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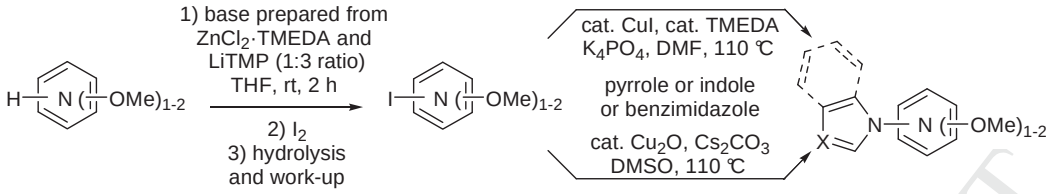
Graphical Abstract



Synthesis of *N*-pyridyl azoles using a deprotometalation-iodolysis-*N*-arylation sequence and evaluation of their antiproliferative activity in melanoma cells

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Abstract:

N-Arylation of pyrrole with 3-iodo-4-methoxypyridine was investigated by copper catalysis under different conditions. The best conditions, that proved to be protocol A (CuI, DMEDA or TMEDA, K_3PO_4, DMF at 110 °C) and above all protocol B (Cu_2O, Cs_2CO_3, DMSO at 110 °C), were applied to the synthesis of various *N*-(methoxypyridyl) pyrroles, indoles and benzimidazoles. The behavior of the different iodinated methoxypyridines was rationalized by evaluating the partial positive charge on the carbon bearing iodine from the ^{1}H NMR chemical shift of the corresponding deiodinated substrates. The reaction was next connected with the deprotometalation-iodolysis step generating iodinated methoxypyridines: straight involvement of the crude iodo intermediates in pyrrole *N*-arylation afforded the expected *N*-(methoxypyridyl) pyrroles in good yields. Several synthesized *N*-(methoxypyridyl) azoles exerted low to moderate antiproliferative activity in A2058 melanoma cells.

1. Introduction

Aromatic heterocycles are present in numerous molecules of chemical or biological interest, as well as in organic materials for different applications. In particular, *N*-(pyridyl) azoles are key skeletons present in pharmaceuticals[1] and in functional materials.[1g,2]

The development of simple methods to build such scaffolds is thus of interest. Among them, deprotonative[3] and dehalogenative[4] metalations, using respectively polar organometallic bases and transition metal catalysts, are powerful tools.

Recently, metallic pairs with which deprotolithiation is followed by "trans-metal trapping"[5] allowed sensitive substrates to be functionalized.[6] Within this context, we have developed the putative pair 1:1 $Zn(TMP)_2$-LiTMP·2LiCl±TMEDA[7] (TMP = 2,2,6,6-tetramethylpiperidino; TMEDA = *N*,*N*,*N*',*N*'-tetramethylethylenediamine), generated from $ZnCl_2$·TMEDA and LiTMP in a 1:3 ratio,[8] for the room temperature functionalization of numerous substrates including pyridines.[9] In addition, copper-catalyzed *N*-arylation of azoles has recently met a huge development.[4a,b,4d-f,10]

We here report our efforts to combine deprotometalation-iodolysis of methoxypyridines with *N*-arylation of azoles for the synthesis of pyridine-based C,N'-linked bis-heterocycles. The antiproliferative activation of the obtained scaffolds in melanoma cells has also been evaluated.

2. Results and Discussion

We recently developed a deprotometalation-iodolysis-*N*-arylation sequence from benzothiophene, benzofuran, benzothiazole and benzoxazole to access various bis-heterocycles.[11] In this study, deprotolithiation followed by *in situ* trans-metal trapping of the five-membered aromatic heterocycles was carried out in THF (THF = tetrahydrofuran) before iodolysis by using a basic combination prepared from $ZnCl_2$·TMEDA and LiTMP in a 1:3 ratio,[8-9,12] and supposed to afford 1:1 $Zn(TMP)_2$-LiTMP·2LiCl±TMEDA.[7-8] The crude iodides were directly involved in the *N*-arylation of different azoles (1.5 equiv) in the presence of metal copper (0.2 equiv), cesium carbonate (2 equiv) and acetonitrile, at the reflux temperature of the solvent for 24 h.[13]

In order to reach *N*-pyridyl azoles, we applied this procedure to the commercially available methoxypyridines **1a**, **2a** and **3a** (Table 1). From 2-methoxypyridine (**1a**), the expected *N*-(2-methoxy-3-pyridyl) azoles were isolated in the case of pyrrole (product **1b**, entry 1), pyrazole (**1c**, entry 2) and benzimidazole (**1d**, entry 3). The low yields are, at least to some extent, due to the insufficient amount of lithium-zinc base used; indeed, 2-methoxypyridine (**1a**) is much more completely deprotometalated by employing 1 equiv of $ZnCl_2$·TMEDA and 3 equiv of LiTMP.[9b] The *N*-arylation of benzimidazole (product **1d**) appears as less efficient, when compared with those of pyrrole and pyrazole.

We previously showed that 3-methoxypyridine (**2a**) can be deprotonated upon treatment by the lithium-zinc base, *in situ* prepared from 0.5 equiv of $ZnCl_2$·TMEDA and 1.5 equiv of LiTMP, in THF at 20 °C for 2 h. The regioselectivity of the reaction is however incomplete; indeed, subsequent quenching with iodine afforded the 4-iodo derivative **2a-I** in 85% yield together with 10% of the 2-iodo derivative **2a-I'**.[9b] Therefore, if the isolation of the *N*-(3-methoxy-2-pyridyl) analogues **2b'**, **2e'**, **2d'** and **2f'** after reacting the crude coming from deprotometalation-iodolysis with pyrrole (entry 4), indole

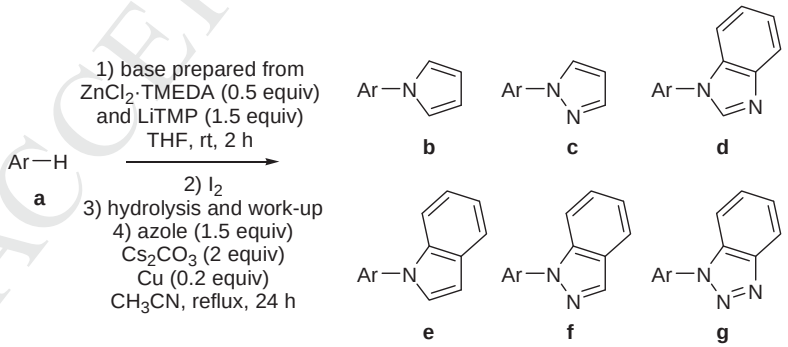
(entry 5), benzimidazole (entry 6) and indazole (entry 7) is not surprising, the absence of *N*-(3-methoxy-4-pyridyl) azoles **2b**, **2e**, **2d** and **2f** is unexpected.

Similarly, whereas 4-methoxypyridine (**3a**) led to 3-iodo-4-methoxypyridine (**3a-I**) in 89% yield after deprotometalation-trapping under the conditions here used, the expected *N*-(4-methoxy-3-pyridyl) azoles **3b**, **3c**, **3f** and **3g** were not identified. Instead, the corresponding *N*-(4-methoxy-2-pyridyl) azoles **3b'**, **3c'**, **3f'** and **3g'** were isolated in low yields (entries 8-11).

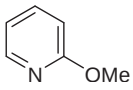
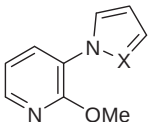
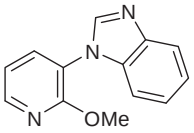
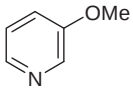
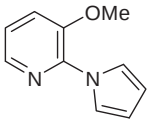
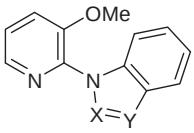
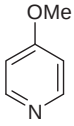
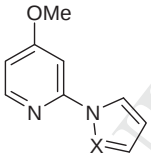
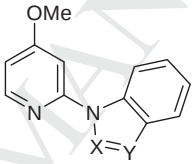
The *N*-(3-methoxy-2-pyridyl) analogues **2b'**, **2e'**, **2d'**, **2f'** and *N*-(4-methoxy-2-pyridyl) azoles **3b'**, **3c'**, **3f'**, **3g'** could be formed by azole *N*-arylation with 2-iodo-3-methoxypyridine (**2a-I'**) and 2-iodo-4-methoxypyridine (**3a-I'**), respectively. Such 2-iodo derivatives **2a-I'** and **3a-I'** can be generated in the course of the deprotometalation-iodolysis reaction. Alternatively, iodine stored by reaction with LiTMP in the course of the iodolysis[14] could work as an oxidant in the coupling step, allowing a cross-dehydrogenative C-N bond formation to occur.[15]

In these reactions, a part of the 3-iodo intermediate **1a-I** (entries 1-3), and all the 4-iodo compound **2a-I** (entries 4-7) or 3-iodo compound **3a-I** (entries 8-11) are not converted by *N*-arylation under the conditions employed.

