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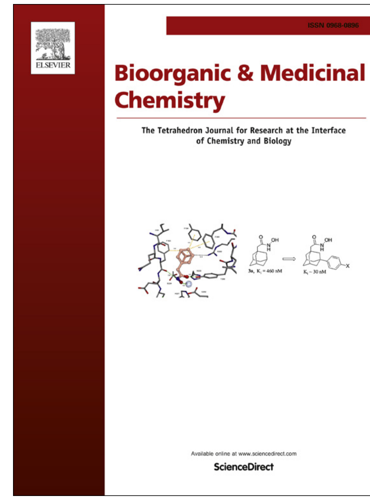

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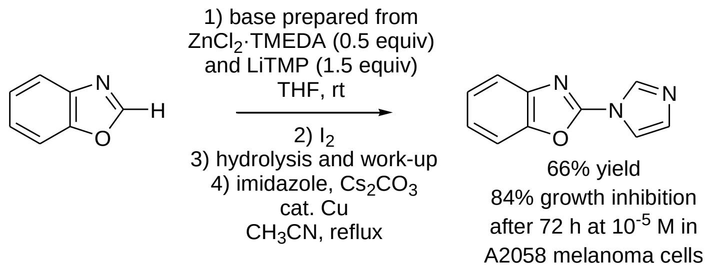
Graphical Abstract



Synthesis of C,N'-linked bis-heterocycles using a deprotometalation-iodination-*N*-arylation sequence and evaluation of their antiproliferative activity in melanoma cells

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Abstract:

Benzothiophene, benzofuran, benzothiazole and benzoxazole were deprotometalated using the lithium-zinc combination prepared from $ZnCl_2$·TMEDA (TMEDA = *N*,*N*,*N'*,*N'*-tetramethylethylenediamine, 1 equiv) and lithium 2,2,6,6-tetramethylpiperidide (LiTMP, 3 equiv). Subsequent interception of the 2-metalated derivatives using iodine as electrophile led to the iodides in 81, 82, 67 and 42% yields, respectively. These yields are higher (10% more) than those obtained using $ZnCl_2$·TMEDA (0.5 equiv) and LiTMP (1.5 equiv), except in the case of benzoxazole (10% less). The crude iodides were involved in the *N*-arylation of pyrrole, indole, carbazole, pyrazole, indazole, imidazole and benzimidazole in the presence of Cu (0.2 equiv) and Cs_2CO_3 (2 equiv), and using acetonitrile as solvent (no other ligand) to provide after 24 h reflux the expected *N*-arylated azoles in yields ranging from 33 to 81%. Using benzotriazole also led to *N*-arylation products, but in lower 34, 39, 36 and 6% yields, respectively. A further study with this azole evidenced the impact of 2,2,6,6-tetramethylpiperidine on the *N*-arylation yields. Most of the C,N'-linked bis-heterocycles thus synthesized (in particular those containing benzimidazole) induced a high growth inhibition of A2058 melanoma cells after a 72 h treatment at 10^{-5} M.

Keywords: five-membered aromatic heterocycles, deprotonative metalation, *N*-arylation, antiproliferative activity, melanoma

1. Introduction

The development of methods for the functionalization of aromatic heterocycles is of interest due to their presence in numerous molecules of chemical or biological importance, as well as in organic materials for different applications.

Deprotometalation is among the first approaches studied, notably owing to its high regioselectivity.[1] Recently, TMP-based lithium-metal combinations (TMP = 2,2,6,6-tetramethylpiperidido), with a metal softer than an alkali metal, appeared as powerful tools for performing both efficient and chemoselective reactions.[2] In this context, our group showed that the bimetal combination prepared from $ZnCl_2$·TMEDA (TMEDA = *N*,*N*,*N'*,*N'*-tetramethylethylenediamine) and LiTMP (3 equiv), and which proved to be 1:1 $Zn(TMP)_2$-LiTMP·2LiCl(±TMEDA),[3] is a powerful alternative to monometal lithium bases.[1a,4]

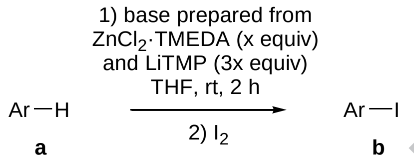
Copper-catalyzed *N*-arylation of azoles has recently benefited from the development of catalyst-base systems.[5] We here report our attempts to associate deprotometalation-iodination of aromatic heterocycles with *N*-arylation of azoles for the synthesis of C,N'-linked bis-heterocycles, as well as the evaluation of the latter for their antiproliferative activity in melanoma cells.

