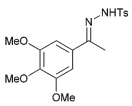
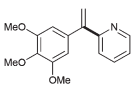
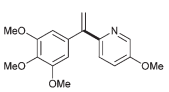
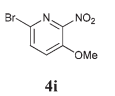
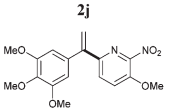
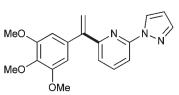
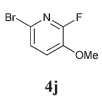
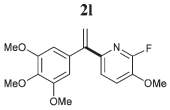
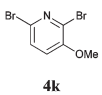
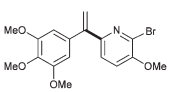
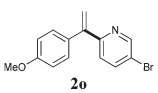
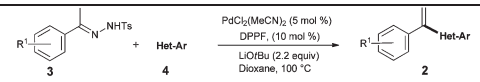
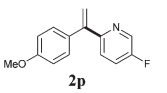
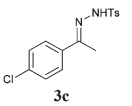
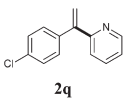
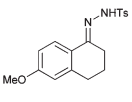
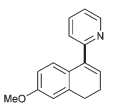
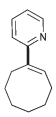
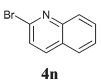
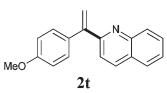
Entry	Hydrazone **3**	Heteroaryl halide **4**	Product **2**	Yield[b] (%)
1	 **3a**	 **4b**	 **2b**	70
2	**3a**	 **4c**	 **2c**	84[c]
3	**3a**	 **4d**	 **2d**	67
4	**3a**	 **4e**	 **2e**	56
5	**3a**	 **4f**	 **2f**	73
6	**3a**	 **4g**	 **2g**	62
7	**3a**	 **4h**	 **2h**	80
8	 **3b**	**4a**	 **2i**	71
9	**3b**	**4b**	 **2j**	63
10	**3b**	 **4i**	 **2k**	65
11	**3b**	**4h**	 **2l**	80
12	**3b**	 **4j**	 **2m**	90
13	**3b**	 **4k**	 **2n**	55
14	**3a**	 **4l**	 **2o**	45

Table 2 *(Contd.)*



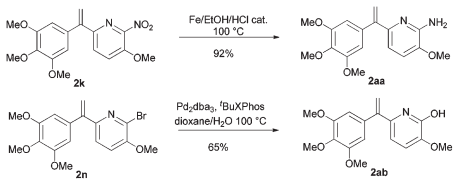
3 4 2

Entry	Hydrazone **3**	Heteroaryl halide **4**	Product **2**	Yield[b] (%)
15	**3a**	 **4m**	 **2p**	72[c]
16	 **3c**	 **4a**	 **2q**	80
17	 **3d**	**4a**	 **2r**	60[c]
18	 **3e**	**4a**	 **2s**	87
19	**3a**	 **4n**	 **2t**	72[c]
20	**3a**	**4o**	**2u**	60
21	**3a**	**4p**	**2v**	52[c]
22	**3a**	**4q**	**2w**	65
23	**3b**	**4r**	**2x**	98
23	**3b**	**4s**	**2y**	80

[a] Unless otherwise stated, the reactions were carried out in a sealed tube with hydrazones **3** (1.5 mmol), heteroaryl halides **4** (1 mmol), $PdCl_2(MeCN)_2$ (5 mol%), DPPF (10 mol%), LiO^tBu (2.2 equiv.) at 100 °C in 3.0 mL of dioxane. [b] Yield of isolated product. [c] $^tBu_2MeP$-HBF_4 (10 mol%) was used in place of DPPF.

4-bromothiazole, and 5-bromo-2-methoxypyrimidine derivatives. In all cases, satisfactory to excellent yields were obtained (Table 2, entries 19–23).

To obtain the closest analogues of the isoCA-4, the nitro group of compound **2k** was reduced by iron powder,[17] producing compound **2aa** in a 92% yield. Treating **2n** with KOH in the presence of Pd_2dba_3, ^{t}BuXPhos in a mixture of dioxane–H_2O: (1/1 v/v) at 100 °C[18] delivered compound **2ab** in a satisfactory 65% isolated yield (Scheme 1).



Scheme 1 Synthesis of the closest analogues of the isoCA-4.

Table 3 Cytotoxic activity of selected α-styrylpyridines, against HCT-116 cells[a]

Compd	GI_{50} [b] (nM) HCT116	ITP IC_{50} [c] (μM)
2b	NC[d]	NC[d]
2h	NC[d]	NC[d]
2i	400 ± 25	NC[d]
2j	250 ± 18	15 ± 2
2k	280 ± 14	NC[d]
2l	180 ± 10	15.3 ± 0.4
2m	100 ± 5	5.3 ± 0.5
2n	1000 ± 80	NC[d]
2aa	7 ± 0.3	2.0 ± 0.4
2ab	40 ± 1	1.9 ± 0.3
isoCA-4	2 ± 0.3	2.0 ± 0.3

[a] HCT116 human colon carcinoma cells. [b] GI_{50}: compound concentration required to decrease cell growth by 50% following a 72 h treatment with the tested drug; values represent the average ± SD of three experiments. [c] ITP: inhibition of tubulin polymerization; IC_{50}: compound concentration required to decrease the rate of microtubule assembly by 50%; values represent the average ± SD of three experiments. [d] NC: GI_{50} or IC_{50} values not calculated owing to the low activity of the compound.

Biological evaluation

A. *In vitro* cell growth inhibition

To characterize the cytotoxic profiles of α-styrylpyridines **2**, selected polyoxygenated compounds listed in Table 3 were tested in a preliminary cytotoxic assay on a human colon carcinoma (HCT116) cell line using isoCA-4 as a reference compound.

As shown in Table 3, replacement of trimethoxyphenyl group by *para*-methoxyphenyl causes the complete loss of the antiproliferative activity and antitubulin potential (compare compounds **2b** and **2j**; **2h** and **2l**). Compounds having the greatest resemblance to isoCA-4 (**2ab**, R = OH) and isoNH$_2$CA-4 (**2aa**, R = NH$_2$) displayed excellent antiproliferative activities; the best result was obtained with compound **2aa**, which inhibited the growth of the HCT-116 cell line in the nanomolar range similarly to isoCA-4. Interestingly, the *in vitro* tubulin assembly assay revealed that **2aa** acts as a potent inhibitor of tubulin polymerization with an IC_{50} of 2.0 μM, which is similar to that of isoCA-4.