Table 1. Deprotometalation-iodolysis of the methoxypyridines **1a**, **2a** and **3a** followed by *N*-arylation of azoles with the crude iodides **1a-I**, **2a-I** and **3a-I**.



Entry	Ar-H	Product, Yield (%)[a]

1 2		**1a**		**1b**, 36[b] **1c**, 32[b]
3				**1d**, 12[b]
4		**2a**		**2b'**, 42[c]
5 6 7				**2e'**, 39[c] **2d'**, 17[c] **2f'**, 10[c]
8 9		**3a**		**3b'**, 14[d] **3c'**, 10[d]
10 11				**3f'**, 9[d] **3g'**, traces[d]

[a] After purification by column chromatography. [b] 2-Methoxypyridine (**1a**, due to incomplete deprotometalation) and 3-iodo-2-methoxypyridine (**1a-I**) were also recovered. [c] 4-Iodo-3-methoxypyridine (**2a-I**) and some 3-methoxypyridine (**2a**) were also recovered, and degradation was noticed. [d] 3-Iodo-4-methoxypyridine (**3a-I**) and some 4-methoxypyridine (**3a**) were also recovered.

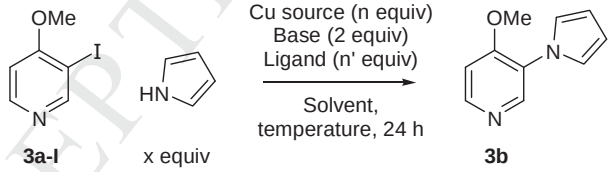
This preliminary study led us to next compare different *N*-arylation procedures to generate *N*-(4-methoxy-3-pyridyl)pyrrole (**3b**), starting from purified 3-iodo-4-methoxypyridine (**3a-I**) and pyrrole (Table 2). First, the protocol using copper and cesium carbonate (2 equiv) at acetonitrile reflux for 24 h was applied;[13] no reaction was observed with either 0.2 or 0.4 equiv of transition metal (entries 1 and 2), in accordance with the results obtained in Table 1 (entries 8-11). It is interesting to notice that *N*-(4-methoxy-2-pyridyl) pyrrole (**3b'**) was not obtained either, allowing to discard both direct addition of copper azolates onto pyridines and conversion of **3a-I** into **3a-I'** by halogen loss followed by halogenation[16] at a different site.

Replacing metal copper by copper(I) oxide (0.1 equiv) and adding salicylaldoxime (Salox) as ligand (0.2 equiv),[17] conditions that worked for the conversion of another iodopyridine,[18] did not furnish either the product **3b** (entry 3). Employing copper(I) iodide without additional ligand under similar conditions[13] only furnished **3b** in very low yields of 8 and 17% by respectively using 0.2 and 1.2 equiv of CuI (entries 4 and 5).

Still with CuI (5 molar %), using potassium triphosphate as base (2 equiv) and DMEDA (DMEDA = *N*,*N'*-dimethylethylenediamine) or TMEDA as ligand (0.1 equiv) in DMF (DMF = *N*,*N*-dimethylformamide) at 110 °C,[19] conditions that worked for the *N*-arylation of benzotriazole (1 equiv) with 3-iodopyridine,[12g] allowed **3b** to be isolated in about 40% yield (entries 6 and 7). The yield dropped to 13% by increasing the amount of TMEDA to 1 equiv (entry 8).

Because azoles can be *N*-arylated with iodopyridines in the presence of copper(I) oxide (0.1 equiv), cesium carbonate (2 equiv) and DMSO (DMSO = dimethylsulfoxide) at 110 °C,[20] we also evaluated this protocol. After 24 h reaction with 1 equiv of pyrrole, **3b** was isolated in 45% yield (entry 9). Doubling the amount of azole furnished **3b** in a slightly higher 55% yield (entry 10).

Table 2. *N*-arylation of pyrrole with purified 3-iodo-4-methoxypyridine (**3a-I**).



3a-I x equiv **3b**

Entry	x	Cu source (n)	Base	Ligand (n')	Solvent, temp.	Yield (%)[a,b]
1	1.5	Cu (0.2)	Cs_2CO_3	-	MeCN, reflux	0
2	1.5	Cu (0.4)	Cs_2CO_3	-	MeCN, reflux	0
3	1	Cu_2O (0.1)	Cs_2CO_3	Salox (0.2)	MeCN, reflux	0
4	1.5	CuI (0.2)	Cs_2CO_3	-	MeCN, reflux	8
5	1.5	CuI (1.2)	Cs_2CO_3	-	MeCN, reflux	17
6	1	CuI (0.05)	K_3PO_4	DMEDA (0.1)	DMF, 110 °C	44
7	1	CuI (0.05)	K_3PO_4	TMEDA (0.1)	DMF, 110 °C	42
8	1	CuI (0.05)	K_3PO_4	TMEDA (1)	DMF, 110 °C	13
9	1	Cu_2O (0.1)	Cs_2CO_3	-	DMSO, 110 °C	45
10	2	Cu_2O (0.1)	Cs_2CO_3	-	DMSO, 110 °C	55

[a] After purification by column chromatography. [b] 3-Iodo-4-methoxypyridine (**3a-I**) and some 4-methoxypyridine (**3a**) were (also) recovered.

Still using pyrrole as azole, we next tested different iodinated methoxypyridines in the best procedures (Table 3). By using potassium triphosphate as base and TMEDA as ligand (0.1 equiv) with copper(I) iodide (0.05 equiv) in DMF at 110 °C (*protocol A*),[19] the expected *N*-pyridyl pyrroles **1b-5b** were isolated in moderate yields, varying between 25% in the case of 3-iodo-2,6-dimethoxypyridine (**5a-I**, entry 17) and 54% for 3-iodo-2-methoxypyridine (**1a-I**, entry 1).

Turning to *protocol B*, with cesium carbonate as base and copper(I) oxide (0.1 equiv) in DMSO at 110 °C, led to the same derivatives **1b-5b** in improved yields. Competitive substitution of the methoxy group at the 4 position was noticed from **3a-I** under these conditions, allowing the bis-pyrrole **3b"** to be also isolated in 7% yield (entry 10). Upon similar treatment, 4-methoxypyridine (**3a**) was converted to *N*-(4-pyrridyl)pyrrole in 5% yield.[21]

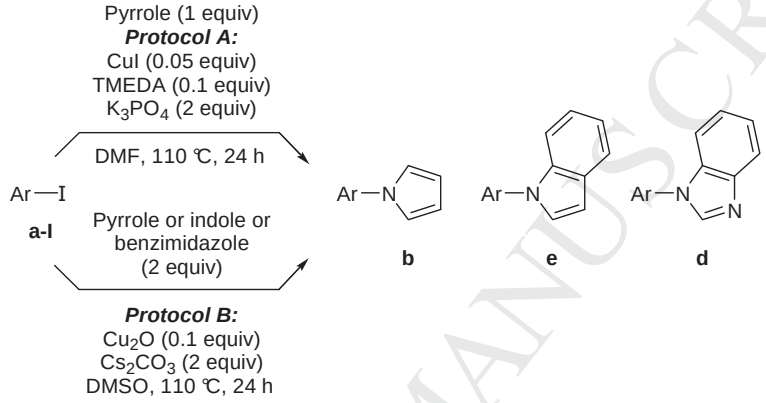
By replacing pyrrole by indole or benzimidazole, the best conditions (*protocol B*) were employed in order to synthesize the corresponding *N*-pyridyl indoles **1e-5e** and *N*-pyridyl benzimidazoles **1d-5d** (Table 3). When compared with those recorded with pyrrole (products **1b-5b**), lower yields were noticed with indole (products **1e-5e**) and, above all, with benzimidazole (products **1d** and **2d**; **3d-5d** not obtained).

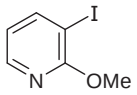
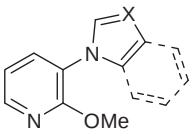
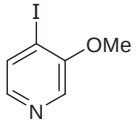
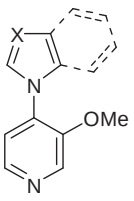
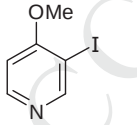
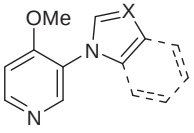
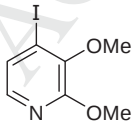
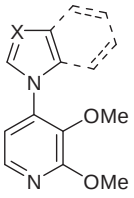
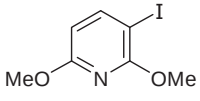
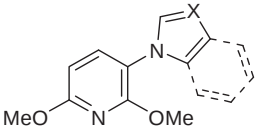
The formation of the *N*-(4-methoxy-3-pyridyl) azoles **3e** and **3d** suffered from important competitive generation of *N*-methyl-indole and -benzimidazole, probably formed with cleavage of the methoxy group (entries 11 and 12). Lithium iodide-mediated cleavage of aryl methyl ethers is known,[22] but this salt is not present in this reaction performed on purified **3a-I**; the side reaction could rather take place between the *N*-metalated azoles and the ether function. Moreover, 4-methoxypyridines are more prone to cleavage than their 2- and 3-methoxylated isomers,[23] a reason explaining why this side reaction more importantly takes place from **3a-I**.