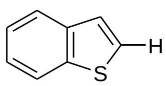
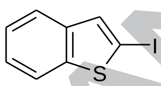
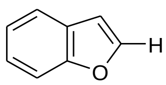
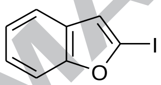
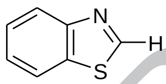
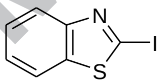
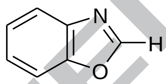
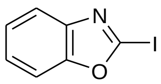
2. Results and Discussion

2.1. Synthesis

To access bis-heterocycles, benzothiophene (**1a**), benzofuran (**2a**), benzothiazole (**3a**) and benzoxazole (**4a**) were chosen as substrates. As previously described,[3c] deprotometalation using the bimetal combination prepared from $ZnCl_2$·TMEDA (0.5 equiv) and LiTMP (1.5 equiv) followed by interception with iodine respectively afforded the derivatives **1b**, **2b**, **3b** and **4b** in 73, 69, 57 and 52% yields (Table 1, entries 1, 3, 5 and 7). Upon treatment with $ZnCl_2$·TMEDA (1 equiv) and LiTMP (3 equiv), which corresponds to doubling the amount of base, it proved possible to increase the yields of the iodides **1b**-**3b** to respectively reach 81, 82 and 67% (entries 2, 4 and 6), but not that of **4b** which dropped to 42% (entry 8). For the latter, such a result could be in relation with the formation of an arylmetal species more prone to ring opening under these conditions.[3c]

Table 1. Deprotometalation-iodination of the heterocycles 1a-4a as a function of the amount of base.

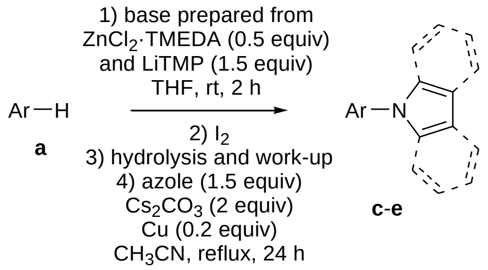


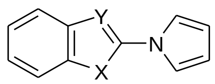
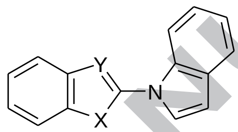
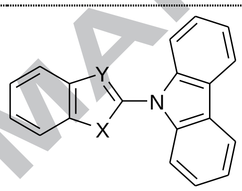
Entry	Ar-H		x	Ar-I	Product, Yield (%)[a]
1	**1a**		0.5		**1b**, 73[3c]
2			1		**1b**, 81
3	**2a**		0.5		**2b**, 69[3c]
4			1		**2b**, 82
5	**3a**		0.5		**3b**, 57[3c]
6			1		**3b**, 67
7	**4a**		0.5		**4b**, 52[3c]
8			1		**4b**, 42

[a] After purification by column chromatography.

We next turned to the *N*-arylation of azoles, first using the crude iodides **1b**-**4b** generated by using $ZnCl_2$·TMEDA (0.5 equiv) and LiTMP (1.5 equiv). After hydrolysis and work-up, we involved them in the reaction with 1.5 equiv of azole using metal copper (0.2 equiv) as transition metal, cesium carbonate (2 equiv) as base, and acetonitrile as solvent at its reflux temperature for 24 hours.[6] Employing pyrrole, indole and carbazole as azole, the expected *N*-arylated azoles **1c**-**4c** (Table 2, entries 1-4), **1d**-**4d** (Table 2, entries 5-8) and **1e**-**4e** (Table 2, entries 9-12) were respectively obtained in overall yields ranging from 31 to 53%. No significant difference was noted using these three different azoles whereas benzothiazole (**3a**) and, to a lesser extent, benzofuran (**2a**) led to slightly higher yields. The compounds **3c** and **1e** were identified unambiguously by X-ray diffraction (Figure 1).