To further characterize the cytotoxicity profiles of these compounds, we investigated the effect of the most active substances **2j**, **2l**, **2m**, **2aa** and **2ab** on the proliferation of the human glioblastoma tumor cell line (U87)[19] as well as human umbilical vein endothelial cell (HUVEC) as a prerequisite for future evaluation of vascular-disrupting properties (Table 4).

Table 4 *In vitro* cell growth inhibitory effects of compounds **4b**, **4d–e** and isoCA-4

GI_{50} [a] (nM)		
Compd	U87[b]	HUVEC[b]
2j	700 ± 50	nd
2l	300 ± 20	nd
2m	300 ± 16	nd
2aa	25 ± 1.5	20 ± 1.5
2ab	80 ± 1.9	35 ± 2
isoCA-4	10 ± 0.5	2.5 ± 0.2

[a] GI_{50}: compound concentration required to decrease cell growth by 50% following a 72 h treatment with the tested drug; values represent the average ± SD of three experiments. [b] U87: human glioblastoma cells; HUVEC: human umbilical vein endothelial cell.

The screening results revealed again that compound **2aa** showed the strongest inhibitory activity against U87 and HUVEC cells ($GI_{50} \leq 25$ nM) (Table 4). This suggests that a polar 2-pyridyl group on this position of ring B has a positive influence on the antimicrotubule and antiproliferative properties. Further *in vitro* assays are under way to assess the potential activity of these new analogues as vascular-disrupting agents. These results confirm that the use of a 2-pyridyl ring is a valuable choice in this RSA study.

Conclusions

To the best of our knowledge, this is the most wide-ranging study that has been described so far for *N*-tosylhydrazones coupling reactions with 2-halogenated pyridines. We have demonstrated that our optimized conditions using $PdCl_2(MeCN)_2$ in combination with DPPF or $^tBu_2MeP\text{-}HBF_4$ allowed us to synthesize an array of substituted α-styrylpyridines **2** in satisfactory to good yields. Attractive features of this catalytic system include its efficiency with a variety of nitrogen-containing heteroaromatic halides including quinoline, pyrazine, benzimidazole, thiazole and pyrimidine derivatives. Among styrylpyridines **2** evaluated, compound **2aa** showed potent inhibition of the tubulin assembly (IC_{50} = 2 μM) and exhibited a strong cytotoxic activity (IC_{50} = 7–25 nM) in a similar range to that of isoCA-4. Such agents interfering with microtubules may prove useful as selective vascular disrupting agents. Investigations of structure–activity relationships in the pyridine series are in progress.

Experimental

Chemistry

Solvent peaks were used as reference values, with $CDCl_3$ at 7.26 ppm for ^{1}H NMR and 77.16 ppm for ^{13}C NMR. Chemical shifts δ are given in ppm, and the following abbreviations are used: singlet (s), doublet (d), doublet of doublet (dd), triplet (t), multiplet (m) and broad singlet (bs). Reaction courses and product mixtures were routinely monitored by TLC on silica

gel, and compounds were visualized under a UVP Mineralight UVGL-58 lamp (254 nm) and with phosphomolybdic acid/Δ, anisaldehyde/Δ, or vanillin/Δ. Flash chromatography was performed using silica gel 60 (40–63 mm, 230–400 mesh) at medium pressure (200 mbar). Fluorobenzene was used as received, and dioxane, dichloromethane, cyclohexane and tetrahydrofuran were dried using the procedures described in Perrin's Purification of Laboratory Chemicals.[20] Organic extracts were, in general, dried over $MgSO_4$ or Na_2SO_4. All the products reported showed ^1H and ^{13}C NMR spectra in agreement with the assigned structures.

General procedure for the preparation of hydrazones[21]

To a rapidly stirred suspension of *p*-toluenesulphonohydrazide (5 mmol) in dry methanol (10 mL) at 60 °C, ketone (5 mmol) was added portion-wise. Within 5–60 min the *N*-tosylhydrazone began to precipitate. The mixture was cooled to 0 °C and the product was collected on a Büchner funnel, washed with petroleum ether and then was dried *in vacuo* to afford the pure product.

Typical procedure for Pd-catalyzed *N*-tosylhydrazones coupling with heteroaryl halides

Method A. *N*-Tosylhydrazone (1.5 mmol), $PdCl_2(MeCN)_2$ (0.05 mmol, 5 mol%), 1,1′-bis(diphenylphosphino)ferrocene (DPPF) (0.1 mmol, 10 mol%), and 3 mL of 1,4-dioxane were mixed under argon for 5 minutes at rt. LiO^tBu (2.2 mmol) was then added, the reaction mixture was stirred for an additional one minute and, finally, heteroaryl halide (1.0 mmol) was added. The resulting mixture was stirred at 100 °C in a sealed tube for 3 h until completion of reaction as was judged by TLC analysis. The crude reaction mixture was allowed to cool to room temperature. EtOAc was added to the mixture, which was filtered through celite. The solvent was evaporated under reduced pressure and the crude residue was purified by flash chromatography on silica gel.

Method B. The same protocol was used as in method A, but the DPPF ligand has been replaced by the di-*tert*-butyl(methyl) phosphonium tetrafluoroborate (^{t}Bu$_2$MeP-HBF$_4$).

2a 2-(1-(4-Methoxyphenyl)vinyl)pyridine was prepared according to method A. Yellow oil (178 mg, 84% yield); TLC: R_f = 0.28 (EtOAc–cyclohexane, 2/8, SiO_2); IR (thin film, neat) ν_{max}/cm^{-1}: 3283, 3262, 2836, 2233, 2085, 1608, 1584, 1510, 1244, 1167, 1031; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.45 (ddd, J = 4.9, 1.9, 0.9 Hz, 1H), 7.46 (td, J = 7.7, 1.9 Hz, 1H), 7.22–6.93 (m, 4H), 6.70 (d, J = 8.7 Hz, 2H), 5.69 (d, J = 1.4 Hz, 1H), 5.38 (d, J = 1.4 Hz, 1H), 3.64 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 159.6 (C), 159.0 (C), 149.4 (CH), 148.7 (C), 136.5 (CH), 133.0 (C), 129.7 (2CH), 123.1 (CH), 122.5 (CH), 116.7 (CH_2), 113.9 (2CH), 55.5 (CH_3); HRMS (ESI): for $C_{14}H_{14}NO$ $(M + H)^+$: m/z calcd 212.1070, found 212.1069.