Only one benzimidazole *N*-arylation by an iodinated methoxypyridine is reported, between 3-iodo-2-methoxypyridine (**1a-I**) and 4-(4-methyl-3-pyridyl)benzimidazole under conditions similar to those of *protocol A*.[24] Besides its possible *N*-methylation, benzimidazole can lead to other side reactions.

Indeed, after *N*-functionalization (by methylation or arylation), it is possible to make the second nitrogen react in turn by *N*-methylation[25] or even *N*-pyridylation.[26] In addition, once demethylated, the resulting pyridinones can also compete with benzimidazole in arylation reactions. Such possibilities could in our case furnish many unwanted products (degradation) under the harsh conditions employed, in particular in the case of the iodo substrates less prone to undergo *N*-arylation reaction.

Table 3. *N*-arylation of azoles with the purified iodides **1a-I**, **2a-I**, **3a-I**, **4a-I** and **5a-I**.



Entry	Ar-I		*Protocol*	Product, Yield (%)[a]	
1		**1a-I**[b]	***A***		**1b**, 54[c]
2			***B***		**1b**, 93
3			***B***		**1e**, 75[c]
4			***B***		**1d**, 60[c]
5		**2a-I**[d]	***A***		**2b**, 39[e]
6			***B***		**2b**, 97
7			***B***		**2e**, 81
8			***B***		**2d**, 75[e]
9		**3a-I**[f]	***A***		**3b**, 42[g]
10			***B***		**3b**, 55[g,h]
11			***B***		**3e**, 27[g,i]
12			***B***		**3d**, 0[g,j]
13		**4a-I**[k]	***A***		**4b**, 35[l]
14			***B***		**4b**, 93
15			***B***		**4e**, 68[l]
16			***B***		**4d**, 0[l]
17		**5a-I**[m]	***A***		**5b**, 25[n]
18			***B***		**5b**, 90
19			***B***		**5e**, 70[n]
20			***B***		**5d**, 0[n]

[a] After purification by column chromatography. [b] Prepared in 98% yield as described previously.[9b] [c] 3-Iodo-2-methoxypyridine (**1a-I**) and some 2-methoxypyridine (**1a**) were also recovered. [d] Prepared in 85% yield as described previously.[9b] [e] 4-Iodo-3-methoxypyridine (**2a-I**) and some 3-methoxypyridine (**2a**) were also recovered, and degradation was noticed. [f] Prepared in 89% yield as described previously.[9b] [g] 3-Iodo-4-methoxypyridine (**3a-I**) and some 4-methoxypyridine (**3a**) were also recovered. [h] 3,4-Bis(1-pyrrolyl)pyridine (**3b"**) was also isolated in 7% yield. [i] *N*-methyl indole was also obtained in 66% yield. [j] *N*-methyl imidazole was also obtained in 40% yield. [k] Prepared in 98% yield as described previously.[9b] [l] 4-Iodo-2,3-dimethoxypyridine (**4a-I**) and some 2,3-dimethoxypyridine (**4a**) were (also) recovered. [m] Prepared in 98% yield as described previously.[9b] [n] 3-Iodo-2,6-dimethoxypyridine (**5a-I**) and some 2,6-dimethoxypyridine (**5a**) were (also) recovered.

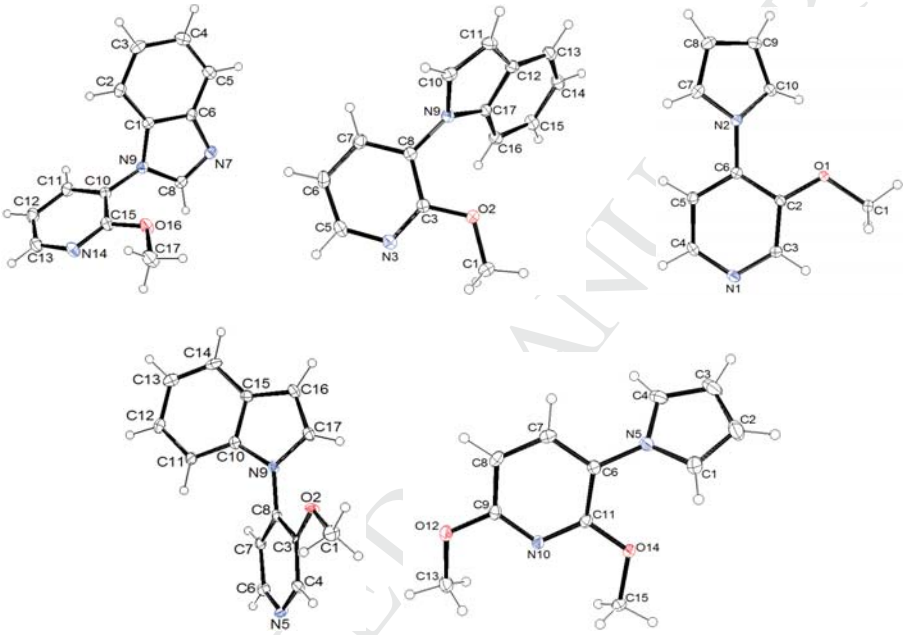


Figure 1. ORTEP diagrams (30% probability) of **1d**, **1e**, **2b**, **2e** and **5b**.

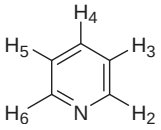
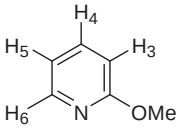
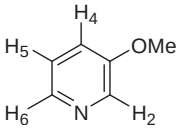
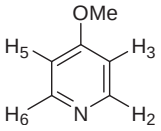
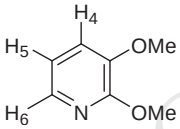
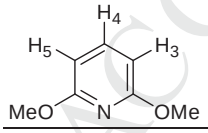
The compounds **1d**, **1e**, **2b**, **2e** and **5b** were identified unambiguously by X-ray diffraction (Figure 1).

We tried to roughly rationalize the results obtained from these *N*-arylations. One can predict that the reactivities of **1a-I**, **2a-I**, **3a-I**, **4a-I** and **5a-I** are related to the partial positive charge on the carbon bearing iodine, as it is for nucleophilic substitution. Handy and Zhang showed that this positive charge can be accounted for by the corresponding ^{1}H NMR chemical shift of the respective deiodinated substrates **1a**, **2a**, **3a**, **4a** and **5a** (Table 4).[27]

First, it can be deduced from these data lower reactivities (lower partial positive charges/chemical shifts) for all the iodinated methoxypyridines from **1a-I** to **5a-I**, when compared with the corresponding

demethoxylated iodopyridines. Next, it is clear that the 3-iodinated methoxypyridines **1a-I**, **3a-I** and **5a-I** are less reactive than the 4-iodinated methoxypyridines **2a-I** and **4a-I** and, above all, the 2-iodinated methoxypyridines **2a-I'** and **3a-I'**, in line with the results recorded. In addition, 4-iodo-2,3-dimethoxypyridine (**4a-I**) appears as less activated than 4-iodo-3-methoxypyridine (**2a-I**) and, above all, 3-iodo-2,6-dimethoxypyridine (**5a-I**) as less reactive than 3-iodo-2-methoxypyridine (**1a-I**), also in accordance with most of the experimental data.

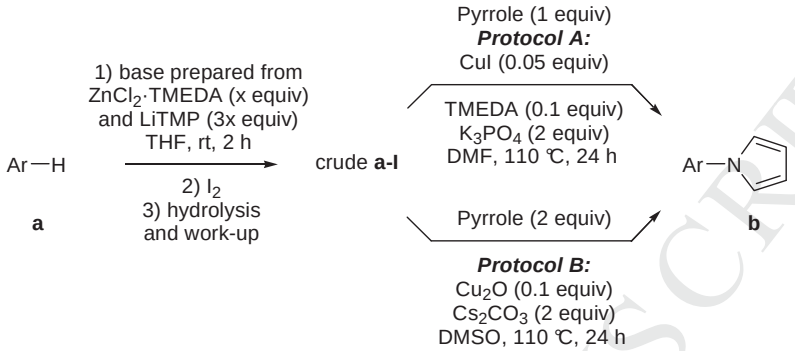
Table 4. ^{1}H NMR chemical shifts (in $CDCl_3$) for pyridine and the deiodinated substrates **1a**, **2a**, **3a**, **4a** and **5a**.

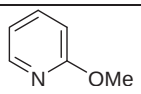
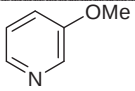
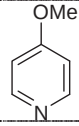
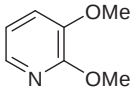
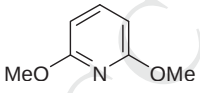
		H_2	H_3	H_4	H_5	H_6
	pyridine	8.59	7.23	7.62	7.23	8.59
	**1a**	-	6.72	7.52	6.82	8.16
	**2a**	8.22	-	7.09	7.08	8.11
	**3a**	8.43	6.81	-	6.81	8.43
	**4a**	-	-	6.95	6.75	7.65
	**5a**	-	6.28	7.44	6.28	-

Finally, by using pyrrole as azole, the protocols A and B were compared for their ability to achieve the deprotometalation-iodolysis-*N*-arylation sequence of the methoxypyridines **1a**-**5a** (Table 5). To this purpose, the recently optimized[9b] deprotometalation-iodolysis conditions were employed. To reach the

N-pyridyl pyrroles **1b**-**5b**, protocol B proved to be a procedure superior to protocol A, furnishing the expected derivatives in yields ranging from 45 to 90%.

Table 5. Deprotometalation-iodolysis of the methoxypyridines **1a**, **2a**, **3a**, **4a** and **5a** followed by *N*-arylation of pyrrole with the crude iodides **1a-I**, **2a-I**, **3a-I**, **4a-I** and **5a-I**.



Entry	Ar-H		x	*Protocol*	Product(s), Yield(s) (%)[a]
1		**1a**	1	***A***	**1b**, 52[b]
2				***B***	**1b**, 86
3		**2a**	0.5	***A***	**2b**, 58[c]
4				***B***	**2b**, 79
5		**3a**	0.5	***A***	**3b**, 35[d]
6				***B***	**3b**, 45
7		**4a**	1	***A***	**4b**, 46[e]
8				***B***	**4b**, 90
9		**5a**	1	***A***	**5b**, 33[f]
10				***B***	**5b**, 88

[a] After purification by column chromatography. [b] 3-Iodo-2-methoxypyridine (**1a-I**) and some 2-methoxypyridine (**1a**) were also recovered. [c] The isomer **2b'** was also isolated in 11% yield. 4-Iodo-3-methoxypyridine (**2a-I**) and some 3-methoxypyridine (**2a**) were also recovered, and degradation was noticed. [d] The isomer **3b'** was also isolated in 6% yield. 3-Iodo-4-methoxypyridine (**3a-I**) and some 4-methoxypyridine (**3a**) were also recovered, and degradation was noticed. [e] 4-Iodo-2,3-dimethoxypyridine (**4a-I**) and some 2,3-dimethoxypyridine (**4a**) were also recovered. [f] 3-Iodo-2,6-dimethoxypyridine (**5a-I**) and some 2,6-dimethoxypyridine (**5a**) were also recovered.

3. Antiproliferative activity in A2058 melanoma cells

The evaluated *N*-(methoxypyridyl) pyrroles and indoles exerted low to moderate antiproliferative activity in A2058 melanoma cells (Figure 2). The best result was obtained with **3e** at 10^{-5} M, which induced 36.4 ± 5.2 % growth inhibition in cells treated for 72 h. No significant difference was noticed between the pyrrole and indole derivatives. Note here that all the synthesized compounds were also tested against a panel of 6 disease-related human kinases: Aurora B; Receptor-Interacting Protein Kinase-3 (RIPK3), Cyclin-dependant kinase 5 (CDK5/p25), glycogen-synthase kinase-3 (GSK3), casein kinase 1 (CK1) and Haspin. None of the compounds described in this article were shown to inhibit significantly the tested kinases (residual activity was above 50% when the kinase is treated with 10^{-5} M of compound, data not shown). The protocol used is as described previously.[28]

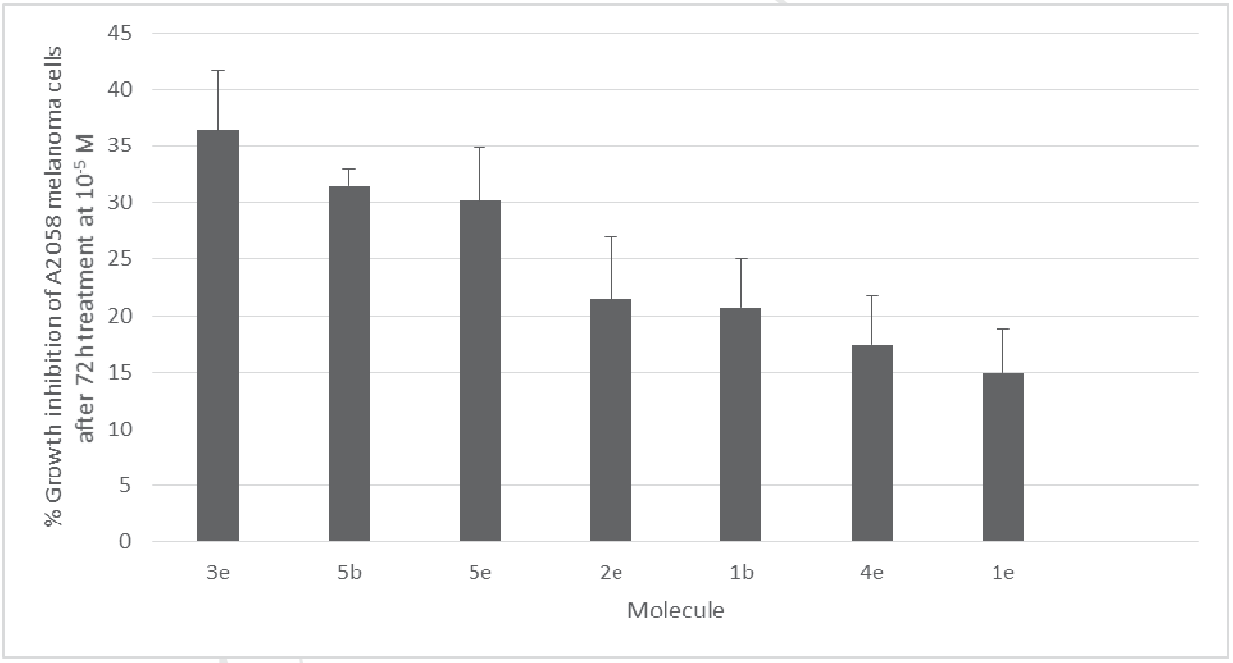


Figure 2: Antiproliferative activity of the compounds **1-5e**, **1b** and **5b** at 10^{-5} M and 72 h in A2058 human melanoma cells.

4. Conclusion

Thus, after preliminary optimization of separate deprotometalation-iodolysis and *N*-arylation steps, it was found possible to combine both reactions in a sequence (either protocol A using CuI, TMEDA,

K_3PO_4, DMF at 110 °C or, above all, protocol B using Cu_2O, Cs_2CO_3, DMSO at 110 °C) that does not require purification of intermediates to reach *N*-pyridyl azoles.

5. Experimental

5.1. General

All the reactions were performed in Schlenk tubes under an argon atmosphere. THF was distilled over sodium/benzophenone. Column chromatography separations were achieved on silica gel (40-63 μm). Melting points were measured on a Kofler apparatus. IR spectra were taken on a Perkin–Elmer Spectrum 100 spectrometer. ^{1}H and ^{13}C Nuclear Magnetic Resonance (NMR) spectra were recorded on a Bruker Avance III spectrometer at 300 and 75 MHz, respectively. ^{1}H chemical shifts (δ) are given in ppm relative to the solvent residual peak, and ^{13}C chemical shifts are relative to the central peak of the solvent signal.[29]

5.1.1. Crystallography. The samples were studied with monochromatized Mo-Kα radiation (λ = 0.71073 Å). X-ray single crystal diffraction data were collected at T = 150(2) K using either APEXII Bruker-AXS diffractometer (compounds **1d**, **1e**, **2e** and **5b**) or D8 VENTURE Bruker AXS diffractometer (compound **2b**). The structure was solved by direct methods using the SIR97 program,[30] and then refined with full-matrix least-square methods based on F^2 (SHELX-97)[31] with the aid of the WINGX program.[32] All non-hydrogen atoms were refined with anisotropic atomic displacement parameters. H atoms were finally included in their calculated positions. Molecular diagrams were generated by ORTEP-3 (version 2.02).[32]

5.2. General procedure 1

To a stirred, cooled (0 °C) solution of 2,2,6,6-tetramethylpiperidine (0.25 mL, 1.5 mmol) in THF (2-3 mL) were successively added BuLi (about 1.6 M hexanes solution, 1.5 mmol) and, 5 min later, $ZnCl_2$·TMEDA[33] (0.13 g, 0.50 mmol). The mixture was stirred for 15 min at 0 °C before introduction of the substrate (1.0 mmol) at 0-10 °C. After 2 h at room temperature, a solution of I_2 (0.38 g, 1.5

mmol) in THF (4 mL) was added. The mixture was stirred overnight before addition of an aqueous saturated solution of $Na_2S_2O_3$ (4 mL) and extraction with AcOEt (3 x 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. To the crude iodide were added Cs_2CO_3 (0.65 g, 2.0 mmol), Cu powder (13 mg, 0.20 mmol), the azole (1.5 mmol) and MeCN (5 mL) and the resulting mixture was heated under reflux for 24 h. Filtration over celite®, washing with AcOEt, removal of the solvent and purification by chromatography on silica gel (the eluent is given in the product description) led to the compound described below.