2b 5-Methoxy-2-(1-(4-methoxyphenyl)vinyl)pyridine was prepared according to method A. Yellow oil (168 mg, 70% yield); TLC: R_f = 0.21 (EtOAc–cyclohexane, 2/8, SiO_2); IR (thin film, neat) ν_{max}/cm^{-1}: 2836, 1992, 1602, 1565, 1511, 1336, 1287, 1267, 1246, 1225, 1179, 1030; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.39–8.30 (m, 1H), 7.32–7.21 (m, 4H), 6.88 (d, J = 8.8 Hz, 2H), 5.81 (d, J = 1.4 Hz, 1H), 5.47 (d, J = 1.4 Hz, 1H), 3.88 (s, 3H), 3.83 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 159.5 (C), 156.8 (C), 155.1 (C), 148.0 (C), 137.0 (CH), 129.7 (2CH), 125.3 (C), 123.5 (CH), 121.1 (CH), 115.5 (CH_2), 113.8 (2CH), 55.8 (OCH_3), 55.5 (OCH_3); HRMS (ESI): for $C_{15}H_{16}NO_2$ $(M + H)^+$: m/z calcd 242.1181, found 242.1178.

2c 2-(1-(4-Methoxyphenyl)vinyl)-5-methylpyridine was prepared according to method B. Yellow oil (189 mg, 84% yield); TLC: R_f = 0.3 (EtOAc–cyclohexane, 2/8, SiO_2); IR (thin film, neat) ν_{max}/cm^{-1}: 1606, 1510, 1993, 1291, 1245, 1179, 1112, 1029; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.47 (s, 1H), 7.51–7.42 (m, 1H), 7.31–7.26 (m, 2H), 7.19 (d, J = 8.0 Hz, 1H), 6.88 (d, J = 8.7 Hz, 2H), 5.83 (d, J = 1.5 Hz, 1H), 5.51 (d, J = 1.5 Hz, 1H), 3.82 (s, 3H), 2.35 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): δ 159.5 (C), 156.3 (C), 149.8 (CH), 148.6 (C), 136.9 (CH), 133.2 (C), 132.1 (C), 129.7 (2CH), 122.5 (CH), 115.9 (CH_2), 113.6 (2CH), 55.4 (OCH_3), 18.2 (CH_3); HRMS (ESI): for $C_{15}H_{16}NO$ $(M + H)^+$: m/z calcd 226.1226, found 226.1222.

2d 3-(Methoxymethoxy)-2-(1-(4-methoxyphenyl)vinyl)-pyridine was prepared according to method A. White solid (182 mg, 67% yield); mp: 92–94 °C; TLC: R_f = 0.6 (EtOAc–cyclohexane, 2/8, SiO_2); IR (thin film, neat) ν_{max}/cm^{-1}: 3437, 3301, 3285, 2237, 2217, 1608, 1579, 1511, 1441, 1290, 1248, 1201, 1180, 1154, 1114, 1074, 1083, 985; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.34 (dd, J = 4.7, 1.4 Hz, 1H), 7.47 (dd, J = 8.4, 1.4 Hz, 1H), 7.35–7.11 (m, 3H), 6.84 (d, J = 8.8 Hz, 2H), 5.80 (d, J = 1.2 Hz, 1H), 5.47 (d, J = 1.2 Hz, 1H), 5.02 (s, 2H), 3.81 (s, 3H), 3.28 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 159.3 (C), 151.4 (C), 150.9 (C), 145.8 (C), 142.5 (CH), 132.9 (C), 127.8 (2CH), 123.5 (CH), 122.8 (CH), 116.0 (CH_2), 113.7 (2CH), 94.7 (OCH_2O), 56.3 (OCH_3), 55.4 (OCH_3); HRMS (ESI): for $C_{16}H_{18}NO_3$ $(M + H)^+$: m/z calcd 272.1287, found 272.1295.

2e 2-(1-(4-Methoxyphenyl)vinyl)pyridin-3-amine was prepared according to method A. Brown solid (127 mg, 56% yield); mp: 122–124 °C; TLC: R_f = 0.06 (EtOAc–cyclohexane, 2/8, SiO_2); IR (thin film, neat) ν_{max}/cm^{-1}: 3359, 3214, 2209, 2189, 2174, 2103, 2020, 1986, 1606, 1511, 1453, 1249, 1182, 1161, 1032; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.11 (dd, J = 4.6, 1.4 Hz, 1H), 7.29 (d, J = 8.9 Hz, 2H), 7.17–6.98 (m, 2H), 6.86 (d, J = 8.9 Hz, 2H), 5.86 (d, J = 0.9 Hz, 1H), 5.49 (d, J = 0.9 Hz, 1H), 3.80 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 159.9 (C), 145.4 (C), 145.2 (C), 140.7 (C), 139.1 (CH), 131.0 (C), 128.0 (2CH), 123.6 (CH), 123.0 (CH), 116.2 (CH_2), 114.2 (2CH), 55.4 (OCH_3); HRMS (ESI): for $C_{14}H_{15}N_2O$ $(M + H)^+$: m/z calcd 227.1179, found 227.1174.

2f 2-(1-(4-Methoxyphenyl)vinyl)-3-nitropyridine was prepared according to method A. Yellow oil (187 mg, 73% yield); TLC: R_f = 0.3 (EtOAc–cyclohexane, 3/7, SiO_2); IR (thin film, neat) ν_{max}/cm^{-1}: 3420, 3395, 3378, 3342, 3307, 3275, 2353, 2151, 2133, 1983, 1560, 1528, 1511, 1458, 1356, 1251, 1026; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.86 (dd, J = 4.7, 1.4 Hz, 1H), 8.17 (dd, J = 8.2, 1.4 Hz, 1H), 7.47 (dd, J = 8.2, 4.8 Hz, 1H), 7.22 (d, J = 8.8 Hz, 2H), 6.84 (d, J = 8.8 Hz, 2H), 5.77 (s, 1H), 5.46 (s, 1H), 3.80 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 159.9 (C), 157.7 (C), 155.6 (C), 152.5 (CH), 146.0 (C), 137.0 (C), 132.3

(CH), 128.1 (2CH), 123.1 (CH), 116.8 (CH_2), 114.1 (2CH), 55.4 (OCH_3); HRMS (ESI): for $C_{14}H_{13}N_2O_3$ $(M + H)^+$: *m*/*z* calcd 257.0921, found 257.0916.