*5.2.1. 2-Methoxy-3-(1-pyrazolyl)pyridine (**1c**).* The general procedure 1 using 2-methoxypyridine (**1a**, 0.11 mL) and pyrazole (0.10 mL) gave **1c** (eluent: heptane-AcOEt 80:20) in 32% yield as a pale yellow oil: IR (ATR): 752, 795, 933, 1016, 1045, 1105, 1189, 1251, 1304, 1394, 1415, 1471, 1521, 1593, 1736, 2956 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.04 (s, 3H), 6.42 (dd, 1H, *J* = 2.5 and 1.8 Hz), 7.00 (dd, 1H, *J* = 7.6 and 5.0 Hz), 7.70 (d, 1H, *J* = 1.4 Hz), 8.07-8.13 (m, 2H), 8.21 (dd, 1H, *J* = 2.5 and 0.5 Hz); ^{13}C NMR ($CDCl_3$) δ 54.0 (CH_3), 106.8 (CH), 117.4 (CH), 124.8 (C), 131.3 (CH), 131.8 (CH), 140.8 (CH), 144.3 (CH), 154.9 (C); HRMS (ESI): calcd for $C_9H_9N_3NaO$ ($[M+Na]^+$) 198.0643, found 198.0641.

*5.2.2. 3-Methoxy-2-(1-pyrryl)pyridine (**2b'**).* The general procedure 1 using 3-methoxypyridine (**2a**, 0.11 mL) and pyrrole (0.10 mL) gave **2b'** (eluent: heptane-AcOEt 20:80) in 42% yield as a yellow oil: IR (ATR): 726, 790, 925, 1016, 1061, 1071, 1114, 1205, 1239, 1279, 1313, 1333, 1394, 1434, 1450, 1472, 1580, 1738, 2839, 2941, 3008 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.89 (s, 3H), 6.35 (t, 2H, *J* = 2.2 Hz), 7.12 (dd, 1H, *J* = 8.1 and 4.5 Hz), 7.31 (dd, 1H, *J* = 8.2 and 1.4 Hz), 7.65 (t, 2H, *J* = 2.2 Hz), 8.07 (dd, 1H, *J* = 4.8 and 1.5 Hz); ^{13}C NMR ($CDCl_3$) δ 55.9 (CH_3), 109.8 (2CH), 120.3 (CH), 121.0 (2CH), 121.2 (CH), 139.7 (CH), 141.9 (C), 146.7 (C); HRMS (ESI): calcd for $C_{10}H_{10}N_2NaO$ ($[M+Na]^+$) 197.0691, found 197.0690.

*5.2.3. 2-(1-Indolyl)-3-methoxypyridine (**2e'**).* The general procedure 1 using 3-methoxypyridine (**2a**, 0.11 mL) and indole (0.12 g) gave **2e'** (eluent: heptane-AcOEt 20:80) in 39% yield as a yellow oil: IR (ATR): 688, 720, 739, 765, 794, 1011, 1124, 1199, 1213, 1239, 1282, 1308, 1329, 1432, 1457, 1519,

1577, 1737, 2837, 2939, 3059 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.85 (s, 3H), 6.79 (dd, 1H, *J* = 3.4 and 0.8 Hz), 7.27-7.40 (m, 4H), 7.73 (d, 1H, *J* = 3.4 Hz), 7.76-7.83 (m, 2H), 8.27 (dd, 1H, *J* = 4.7 and 1.5 Hz); ^{13}C NMR ($CDCl_3$) δ 55.7 (CH_3), 103.8 (CH), 112.7 (CH), 120.2 (CH), 120.7 (CH), 120.7 (CH), 122.3 (CH), 122.4 (CH), 128.1 (CH), 129.2 (C), 136.0 (C), 139.8 (CH), 142.1 (C), 148.5 (C); HRMS (ESI): calcd for $C_{14}H_{12}N_2NaO$ ($[M+Na]^+$) 247.0847, found 247.0846.

*5.2.4. 2-(1-Benzimidazolyl)-3-methoxypyridine (**2d'**).* The general procedure 1 using 3-methoxypyridine (**2a**, 0.11 mL) and benzimidazole (0.12 g) gave **2d'** (eluent: heptane-AcOEt 20:80) in 17% yield as a pale yellow oil: IR (ATR): 745, 766, 786, 796, 1009, 1126, 1209, 1238, 1285, 1435, 1461, 1480, 1492, 1578, 1737, 2841, 3075, 3390 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.80 (s, 3H), 7.19-7.28 (m, 3H), 7.34 (dd, 1H, *J* = 8.2 and 1.3 Hz), 7.75-7.79 (m, 2H), 8.13 (dd, 1H, *J* = 4.7 and 1.4 Hz), 8.43 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 56.0 (CH_3), 113.2 (CH), 120.1 (CH), 120.4 (CH), 123.0 (CH), 123.2 (CH), 123.7 (CH), 133.2 (C), 139.7 (C), 140.1 (CH), 143.0 (C), 143.3 (C), 148.1 (CH); HRMS (ESI): calcd for $C_{13}H_{11}N_3NaO$ ($[M+Na]^+$) 248.0800, found 248.0803.

*5.2.5. 2-(1-Indazolyl)-3-methoxypyridine (**2f'**).* The general procedure 1 using 3-methoxypyridine (**2a**, 0.11 mL) and indazole (0.11 g) gave **2f'** (eluent: heptane-AcOEt 20:80) in 10% yield as a pale yellow oil: IR (ATR): 751, 774, 797, 990, 1007, 1130, 1203, 1228, 1284, 1416, 1435, 1453, 1470, 1497, 1575, 1614, 1737, 2839, 2940, 3061 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.86 (s, 3H), 7.21 (ddd, 1H, *J* = 7.8, 6.9 and 0.9 Hz), 7.33 (dd, 1H, *J* = 8.1 and 4.5 Hz), 7.37-7.47 (m, 2H), 7.59 (dq, 1H, *J* = 8.4 and 0.9 Hz), 7.77 (dt, 1H, *J* = 8.1 and 1.1 Hz), 8.22 (dd, 1H, *J* = 4.8 and 1.5 Hz), 8.26 (d, 1H, *J* = 0.9 Hz); ^{13}C NMR ($CDCl_3$) δ 56.2 (CH_3), 111.9 (CH), 120.9 (CH), 120.9 (C), 121.0 (CH), 121.7 (CH), 123.9 (CH), 124.7 (C), 127.1 (CH), 136.2 (CH), 140.1 (CH), 141.9 (C), 149.6 (C); HRMS (ESI): calcd for $C_{13}H_{11}N_3NaO$ ($[M+Na]^+$) 248.0800, found 248.0800.

*5.2.6. 4-Methoxy-2-(1-pyrryl)pyridine (**3b'**).* The general procedure 1 using 4-methoxypyridine (**3a**, 0.11 mL) and pyrrole (0.10 mL) gave **3b'** (eluent: heptane-AcOEt 20:80) in 14% yield as a yellow oil: IR (ATR): 684, 727, 805, 909, 1013, 1084, 1175, 1187, 1280, 1293, 1399, 1437, 1475, 1569, 1737,

2223, 2844, 2940 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.90 (s, 3H), 6.34 (t, 2H, *J* = 2.2 Hz), 6.67 (dd, 1H, *J* = 5.9 and 2.2 Hz), 6.80 (d, 1H, *J* = 2.1 Hz), 7.48 (t, 2H, *J* = 2.3 Hz), 8.25 (d, 1H, *J* = 6.0 Hz); ^{13}C NMR ($CDCl_3$) δ 55.6 (CH_3), 97.5 (CH), 107.0 (CH), 111.4 (2CH), 118.4 (2CH), 149.8 (CH), 153.1 (C), 167.9 (C); HRMS (ESI): calcd for $C_{10}H_{10}N_2NaO$ ($[M+Na]^+$) 197.0691, found 197.0689.

*5.2.7. 4-Methoxy-2-(1-pyrazolyl)pyridine (**3c'**).* The general procedure 1 using 4-methoxypyridine (**3a**, 0.11 mL) and pyrazole (0.10 mL) gave **3c'** (eluent: heptane-AcOEt 20:80) in 10% yield as a yellow powder: mp 60 °C; IR (ATR): 753, 814, 844, 879, 947, 1030, 1043, 1097, 1183, 1202, 1218, 1289, 1385, 1403, 1437, 1458, 1492, 1519, 1574, 1596 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.93 (s, 3H), 6.45 (dd, 1H, *J* = 2.5 and 1.7 Hz), 6.72 (dd, 1H, *J* = 5.8 and 2.4 Hz), 7.52 (d, 1H, *J* = 2.3 Hz), 7.72 (d, 1H, *J* = 1.0 Hz), 8.20 (d, 1H, *J* = 5.8 Hz), 8.55 (dd, 1H, *J* = 2.5 and 0.5 Hz); ^{13}C NMR ($CDCl_3$) δ 55.7 (CH_3), 97.1 (CH), 107.8 (CH), 109.6 (CH), 127.4 (CH), 142.0 (CH), 149.0 (CH), 153.4 (C), 167.9 (C); HRMS (ESI): calcd for $C_9H_9N_3NaO$ ($[M+Na]^+$) 198.0643, found 198.0642.

*5.2.8. 2-(1-Indazolyl)-4-methoxypyridine (**3f'**).* The general procedure 1 using 4-methoxypyridine (**3a**, 0.11 mL) and indazole (0.11 g) gave **3f'** (eluent: heptane-AcOEt 20:80) in 9% yield as a pale yellow oil: IR (ATR): 750, 845, 858, 911, 1011, 1038, 1167, 1244, 1302, 1350, 1433, 1450, 1469, 1487, 1569, 1581, 1600, 1718, 2940 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.87 (s, 3H), 6.71 (dd, 1H, *J* = 5.8 and 2.3 Hz), 7.27 (ddd, 1H, *J* = 7.9, 7.0 and 0.8 Hz), 7.51 (ddd, 1H, *J* = 8.2, 7.0 and 1.0 Hz), 7.57 (d, 1H, *J* = 2.3 Hz), 7.65 (dt, 1H, *J* = 8.0 and 0.8 Hz), 8.19 (s, 1H), 8.32 (d, 1H, *J* = 5.7 Hz), 8.85 (dt, 1H, *J* = 8.6 and 0.8 Hz); ^{13}C NMR ($CDCl_3$) δ 55.6 (CH_3), 97.7 (CH), 108.6 (CH), 115.6 (CH), 120.8 (CH), 122.6 (CH), 126.1 (C), 128.1 (CH), 136.8 (CH), 139.1 (C), 148.8 (CH), 156.2 (C), 167.5 (C); HRMS (ESI): calcd for $C_{13}H_{11}N_3NaO$ ($[M+Na]^+$) 248.0800, found 248.0799.

*5.2.9. 2-(1-Benzotriazolyl)-4-methoxypyridine (**3g'**).* The general procedure 1 using 4-methoxypyridine (**3a**, 0.11 mL) and benzotriazole (0.12 g) gave **3g'** (eluent: heptane-AcOEt 20:80) as traces as a grey powder: mp 120 °C; IR (ATR): 752, 769, 812, 847, 1027, 1059, 1233, 1257, 1288, 1306, 1456, 1480, 1571, 1605, 1738, 2945 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.99 (s, 3H), 6.86 (dd, 1H, *J* = 5.7

and 2.1 Hz), 7.45 (ddd, 1H, *J* = 8.4, 7.2 and 1.2 Hz), 7.60 (ddd, 1H, *J* = 8.1, 6.9 and 1.2 Hz), 7.82 (d, 1H, *J* = 2.4 Hz), 8.12 (dd, 1H, *J* = 8.1 and 0.6 Hz), 8.40 (d, 1H, *J* = 5.7 Hz), 8.66 (dd, 1H, *J* = 8.4 and 0.9 Hz); ^{13}C NMR ($CDCl_3$) δ 55.9 (CH_3), 99.2 (CH), 110.5 (CH), 115.1 (CH), 119.9 (CH), 125.0 (CH), 128.9 (CH), 131.9 (C), 146.9 (C), 149.3 (CH), 153.5 (C), 167.8 (C); HRMS (ESI): calcd for $C_{12}H_{10}N_4NaO$ ($[M+Na]^+$) 249.0752, found 249.0750.

5.3. General procedure 2

A mixture of the required iodide (1.0 mmol), Cu_2O (0.10 g, 0.10 mmol), Cs_2CO_3 (0.65 g, 2.0 mmol), the required azole (2.0 mmol) and DMSO (0.5 mL) was stirred for 24 h at 110 °C. After cooling to room temperature, the mixture was diluted with AcOEt (10 mL) and filtered over celite®. Washing with AcOEt, removal of the solvent and purification by chromatography on silica gel (the eluent is given in the product description) led to the compound described below.

*5.3.1. 2-Methoxy-3-(1-pyrryl)pyridine (**1b**).* The general procedure 2 using 3-iodo-2-methoxypyridine (**1a-I**, 0.24 g) and pyrrole (0.14 mL) gave **1b** (eluent: heptane-AcOEt 80:20) in 93% yield as a yellow oil: IR (ATR): 721, 762, 794, 922, 1009, 1074, 1104, 1225, 1245, 1307, 1336, 1413, 1468, 1493, 1591, 1723, 2951 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.04 (s, 3H), 6.37 (t, 2H, *J* = 2.2 Hz), 6.98 (dd, 1H, *J* = 7.5 and 4.8 Hz), 7.07 (t, 2H, *J* = 2.2 Hz), 7.57 (dd, 1H, *J* = 7.5 and 1.8 Hz), 8.12 (dd, 1H, *J* = 4.8 and 1.7 Hz); ^{13}C NMR ($CDCl_3$) δ 53.9 (CH_3), 109.7 (2CH), 117.1 (CH), 121.8 (2CH), 125.3 (C), 132.5 (CH), 144.1 (CH), 157.1 (C); HRMS (ESI): calcd for $C_{10}H_{10}N_2NaO$ ($[M+Na]^+$) 197.0691, found 197.0695.

*5.3.2. 3-(1-Indolyl)-2-methoxypyridine (**1e**).* The general procedure 2 using 3-iodo-2-methoxypyridine (**1a-I**, 0.24 g) and indole (0.23 g) gave **1e** (eluent: heptane-AcOEt-NEt_3 78:20:2) in 75% yield as a pale yellow powder: mp 70 °C; IR (ATR): 693, 722, 736, 747, 763, 838, 1015, 1128, 1197, 1225, 1242, 1253, 1288, 1334, 1347, 1423, 1454, 1481, 1512, 1522, 1583, 1736, 2845, 2934, 3054 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.84 (s, 3H), 6.57 (d, 1H, *J* = 3.3 Hz), 6.88 (dd, 1H, *J* = 7.5 and 5.1 Hz), 7.04-7.11 (m, 3H), 7.17 (d, 1H, *J* = 3.3 Hz), 7.53-7.57 (m, 2H), 8.09 (dd, 1H, *J* = 4.8 and 1.8 Hz); ^{13}C NMR ($CDCl_3$) δ 53.8 (CH_3), 103.4 (CH), 110.6 (CH), 116.9 (CH), 120.4 (CH), 121.1 (CH), 122.3 (CH), 123.2 (C),

128.8 (C), 128.9 (CH), 135.5 (CH), 136.6 (C), 145.4 (CH), 158.9 (C). *Crystal data for* ***1e:*** $C_{14}H_{12}N_2O$, M = 224.26, monoclinic, $P\ 2_1/c$, a = 7.8318(3), b = 19.3628(9), c = 8.2262(3) Å, β = 114.879(2) °, V = 1131.70(8) Å^3, Z = 4, d = 1.316 g cm^{-3}, μ = 0.085 mm^{-1}. A final refinement on F^2 with 2538 unique intensities and 156 parameters converged at $\omega R(F^2)$ = 0.1016 ($R(F)$ = 0.0396) for 2051 observed reflections with $I > 2\sigma(I)$. CCDC 1484541.