2g 2-(1-(4-Methoxyphenyl)vinyl)-3-(trifluoromethyl)-pyridine was prepared according to method A. Yellow oil (173 mg, 62% yield); TLC: R_f = 0.4 (EtOAc–cyclohexane, 5/5, SiO_2); IR (thin film, neat) ν_{max}/cm^{-1}: 2157, 1608, 1571, 1512, 1452, 1313, 1290, 1250, 1135, 1115, 1088, 1064, 1027, 907; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.82 (dd, *J* = 4.8, 1.0 Hz, 1H), 8.05 (dd, *J* = 8.1, 1.0 Hz, 1H), 7.39 (ddd, *J* = 8.1, 4.9, 1.0 Hz, 1H), 7.19 (d, *J* = 9.0 Hz, 2H), 6.83 (d, *J* = 9.0 Hz, 2H), 5.87 (s, 1H), 5.23 (s, 1H), 3.79 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 159.6 (C), 159.1 (C), 152.1 (CH), 145.7 (C), 134.9 (q, *J* = 4.8 Hz, CH), 131.8 (C), 128.0 (2CH), 125.5 (q, *J* = 31.6 Hz, C), 122.0 (CH), 123.6 (q, *J* = 273.3 Hz, C), 115.6 (CH_2), 114.0 (2CH), 55.36 (OCH_3); ^{19}F NMR (188 MHz, $CDCl_3$) δ −59.1; HRMS (ESI): for $C_{15}H_{13}F_3NO$ $(M + H)^+$: *m*/*z* calcd 280.0944, found 280.0931.

2h 2-(1-(4-Methoxyphenyl)vinyl)-6-(1*H*-pyrazol-1-yl)pyridine was prepared according to method A. Yellow solid (222 mg, 80% yield); mp: 69–71 °C; TLC: R_f = 0.6 (EtOAc–cyclohexane, 3/7, SiO_2); IR (thin film, neat) ν_{max}/cm^{-1}: 1609, 1592, 1509, 1464, 1433, 1392, 1341, 1286, 1245, 1203, 1172, 1093, 1035; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.59 (d, *J* = 2.5 Hz, 1H), 7.91 (d, *J* = 8.1 Hz, 1H), 7.80–7.69 (m, 2H), 7.33 (d, *J* = 8.7 Hz, 2H), 7.15 (d, *J* = 7.6 Hz, 1H), 6.92 (d, *J* = 8.7 Hz, 2H), 6.48–6.40 (m, 1H), 6.09 (d, *J* = 1.6 Hz, 1H), 5.57 (d, *J* = 1.6 Hz, 1H), 3.85 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 159.6 (C), 157.0 (C), 151.0 (C), 147.9 (C), 142.1 (CH), 139.1 (CH), 132.6 (C), 129.9 (2CH), 127.3 (CH), 120.3 (CH), 117.3 (CH_2), 113.8 (2CH), 111.1 (CH), 107.7 (CH), 55.5 (OCH_3); HRMS (ESI): for $C_{17}H_{16}N_3O$ $(M + H)^+$: *m*/*z* calcd 278.1274, found 278.1288.

2i 2-(1-(3,4,5-Trimethoxyphenyl)vinyl)pyridine was prepared according to method A. Yellow oil (193 mg, 71% yield); TLC: R_f = 0.1 (EtOAc–cyclohexane, 2/8, SiO_2); IR (thin film, neat) ν_{max}/cm^{-1}: 2829, 2160, 1580, 1503, 1466, 1411, 1349, 1235, 1184, 1125, 1006; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.68–8.62 (m, 1H), 7.67 (td, *J* = 7.8, 1.8 Hz, 1H), 7.33 (d, *J* = 7.8 Hz, 1H), 7.24–7.19 (m, 1H), 6.56 (s, 2H), 5.96 (d, *J* = 1.4 Hz, 1H), 5.59 (d, *J* = 1.4 Hz, 1H), 3.88 (s, 3H), 3.82 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 158.6 (C), 153.2 (2C), 149.5 (CH), 149.4 (C), 136.5 (CH), 136.2 (C), 134.0 (C), 123.1 (CH), 122.7 (CH), 117.6 (CH_2), 106.0 (2CH), 61.0 (OCH_3), 56.3 (2OCH_3); HRMS (ESI): for $C_{16}H_{18}NO_3$ $(M + H)^+$: *m*/*z* calcd 272.1287, found 272.1274.

2j 5-Methoxy-2-(1-(3,4,5-trimethoxyphenyl)vinyl)pyridine was prepared according to method A. Yellow oil (190 mg, 63% yield); TLC: R_f = 0.24 (EtOAc–cyclohexane, 5/5, SiO_2); IR (thin film, neat) ν_{max}/cm^{-1}: 2832, 1580, 1504, 1411, 1350, 1288, 1265, 1236, 1223, 1181, 1124, 1029, 1007, 947; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.34 (d, *J* = 3.0 Hz, 1H), 7.31–7.22 (m, 1H), 7.15 (dd, *J* = 8.7, 3.0 Hz, 1H), 6.55 (s, 2H), 5.84 (d, *J* = 1.5 Hz, 1H), 5.47 (d, *J* = 1.5 Hz, 1H), 3.88 (s, 3H), 3.87 (s, 3H), 3.82 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 155.1 (C), 153.1 (2C), 151.1 (C), 148.8 (C), 137.2 (CH), 136.6 (C), 135.9 (C), 123.4 (CH), 120.6 (CH), 116.0 (CH_2), 105.9 (2CH), 61.0 (OCH_3), 56.2 (2OCH_3), 55.8 (OCH_3); HRMS (ESI): for $C_{17}H_{20}NO_4$ $(M + H)^+$: *m*/*z* calcd 302.1387, found 302.1402.

2k 3-Methoxy-2-nitro-6-(1-(3,4,5-trimethoxyphenyl)vinyl)-pyridine was prepared according to method A. Yellow solid (225 mg, 65% yield); mp: 128–130 °C; TLC: R_f = 0.17 (EtOAc–cyclohexane, 5/5, SiO_2); IR (thin film, neat) ν_{max}/cm^{-1}: 1580, 1542, 1505, 1470, 1412, 1344, 1288, 1236, 1184, 1027, 1006; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.47 (d, *J* = 8.7 Hz, 1H), 7.43 (d, *J* = 8.7 Hz, 1H), 6.59 (s, 2H), 6.07 (d, *J* = 1.2 Hz, 1H), 5.57 (d, *J* = 1.2 Hz, 1H), 3.99 (s, 3H), 3.91 (s, 3H), 3.86 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 153.3 (2C), 153.1 (C), 148.5 (C), 146.5 (C), 146.2 (C), 138.3 (C), 135.2 (C), 127.2 (CH), 122.6 (CH), 118.7 (CH_2), 106.0 (2CH), 61.1 (OCH_3), 56.8 (OCH_3), 56.4 (2OCH_3); HRMS (ESI): for $C_{17}H_{19}N_2O_6$ $(M + H)^+$: *m*/*z* calcd 347.1238, found 347.1226.