*5.3.3. 3-(1-Benzimidazolyl)-2-methoxypyridine (**1d**).* The general procedure 2 using 3-iodo-2-methoxypyridine (**1a-I**, 0.24 g) and benzimidazole (0.24 g) gave **1d** (eluent: heptane-AcOEt 80:20) in 60% yield as a beige powder: mp 104 °C, IR (ATR): 738, 763, 1018, 1125, 1170, 1213, 1239, 1339, 1377, 1455, 1477, 1575, 1611, 1623, 1776, 1929, 3056, 3142 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.97 (s, 3H), 7.09 (dd, 1H, J = 7.5 and 5.0 Hz), 7.31-7.37 (m, 3H), 7.74 (dd, 1H, J = 7.5 and 1.8 Hz), 7.88-7.91 (m, 1H), 8.17 (br s, 1H), 8.29 (dd, 1H, J = 5.0 and 1.7 Hz); ^{13}C NMR ($CDCl_3$) δ 54.1 (CH_3), 110.6 (CH), 117.1 (CH), 120.0 (C), 120.6 (CH), 122.9 (CH), 123.7 (CH), 135.0 (CH), 143.5 (CH), 146.8 (CH), 158.5 (C), 2 C not seen. *Crystal data for* ***1d:*** $4(C_{13}H_{11}N_3O)$, M = 900.99, monoclinic, $P\ 2_1/n$, a = 25.2017(7), b = 7.4141(2), c = 25.3329(7) Å, β = 108.2920(10) °, V = 4494.2(2) Å^3, Z = 4, d = 1.332 g cm^{-3}, μ = 0.088 mm^{-1}. A final refinement on F^2 with 10235 unique intensities and 617 parameters converged at $\omega R(F^2)$ = 0.2357 ($R(F)$ = 0.0776) for 7761 observed reflections with $I > 2\sigma(I)$. CCDC 1484540.

*5.3.4. 3-Methoxy-4-(1-pyrryl)pyridine (**2b**).* The general procedure 2 using 4-iodo-3-methoxypyridine (**2a-I**, 0.24 g) and pyrrole (0.14 mL) gave **2b** (eluent: heptane-AcOEt 20:80) in 97% yield as a pale yellow powder: mp 54 °C; IR (ATR): 671, 724, 806, 924, 1014, 1059, 1074, 1240, 1290, 1320, 1342, 1418, 1470, 1514, 1575, 1584, 2833 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.93 (s, 3H), 6.34 (t, 2H, J = 2.3 Hz), 7.17 (t, 2H, J = 2.4 Hz), 7.19 (d, 1H, J = 5.4 Hz), 8.26 (d, 1H, J = 5.1 Hz), 8.38 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 56.5 (CH_3), 110.4 (2CH), 117.4 (CH), 121.3 (2CH), 135.9 (CH), 136.0 (C), 143.6 (CH), 147.4 (C). *Crystal data for* ***2b:*** $C_{10}H_{10}N_2O$, M = 174.20, orthorhombic, $P\ c\ a\ 2_1$, a = 7.5200(4), b = 16.8481(8), c = 6.7791(3) Å, V = 858.90(7) Å^3, Z = 4, d = 1.347 g cm^{-3}, μ = 0.090 mm^{-1}. A final

refinement on F^2 with 1853 unique intensities and 119 parameters converged at $\omega R(F^2) = 0.0903$ ($R(F) = 0.0375$) for 1663 observed reflections with $I > 2\sigma(I)$. CCDC 1484542.

*5.3.5. 4-(1-Indolyl)-3-methoxypyridine (**2e**).* The general procedure 2 using 4-iodo-3-methoxypyridine (**2a-I**, 0.24 g) and indole (0.23 g) gave **2e** (eluent: heptane-AcOEt-NEt_3 20:78:2) in 81% yield as a beige powder: mp 134 °C; IR (ATR): 692, 722, 736, 747, 763, 838, 1016, 1128, 1178, 1197, 1226, 1242, 1253, 1288, 1334, 1347, 1423, 1454, 1511, 1522, 1581, 1737, 3053 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.92 (s, 3H), 6.76 (dd, 1H, J = 3.3 and 0.9 Hz), 7.21-7.31 (m, 2H), 7.39-7.44 (m, 3H), 7.71-7.75 (m, 1H), 8.42 (d, 1H, J = 5.1 Hz), 8.55 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 56.5 (CH_3), 104.3 (CH), 111.0 (CH), 120.5 (C), 120.9 (CH), 121.1 (CH), 122.6 (CH), 128.5 (CH), 129.1 (CH), 135.2 (C), 135.8 (C), 136.2 (CH), 143.5 (CH), 149.4 (C). *Crystal data for **2e**:* 4($C_{14}H_{12}N_2O$), M = 897.02, monoclinic, *C c*, a = 10.5675(9), b = 10.5257(9), c = 39.948(4) Å, β = 90.131(4) °, V = 4443.4(7) $Å^3$, Z = 4, d = 1.341 g cm^{-3}, μ = 0.086 mm^{-1}. A final refinement on F^2 with 7585 unique intensities and 618 parameters converged at $\omega R(F^2) = 0.1162$ ($R(F) = 0.0476$) for 7060 observed reflections with $I > 2\sigma(I)$. CCDC 1484543.

*5.3.6. 4-(1-Benzimidazolyl)-3-methoxypyridine (**2d**).* The general procedure 2 using 4-iodo-3-methoxypyridine (**2a-I**, 0.24 g) and benzimidazole (0.24 g) gave **2d** (eluent: heptane-AcOEt 20:80 then MeOH-AcOEt 5:95) in 75% yield as a pale yellow powder: mp 112 °C; IR (ATR): 698, 744, 765, 833, 1015, 1190, 1260, 1293, 1418, 1456, 1493, 1514, 1584, 3065, 3417 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.93 (s, 3H), 7.29-7.39 (m, 3H), 7.41 (d, 1H, J = 4.8 Hz), 7.82-7.86 (m, 1H), 8.18 (s, 1H), 8.41 (d, 1H, J = 5.1 Hz), 8.53 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 56.6 (CH_3), 110.7 (CH), 119.6 (CH), 120.6 (CH), 123.2 (CH), 124.0 (CH), 131.9 (C), 133.1 (C), 136.0 (CH), 143.1 (CH), 143.4 (C), 143.6 (CH), 148.9 (C); HRMS (ESI): calcd for $C_{13}H_{11}N_3NaO$ ($[M+Na]^+$) 248.0800, found 248.0800.

*5.3.7. 4-Methoxy-3-(1-pyrryl)pyridine (**3b**).* The general procedure 2 using 3-iodo-4-methoxypyridine (**3a-I**, 0.24 g) and pyrrole (0.14 mL) gave **3b** (eluent: heptane-AcOEt 20:80) in 55% yield as a whitish powder: mp 58 °C; IR (ATR): 699, 712, 739, 804, 829, 921, 1019, 1070, 1278, 1293, 1337, 1476, 1510, 1585, 3126 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.90 (s, 3H), 6.35 (t, 2H, J = 2.1 Hz), 6.94 (d, 1H, J = 5.7

Hz), 6.98 (t, 2H, *J* = 2.3 Hz), 8.43 (d, 1H, *J* = 5.7 Hz), 8.47 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 55.8 (CH_3), 107.2 (CH), 109.6 (2CH), 121.9 (2CH), 127.2 (C), 146.1 (CH), 149.4 (CH), 158.6 (C); HRMS (ESI): calcd for $C_{10}H_{10}N_2NaO$ ($[M+Na]^+$) 197.0691, found 197.0693. *3,4-Bis(1-pyrryl)pyridine (**3b"**)* was also isolated in 7% yield as a greenish powder: mp 88 °C; IR (ATR): 725, 842, 1022, 1064, 1340, 1422, 1483, 1507, 1570, 1589, 3102 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.26 (t, 2H, *J* = 2.1 Hz), 6.33 (t, 2H, *J* = 2.1 Hz), 6.49 (t, 2H, *J* = 2.3 Hz), 6.63 (t, 2H, *J* = 2.1 Hz), 7.35 (d, 1H, *J* = 5.1 Hz), 8.61 (br d, 1H), 8.66 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 111.1 (2CH), 111.8 (2CH), 118.6 (CH), 120.3 (2CH), 121.5 (2CH), 130.1 (C), 142.4 (C), 149.3 (CH), 149.8 (CH).

*5.3.8. 3-(1-Indolyl)-4-methoxypyridine (**3e**).* The general procedure 2 using 3-iodo-4-methoxypyridine (**3a-I**, 0.24 g) and indole (0.23 g) gave **3e** (eluent: MeOH-AcOEt 5:95) in 27% yield as a yellow oil; IR (ATR): 742, 764, 809, 1022, 1189, 1213, 1226, 1295, 1334, 1441, 1459, 1506, 1516, 1572, 1587, 1740, 3039 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.85 (s, 3H), 6.72 (d, 1H, *J* = 3.3 Hz), 7.01 (d, 1H, *J* = 5.7 Hz), 7.15-7.23 (m, 3H), 7.25 (d, 1H, *J* = 3.3 Hz), 7.68-7.72 (m, 1H), 8.56 (d, 1H, *J* = 5.7 Hz), 8.58 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 55.8 (CH_3), 103.6 (CH), 107.5 (CH), 110.6 (CH), 120.4 (CH), 121.1 (CH), 122.4 (CH), 125.4 (C), 128.7 (C), 129.0 (CH), 136.9 (C), 148.8 (CH), 150.5 (CH), 160.6 (C); HRMS (ESI): calcd for $C_{14}H_{12}N_2NaO$ ($[M+Na]^+$) 247.0847, found 247.0846.