2l 2-(1*H*-Pyrazol-1-yl)-6-(1-(3,4,5-trimethoxyphenyl)vinyl)-pyridine was prepared according to method A. Yellow oil (270 mg, 80% yield); TLC: R_f = 0.48 (EtOAc–cyclohexane, 3/7, SiO_2); IR (thin film, neat) ν_{max}/cm^{-1}: 3488, 1570, 1504, 1467, 1412, 1392, 1348, 1332, 1236, 1203, 1126, 1039, 1008; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.61 (dd, *J* = 2.6, 0.7 Hz, 1H), 7.91 (dd, *J* = 8.2, 0.7 Hz, 1H), 7.78–7.70 (m, 2H), 7.15 (dd, *J* = 7.6, 0.7 Hz, 1H), 6.61 (s, 2H), 6.45 (dd, *J* = 2.6, 1.7 Hz, 1H), 6.18 (d, *J* = 1.6 Hz, 1H), 5.59 (d, *J* = 1.6 Hz, 1H), 3.90 (s, 3H), 3.83 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 156.4 (C), 153.1 (2C), 151.1 (C), 148.3 (C), 142.2 (CH), 139.2 (CH), 138.1 (C), 135.9 (C), 127.2 (CH), 120.3 (CH), 118.2 (CH_2), 111.3 (CH), 107.8 (CH), 106.1 (2CH), 61.0 (OCH_3), 56.3 (2OCH_3); HRMS (ESI): for $C_{19}H_{20}N_3O_3$ $(M + H)^+$: *m*/*z* calcd 338.1499, found 338.1483.

2m 2-Fluoro-3-methoxy-6-(1-(3,4,5-trimethoxyphenyl)vinyl)-pyridine was prepared according to method A. Yellow solid (287 mg, 90% yield); mp: 106–108 °C; TLC: R_f = 0.28 (EtOAc–cyclohexane, 3/7, SiO_2); IR (thin film, neat) ν_{max}/cm^{-1}: 3394, 3364, 3193, 3107, 3018, 2355, 2186, 2170, 2027, 1979, 1580, 1504, 1472, 1430, 1411, 1344, 1255, 1236, 1128, 1006; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.26–7.17 (m, 1H), 7.09 (dd, *J* = 8.1, 1.0 Hz, 1H), 6.58 (s, 2H), 6.02 (d, *J* = 1.5 Hz, 1H), 5.46 (d, *J* = 1.5 Hz, 1H), 3.94 (s, 3H), 3.90 (s, 3H), 3.85 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 153.2 (2C), 152.8 (d, *J* = 239.1 Hz) (C), 147.1 (C), 146.3 (d, *J* = 12.0 Hz) (C), 142.2 (d, *J* = 26.2 Hz) (C), 138.1 (C), 136.0 (C), 121.5 (d, *J* = 4.3 Hz, CH), 120.6 (d, *J* = 3.7 Hz, CH), 117.1 (CH_2), 106.1 (2CH), 61.1 (OCH_3), 56.5 (OCH_3), 56.3 (2OCH_3); ^{19}F NMR (188 MHz, $CDCl_3$) δ −81.2; HRMS (ESI): for $C_{17}H_{19}FNO_4$ $(M + H)^+$: *m*/*z* calcd 320.1293, found 320.1282.

2n 2-Bromo-3-methoxy-6-(1-(3,4,5-trimethoxyphenyl)vinyl)-pyridine was prepared according to method A. Brown solid (208 mg, 55% yield); mp: 120–122 °C; TLC: R_f = 0.63 (EtOAc–cyclohexane, 5/5, SiO_2); IR (thin film, neat) ν_{max}/cm^{-1}: 1580, 1549, 1503, 1453, 1430, 1411, 1341, 1298, 1234, 1183, 1124, 1073, 1005; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.14 (d, *J* = 8.3 Hz, 1H), 7.05 (d, *J* = 8.3 Hz, 1H), 6.57 (s, 2H), 6.02 (d, *J* = 1.4 Hz, 1H), 5.47 (d, *J* = 1.4 Hz, 1H), 3.93 (s, 3H), 3.88 (s, 3H), 3.83 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 153.0 (2C), 152.0 (C), 150.4 (C), 146.9 (C), 137.9 (C), 135.8 (C), 132.1 (C), 122.5 (CH), 118.5 (CH), 117.1 (CH_2), 105.9 (2CH), 60.9 (OCH_3), 56.4 (OCH_3), 56.2 (2OCH_3); HRMS (ESI): for $C_{17}H_{19}BrNO_4$ $(M + H)^+$: *m*/*z* calcd 380.0492, found 380.0474.

2o 5-Bromo-2-(1-(4-methoxyphenyl)vinyl)pyridine was prepared according to method A. Yellow oil (130 mg, 45% yield); TLC: R_f = 0.61 (EtOAc–cyclohexane, 2/8, SiO_2); IR (thin film, neat) ν_{max}/cm^{-1}: 3392, 3192, 3170, 1993, 1974, 1607, 1571, 1511, 1461, 1291, 1248, 1180, 1093, 1033, 1004; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.7 (d, J = 2.4 Hz, 1H), 7.8 (dd, J = 8.4, 2.4 Hz, 1H), 7.3–7.2 (m, 3H), 6.9 (d, J = 8.8 Hz, 2H), 5.9 (d, J = 1.2 Hz, 1H), 5.6 (d, J = 1.2 Hz, 1H), 3.8 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 159.1 (C), 158.8 (C), 150.3 (CH), 147.5 (C), 139.3 (CH), 133.0 (C), 129.7 (2CH), 124.3 (CH), 119.6 (C), 117.6 (CH_2), 114.0 (2CH), 55.5 (OCH_3); HRMS (ESI): for $C_{14}H_{13}BrNO$ $(M + H)^+$: m/z calcd 290.0175, found 290.0165.

2p 5-Fluoro-2-(1-(4-methoxyphenyl)vinyl)pyridine was prepared according to method B. Yellow oil (165 mg, 72% yield); TLC: R_f = 0.51 (EtOAc–cyclohexane, 2/8, SiO_2); IR (thin film, neat) ν_{max}/cm^{-1}: 2925, 1657, 1601, 1580, 1511, 1477, 1382, 1333, 1306, 1248, 1224, 1181, 1151, 1115, 1032, 934; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.44–8.33 (m, 1H), 7.30–7.14 (m, 4H), 6.81 (d, J = 8.7 Hz, 2H), 5.73 (d, J = 1.4 Hz, 1H), 5.45 (d, J = 1.4 Hz, 1H), 3.74 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 159.6 (C), 158.9 (d, J = 256.3 Hz) (C), 155.3 (d, J = 3.75 Hz) (C), 147.8 (C), 137.6 (d, J = 23.6 Hz) (CH), 132.8 (C), 129.6 (2CH), 123.8 (d, J = 4.2 Hz) (CH), 123.0 (d, J = 18.4 Hz) (CH), 116.5 (CH_2), 113.9 (2CH), 55.6 (OCH_3); ^{19}F NMR (188 MHz, $CDCl_3$) δ (ppm): −127.1; HRMS (ESI): for $C_{14}H_{13}FNO$ $(M + H)^+$: m/z calcd 230.0976, found 230.0979.

2q 2-(1-(4-Chlorophenyl)vinyl)pyridine was prepared according to method A. Yellow oil (172 mg, 80% yield); TLC: R_f = 0.21 (EtOAc–cyclohexane, 2/8, SiO_2); IR (thin film, neat) ν_{max}/cm^{-1}: 1584, 1563, 1489, 1467, 1430, 1394, 1150, 1090, 1014; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.60 (d, J = 7.7 Hz, 1H), 7.63 (td, J = 7.7, 1.5 Hz, 1H), 7.33–7.15 (m, 6H), 5.95 (s, 1H), 5.58 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 158.2 (C), 149.4 (CH), 148.1 (C), 138.8 (C), 136.8 (CH), 134.0 (C), 129.9 (2CH), 128.7 (2CH), 122.9 (CH), 122.8 (CH), 118.5 (CH_2); HRMS (ESI): for $C_{13}H_{11}ClN$ $(M + H)^+$: m/z calcd 216.0575, found 216.0575.

2r 2-(6-Methoxy-3,4-dihydronaphthalen-1-yl)pyridine was prepared according to method B. Yellow oil (143 mg, 60% yield); TLC: R_f = 0.18 (EtOAc–cyclohexane, 3/7, SiO_2); IR (thin film, neat) ν_{max}/cm^{-1}: 1580, 1503, 1465, 1408, 1343, 1289, 1233, 1182, 1124, 1032, 1008; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.66 (d, J = 4.9 Hz, 1H), 7.73 (td, J = 7.9, 1.7 Hz, 1H), 7.42 (d, J = 7.9 Hz, 1H), 7.25 (dt, J = 4.9, 1.7 Hz, 1H), 7.02 (d, J = 8.5 Hz, 1H), 6.77 (d, J = 2.6 Hz, 1H), 6.66 (dd, J = 8.5, 2.6 Hz, 1H), 6.31 (t, J = 4.9 Hz, 1H), 3.80 (s, 3H), 2.84 (t, J = 7.9 Hz, 2H), 2.44 (td, J = 7.9, 4.9 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 159.1 (C), 158.9 (C), 149.3 (CH), 138.9 (C), 136.6 (CH), 128.3 (CH), 128.3 (C), 127.2 (C), 126.6 (CH), 123.5 (CH), 122.1 (CH), 113.9 (CH), 111.1 (CH), 55.40 (OCH_3), 28.8 (CH_2), 23.6 (CH_2); HRMS (ESI): for $C_{16}H_{16}NO$ $(M + H)^+$: m/z calcd 238.1226, found 238.1220.

2s (*E*)-2-Cyclooctenylpyridine was prepared according to method A. Yellow oil (163 mg, 87% yield); TLC: R_f = 0.56 (EtOAc–cyclohexane, 1/9, SiO_2); IR (thin film, neat) ν_{max}/cm^{-1}: 2922, 2849, 1585, 1563, 1465, 1428, 1249; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.60–8.53 (m, 1H), 7.62 (td, J = 7.8, 1.9 Hz, 1H), 7.43 (dt, J = 8.1, 1.0 Hz, 1H), 7.10 (ddd, J = 7.4, 4.9, 1.1 Hz, 1H), 6.63 (t, J = 8.4 Hz, 1H), 2.80–2.73 (m, 2H), 2.42–2.30 (m, 2H), 1.75–1.38 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 159.2 (C), 148.8 (CH), 139.8 (C), 136.6 (CH), 132.0 (CH), 121.4 (CH), 119.9 (CH), 29.9 (CH_2), 29.4 (CH_2), 27.7 (CH_2), 27.1 (CH_2), 26.5 (CH_2), 26.3 (CH_2); HRMS (ESI): for $C_{13}H_{18}N$ $(M + H)^+$: m/z calcd 188.1434, found 188.1427.

2t 2-(1-(4-Methoxyphenyl)vinyl)quinoline was prepared according to method B. Brown solid (188 mg, 72% yield); mp: 71–73 °C; TLC: R_f = 0.47 (EtOAc–cyclohexane, 2/8, SiO_2); IR (thin film, neat) ν_{max}/cm^{-1}: 1608, 1511, 1461, 1285, 1246, 1166, 1115, 1031; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.15 (d, J = 8.6 Hz, 1H), 8.09 (d, J = 8.6 Hz, 1H), 7.81 (dd, J = 8.2, 1.2 Hz, 1H), 7.72 (ddd, J = 8.4, 6.9, 1.5 Hz, 1H), 7.53 (ddd, J = 8.2, 6.9, 1.2 Hz, 1H), 7.39 (d, J = 8.5 Hz, 1H), 7.37–7.31 (m, 2H), 6.91 (d, J = 8.4 Hz, 2H), 5.98 (d, J = 1.4 Hz, 1H), 5.71 (d, J = 1.4 Hz, 1H), 3.84 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 159.6 (C), 159.4 (C), 151.9 (C), 149.1 (C), 148.1 (C), 136.2 (CH), 132.7 (C), 129.9 (CH), 129.7 (3CH), 127.5 (CH), 126.6 (CH), 121.4 (CH), 117.5 (CH_2), 113.9 (2CH), 55.45 (OCH_3); HRMS (ESI): for $C_{18}H_{16}NO$ $(M + H)^+$: m/z calcd 262.1226, found 262.1224.

2u 2-(1-(4-Methoxyphenyl)vinyl)pyrazine was prepared according to method A. Yellow oil (127 mg, 60% yield); TLC: R_f = 0.26 (EtOAc–cyclohexane, 2/8, SiO_2); IR (thin film, neat) ν_{max}/cm^{-1}: 1731, 1652, 1597, 1548, 1511, 1467, 1400, 1305, 1247, 1169, 1016; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.62 (d, J = 1.6 Hz, 1H), 8.58 (dd, J = 2.5, 1.6 Hz, 1H), 8.49 (d, J = 2.5 Hz, 1H), 7.28 (d, J = 8.8 Hz, 2H), 6.91 (d, J = 8.8 Hz, 2H), 5.92 (d, J = 1.1 Hz, 1H), 5.66 (d, J = 1.1 Hz, 1H), 3.83 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 159.9 (C), 154.6 (C), 146.1 (C), 144.3 (CH), 144.0 (CH), 143.4 (CH), 131.7 (C), 129.6 (2CH), 118.4 (CH_2), 114.1 (2CH), 55.5 (OCH_3); HRMS (ESI): for $C_{13}H_{13}N_2O$ $(M + H)^+$: m/z calcd 213.1022, found 213.1026.