*5.3.9. 2,3-Dimethoxy-4-(1-pyrryl)pyridine (**4b**).* The general procedure 2 using 4-iodo-2,3-dimethoxypyridine (**4a-I**, 0.27 g) and pyrrole (0.14 mL) gave **4b** (eluent: heptane-AcOEt 20:80) in 93% yield as a yellow oil: IR (ATR): 724, 811, 945, 994, 1088, 1161, 1219, 1259, 1294, 1352, 1395, 1457, 1500, 1593, 1736, 2845, 2950 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.67 (s, 3H), 4.04 (s, 3H), 6.34 (t, 2H, *J* = 2.3 Hz), 6.86 (d, 1H, *J* = 5.4 Hz), 7.20 (t, 2H, *J* = 2.3 Hz), 7.87 (d, 1H, *J* = 5.4 Hz); ^{13}C NMR ($CDCl_3$) δ 54.0 (CH_3), 60.3 (CH_3), 110.6 (2CH), 112.0 (CH), 121.1 (2CH), 135.2 (C), 140.1 (C), 141.4 (CH), 159.5 (C); HRMS (ESI): calcd for $C_{11}H_{12}N_2NaO_2$ ($[M+Na]^+$) 227.0796, found 227.0798.

*5.3.10. 4-(1-Indolyl)-2,3-dimethoxypyridine (**4e**).* The general procedure 2 using 4-iodo-2,3-dimethoxypyridine (**4a-I**, 0.27 g) and indole (0.23 g) gave **4e** (eluent: heptane-AcOEt-NEt_3 85:5:10) in

68% yield as a yellow oil: IR (ATR): 719, 739, 762, 821, 985, 1058, 1092, 1145, 1171, 1221, 1265, 1303, 1343, 1396, 1451, 1466, 1490, 1590, 2948 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.51 (s, 3H), 4.09 (s, 3H), 6.72 (dd, 1H, *J* = 3.6 and 0.9 Hz), 7.07 (d, 1H, *J* = 5.4 Hz), 7.17-7.28 (m, 2H), 7.40 (d, 1H, *J* = 3.3 Hz), 7.43-7.47 (m, 1H), 7.68 (dd, 1H, *J* = 7.2 and 2.1 Hz), 7.98 (d, 1H, *J* = 5.4 Hz); ^{13}C NMR ($CDCl_3$) δ 54.1 (CH_3), 60.6 (CH_3), 104.7 (CH), 111.2 (CH), 114.8 (CH), 121.0 (CH), 121.1 (CH), 122.7 (CH), 128.5 (CH), 129.2 (C), 135.8 (C), 137.7 (C), 139.3 (C), 141.2 (CH), 159.5 (C); HRMS (ESI): calcd for $C_{15}H_{14}N_2NaO_2$ ($[M+Na]^+$) 277.0953, found 277.0950.

*5.3.11. 2,6-Dimethoxy-3-(1-pyrryl)pyridine (**5b**).* The general procedure 2 using 3-iodo-2,6-dimethoxypyridine (**5a-I**, 0.27 g) and pyrrole (0.14 mL) gave **5b** (eluent: heptane-AcOEt 20:80) in 90% yield as a beige powder: mp 58 °C; IR (ATR): 690, 721, 809, 955, 1008, 1038, 1068, 1230, 1246, 1279, 1305, 1342, 1393, 1456, 1497, 1589, 1735, 2949 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.02 (s, 3H), 4.04 (s, 3H), 6.37 (t, 2H, *J* = 2.1 Hz), 6.41 (d, 1H, *J* = 8.1 Hz), 6.98 (t, 2H, *J* = 2.1 Hz), 7.54 (d, 1H, *J* = 8.4 Hz); ^{13}C NMR ($CDCl_3$) δ 53.7 (CH_3), 53.8 (CH_3), 100.9 (CH), 108.9 (2CH), 117.5 (C), 121.9 (2CH), 136.6 (CH), 155.8 (C), 160.9 (C). *Crystal data for **5b**:* $C_{11}H_{12}N_2O_2$, *M* = 204.23, triclinic, *P* -1, *a* = 7.2557(8), *b* = 7.3465(7), *c* = 9.8113(11) Å, α = 97.939(4), β = 92.874(5), γ = 95.531(4) °, *V* = 514.49(9) $Å^3$, *Z* = 2, *d* = 1.318 g cm^{-3}, μ = 0.093 mm^{-1}. A final refinement on F^2 with 2331 unique intensities and 138 parameters converged at $\omega R(F^2)$ = 0.1017 ($R(F)$ = 0.0414) for 1827 observed reflections with $I > 2\sigma(I)$. CCDC 1484505.

*5.3.12. 2,6-Dimethoxy-3-(1-indolyl)pyridine (**5e**).* The general procedure 2 using 3-iodo-2,6-dimethoxypyridine (**5a-I**, 0.27 g) and indole (0.23 g) gave **5e** (eluent: heptane-AcOEt-NEt_3 78:20:2) in 70% yield as a yellow oil; IR (ATR): 723, 738, 763, 813, 1011, 1036, 1097, 1188, 1213, 1225, 1271, 1303, 1375, 1389, 1425, 1456, 1484, 1514, 1585, 1605, 1740, 2949, 2981 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.02 (s, 3H), 4.09 (s, 3H), 6.52 (d, 1H, *J* = 8.4 Hz), 6.76 (d, 1H, *J* = 3.0 Hz), 7.24-7.32 (m, 4H), 7.68 (d, 1H, *J* = 8.4 Hz), 7.75-7.79 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 53.8 (CH_3), 54.0 (CH_3), 101.2 (CH), 102.8 (CH), 110.5 (CH), 114.9 (C), 120.1 (CH), 121.0 (CH), 122.1 (CH), 128.5 (C), 129.3 (CH), 137.1 (C),

139.3 (CH), 157.8 (C), 161.9 (C); HRMS (ESI): calcd for $C_{15}H_{14}N_2NaO_2$ ($[M+Na]^+$) 277.0953, found 277.0952.

5.4. Biological evaluation

The antiproliferative activity of *N*-pyridyl azoles was studied in the A2058 (ATCC® CRL-11147) cell line. A2058 are highly invasive human epithelial adherent melanoma cells, derived from lymph nodes metastatic cells obtained from a 43 years male patient. They are tumorigenic at 100% frequency in nude mice, and considered as very resistant to anticancer drugs. All cell culture experiments were performed at 37 °C. Cells were grown to confluence in 75 cm² flasks in DMEM supplemented with 10% fetal calf serum (FCS) and 1% Penicillin-streptomycin (Dominique Dutscher, France), in a 5% CO_2 humidified atmosphere. Molecules were solubilized in DMSO at 10^{-3} M and diluted in the cell culture medium to obtain 2.10^{-5} M solutions. Confluent cells were trypsinized and centrifuged in FCS at 1500 *g* for 5 min. The supernatant containing trypsin was discarded and the cell pellet was suspended in cell culture medium to obtain a 4.10^4 cell.mL^{-1} suspension. At t0, 50 µL of the 2.10^{-5} M molecules solutions were deposited in a 96-wells flat bottom microplate, and 50 µL of the cell suspension were added. The 2000 cells were then grown for 72 h in the cell culture medium containing 10^{-5} M molecules. At t72, 20µL of a 5g.L^{-1} MTT solution were added in each well of the microplate, allowing living cells containing a functional mitochondrial succinate deshydrogenase to metabolize MTT to the corresponding blue formazan salt for 4 h. The cell culture medium was removed using an Eppendorf epMotion 5070 pipeting robot (Eppendorf, France) and formazan crystals were dissolved in 200 µL DMSO. Microplates were placed at 37 °C for 5 min to solubilize formazan crystals and absorbance was read at 550 nm using a VERSAmax microplate reader (Molecular devices, France). The percentage of growth inhibition was calculated as GI (%) = 100- ((A550 nm sample – A550 nm BG) / (A550 nm control – A550 nm BG)) x 100 with:

- A550 nm sample: median absorbance of 8 wells containing cells treated with 10^{-5}M molecule

- A550 nm BG: median background absorbance of 8 wells containing control cell culture medium + 1% DMSO

- A550 nm control: median absorbance of 8 wells containing cells grown in control cell culture medium + 1% DMSO.

Data are expressed as GI(%) + sem (%) from 3 independent assays.

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Supplementary data. Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx.

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