2v 2-(1-(4-Methoxyphenyl)vinyl)-1-methyl-1*H*-benzo[*d*]-imidazole was prepared according to method B. Yellow oil (137 mg, 52% yield); TLC: R_f = 0.11 (EtOAc–cyclohexane, 2/8, SiO_2); IR (thin film, neat) ν_{max}/cm^{-1}: 1606, 1513, 1461, 1438, 1326, 1301, 1247, 1179, 1122, 1029; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.89–7.77 (m, 1H), 7.37–7.21 (m, 5H), 6.87 (d, J = 8.9 Hz, 2H), 5.97 (d, J = 0.8 Hz, 1H), 5.74 (d, J = 0.8 Hz, 1H), 3.82 (s, 3H), 3.50 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 160.1 (C), 153.9 (C), 151.3 (C), 138.7 (C), 136.1 (C), 130.8 (C), 128.1 (2CH), 123.0 (CH), 122.5 (CH), 120.1 (CH), 119.7 (CH_2), 114.3 (2CH), 109.6 (CH), 55.5 (OCH_3), 31.2 (NCH_3); HRMS (ESI): for $C_{17}H_{17}N_2O$ $(M + H)^+$: m/z calcd 265.1335, found 265.1327.

2w 4-(1-(4-Methoxyphenyl)vinyl)thiazole was prepared according to method A. Yellow oil (141 mg, 65% yield); TLC: R_f = 0.49 (EtOAc–cyclohexane, 2/8, SiO_2); IR (thin film, neat) ν_{max}/cm^{-1}: 3275, 3212, 3192, 3137, 2219, 2187, 1967, 1605, 1511, 1463, 1293, 1246, 1176, 1032; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.83 (d, J = 2.0 Hz, 1H), 7.36 (d, J = 8.8 Hz, 2H), 7.10 (d, J = 2.0 Hz, 1H), 6.91 (d, J = 8.8 Hz, 2H), 6.05 (d, J = 1.7 Hz, 1H), 5.44 (d, J = 1.7 Hz, 1H), 3.84 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 159.63 (C), 157.0 (C), 152.8 (CH), 142.5 (C), 133.1 (C), 129.6 (2CH), 116.2 (CH), 115.8 (CH_2), 113.9 (2CH),

55.5 (OCH_3); HRMS (ESI): for $C_{12}H_{12}NOS$ $(M + H)^+$: *m*/*z* calcd 218.0634, found 218.0630.

2x 2-Methoxy-5-(1-(3,4,5-trimethoxyphenyl)vinyl)pyridine was prepared according to method A. Yellow oil (295 mg, 98% yield); TLC: R_f = 0.42 (EtOAc–cyclohexane, 3/7, SiO_2); IR (thin film, neat) ν_{max}/cm^{-1}: 1599, 1579, 1491, 1463, 1410, 1368, 1342, 1287, 1234, 1182, 1124, 1005; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.18 (d, J = 2.4 Hz, 1H), 7.52 (dd, J = 8.6, 2.4 Hz, 1H), 6.71 (d, J = 8.6 Hz, 1H), 6.52 (s, 2H), 5.38 (s, 2H), 3.96 (s, 3H), 3.86 (s, 3H), 3.81 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 164.0 (C), 153.2 (2C), 146.8 (C), 146.3 (CH), 138.6 (CH), 138.2 (C), 136.7 (C), 130.4 (C), 113.6 (CH_2), 110.3 (CH), 105.6 (2CH), 61.0 (OCH_3), 56.3 ($2OCH_3$), 53.7 (OCH_3); HRMS (ESI): for $C_{17}H_{20}NO_4$ $(M + H)^+$: *m*/*z* calcd 302.1387, found 302.1389.

2y 2-Methoxy-5-(1-(3,4,5-trimethoxyphenyl)vinyl)-pyrimidine was prepared according to method A. Yellow oil (242 mg, 80% yield); TLC: R_f = 0.49 (EtOAc–cyclohexane, 3/7, SiO_2); IR (thin film, neat) ν_{max}/cm^{-1}: 1710, 1592, 1548, 1504, 1475, 1409, 1327, 1237, 1172, 1125, 1004; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.49 (s, 2H), 6.50 (s, 2H), 5.47 (s, 1H), 5.42 (s, 1H), 4.04 (s, 3H), 3.87 (s, 3H), 3.82 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 165.4 (C), 158.6 (2CH), 153.4 (2C), 143.8 (C), 138.6 (C), 135.6 (C), 128.7 (C), 114.9 (2CH), 105.4 (CH_2), 61.1 (OCH_3), 56.4 ($2OCH_3$), 55.2 (OCH_3); HRMS (ESI): for $C_{16}H_{19}N_2O_4$ $(M + H)^+$: *m*/*z* calcd 303.1339, found 303.1339.

2z 2-Methoxy-5-(1-(4-methoxyphenyl)vinyl)pyrimidine was prepared according to method A. Yellow solid (206 mg, 85% yield); mp: 66–68 °C; TLC: R_f = 0.45 (EtOAc–cyclohexane, 3/7, SiO_2); IR (thin film, neat) ν_{max}/cm^{-1}: 1608, 1589, 1546, 1510, 1472, 1409, 1321, 1289, 1248, 1179, 1127, 1029; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.46 (s, 2H), 7.24 (d, J = 8.8 Hz, 2H), 6.88 (d, J = 8.8 Hz, 2H), 5.45 (s, 1H), 5.33 (s, 1H), 4.04 (s, 3H), 3.82 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 165.3 (C), 160.0 (C), 158.6 (2CH), 143.1 (2C), 132.3 (C), 129.1 (2CH), 114.1 (2CH), 113.9 (CH_2), 55.5 (OCH_3), 55.2 (OCH_3); HRMS (ESI): for $C_{14}H_{15}N_2O_2$ $(M + H)^+$: *m*/*z* calcd 243.1128, found 243.1130.

2aa 3-Methoxy-6-(1-(3,4,5-trimethoxyphenyl)vinyl)pyridin-2-amine was prepared according to a method described by Merlic *et al.*[17] Iron powder (162 mg, 2.89 mmol) and concentrated hydrochloric acid (*ca*. 10 mg) were added to a solution of 3-methoxy-2-nitro-6-(1-(3,4,5-trimethoxyphenyl)vinyl)pyridine (100 mg, 0.29 mmol) in EtOH (1.5 mL) and water (0.3 mL), and the mixture was heated to reflux for 90 min. EtOAc (5 mL) was added to the mixture, and it was dried with $MgSO_4$. After filtration and evaporation of the solvent, the residue was purified by chromatography to give the amino product. Compound **2aa** was obtained as a white solid (85 mg, 92% yield); mp = 106–108 °C; TLC: R_f = 0.15 (EtOAc–cyclohexane, 5/5, SiO_2); IR (thin film, neat) ν_{max}/cm^{-1}: 3390, 2249, 1624, 1577, 1505, 1477, 1410, 1348, 1238, 1167, 1125, 1061, 1005; ^1H NMR (300 MHz, CD_3COCD_3) δ (ppm): 6.95 (d, J = 8.0 Hz, 1H), 6.64 (s, 2H), 6.52 (d, J = 8.0 Hz, 1H), 5.85 (d, J = 2.4 Hz, 1H), 5.55–5.05 (m, 3H), 3.84 (s, 3H), 3.80 (s, 6H), 3.76 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 154.0 (2C), 150.9 (C), 150.2 (C), 148.0 (C), 142.9 (C), 139.0 (C), 138.0 (C), 115.7 (CH), 114.6 (CH_2), 113.2 (CH), 107.3 (2CH), 60.7 (OCH_3), 56.6 ($2OCH_3$), 55.8 (OCH_3); HRMS (ESI): for $C_{17}H_{21}N_2O_4$ $(M + H)^+$: *m*/*z* calcd 317.1488, found 317.1496.

2ab 3-Methoxy-6-(1-(3,4,5-trimethoxyphenyl)vinyl)pyridin-2-ol was prepared according to a method described by Buchwald *et al.*[18] In a sealed tube, Pd_2dba_3 (14 mg, 0.015 mmol), ^{t}Bu XPhos (25 mg, 0.06 mmol), 2-bromo-3-methoxy-6-(1-(3,4,5-trimethoxyphenyl)vinyl)pyridine (148 mg, 0.39 mmol) and KOH (43 mg, 0.77 mmol) were charged. Dioxane–water (1 : 1) (1 mL) was then added. The mixture was stirred in a preheated oil bath (90 °C) until the aryl halide was consumed as judged by TLC (6 h). The reaction mixture was cooled to room temperature, carefully acidified with dilute aqueous HCl. The resulting mixture was extracted with ethyl acetate. The separated organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. Compound **2ab** was obtained as a brown solid (80 mg, 65% yield); mp = 199–200 °C; TLC: R_f = 0.20 (EtOAc, SiO_2); IR (thin film, neat) ν_{max}/cm^{-1}: 3387, 3282, 2174, 2022, 1656, 1622, 1576, 1505, 1465, 1451, 1413, 1336, 1279, 1233, 1178, 1125, 1016; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 9.23 (bs, 1H), 6.66 (d, J = 7.7 Hz, 1H), 6.51 (s, 2H), 6.20 (d, J = 7.7 Hz, 1H), 5.57 (s, 1H), 5.41 (s, 1H), 3.88 (s, 3H), 3.85 (s, 3H), 3.84 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 158.7 (C), 153.3 (2C), 150.0 (C), 143.0 (C), 138.6 (C), 136.3 (C), 134.1 (C), 115.7 (CH), 113.9 (CH), 106.4 (2CH), 106.2 (CH_2), 61.0 (OCH_3), 56.4 ($2OCH_3$), 56.0 (OCH_3); HRMS (ESI): for $C_{17}H_{20}NO_5$ $(M + H)^+$ calcd 318.1336, found 318.1331.

Biology

Cell culture and proliferation assay. Cancer cell lines were obtained from the American type Culture Collection (Rockville, MD) and were cultured according to the supplier's instructions. HCT116 colorectal carcinoma cells were grown in RPMI 1640 containing 10% FCS and 1% glutamine. Cell lines were maintained at 37 °C in a humidified atmosphere containing 5% CO_2. Human umbilical vein endothelial cells (HUVECs) were obtained from Clonetics (Lonza; Walkersville, MD, USA) and cultured according to the supplier's instructions. U87 human glioblastoma were grown in Dulbecco's modified Eagle's medium (DMEM) containing glucose (4.5 g l^{-1}) supplemented with fetal calf serum (FCS, 10%) and glutamine (1%). Briefly, HUVECs from three to six passages were subcultured to confluence onto 0.2% gelatin-coated tissue culture flasks in endothelial cell growth medium (EGM2) containing growth factors and 2% FCS. All cell lines were maintained at 37 °C in a humidified atmosphere containing 5% CO_2. Cell viability was assessed using a Promega CellTiter-Blue™ reagent according to the manufacturer's instructions. Cells were seeded in 96-well plates (5×10^3 cells per well) containing 50 μL growth medium. After 24 h of culture, the cells were supplemented with 50 μL of the tested compound dissolved in DMSO (less than 0.1% in each preparation). After 72 h of incubation, 20 μL of resazurin was added for 2 h before recording fluorescence (λ_{ex} = 560 nm, λ_{em} = 590 nm) using a Victor microtiter plate fluorimeter (Perkin-Elmer, USA). The GI_{50} corresponds to the concentration of the tested compound that

caused a decrease of 50% in fluorescence of drug treated cells compared with untreated cells. Experiments were performed in triplicate. The GI_{50} values for all compounds were compared to the GI_{50} of isoCA-4 and measured the same day under the same conditions.

Tubulin binding assay. Sheep brain tubulin was purified according to the method of Shelanski[22] by two cycles of assembly–disassembly and then dissolved in the assembly buffer containing 0.1 M MES, 0.5 mM $MgCl_2$, 1 mM EGTA, and 1 mM GTP, pH 6.6 (the concentration of tubulin was about 2–3 mg mL^{-1}). Tubulin assembly was monitored by fluorescence according to a reported procedure[23] using DAPI as a fluorescent molecule. Assays were realized on 96-well plates prepared with Biomek NKMC and Biomek 3000 from Beckman Coulter and read at 37 °C on a Wallac Victor fluorimeter from Perkin Elmer. The IC_{50} value of each compound was determined as the concentration which decreased the maximum assembly rate of tubulin by 50% compared to the rate in the absence of the compound. The IC_{50} values for all compounds were compared to the IC_{50} of CA4 and isoCA-4 and measured the same day under the same conditions.

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