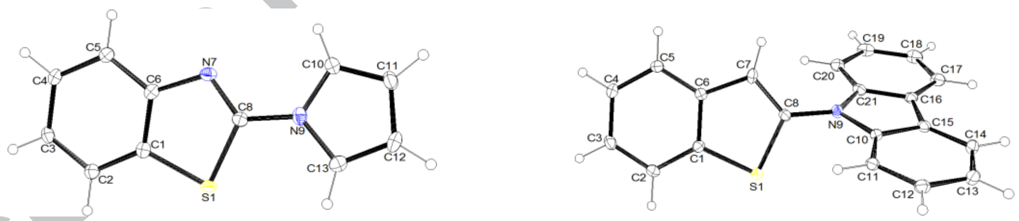
Table 2. Deprotometalation-iodination of the heterocycles 1a-4a followed by *N*-arylation of pyrrole, indole and carbazole with the crude iodides 1b-4b.



Entry	Ar-H	X, Y	Product, Yield (%)[a]	
1	**1a**	S, CH		**1c**, 43
2	**2a**	O, CH		**2c**, 48
3	**3a**	S, N		**3c**, 48
4	**4a**	O, N		**4c**, 40
5	**1a**	S, CH		**1d**, 33
6	**2a**	O, CH		**2d**, 31
7	**3a**	S, N		**3d**, 53
8	**4a**	O, N		**4d**, 45
9	**1a**	S, CH		**1e**, 32
10	**2a**	O, CH		**2e**, 45
11	**3a**	S, N		**3e**, 50
12	**4a**	O, N		**4e**, 42

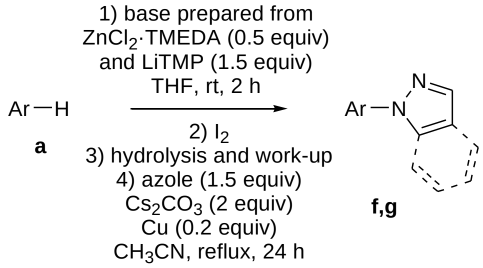
[a] After purification by column chromatography.

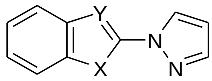
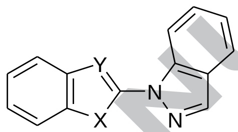
Figure 1. ORTEP diagrams (30% probability) of the compounds 3c and 1e.



The same conclusions could be drawn using pyrazole and indazole as azole, with overall yields between 40 and 54% for the compounds **1f**-**4f** (Table 3, entries 1-4) and **1g**-**4g** (Table 3, entries 5-8), respectively, as well as imidazole and benzimidazole, with 36-81% yields for the compounds **1h**-**4h** (Table 4, entries 1-4) and **1i**-**4i** (Table 4, entries 5-8), respectively. The structures of **1f**, **1g**, **2g** and **4g** (Figure 2), as well as those of **1h**, **2h** and **2i** (Figure 3) were confirmed by X-ray diffraction.

Table 3. Deprotometalation-iodination of the heterocycles 1a-4a followed by *N*-arylation of pyrazole and indazole with the crude iodides 1b-4b.



Entry	Ar-H	X, Y	Product, Yield (%)[a]	
1	**1a**	S, CH		**1f**, 47
2	**2a**	O, CH		**2f**, 54
3	**3a**	S, N		**3f**, 48
4	**4a**	O, N		**4f**, 41
5	**1a**	S, CH		**1g**, 46
6	**2a**	O, CH		**2g**, 40
7	**3a**	S, N		**3g**, 53
8	**4a**	O, N		**4g**, 44

[a] After purification by column chromatography.

Figure 2. ORTEP diagrams (30% probability) of the compounds 1f, 1g, 2g and 4g.

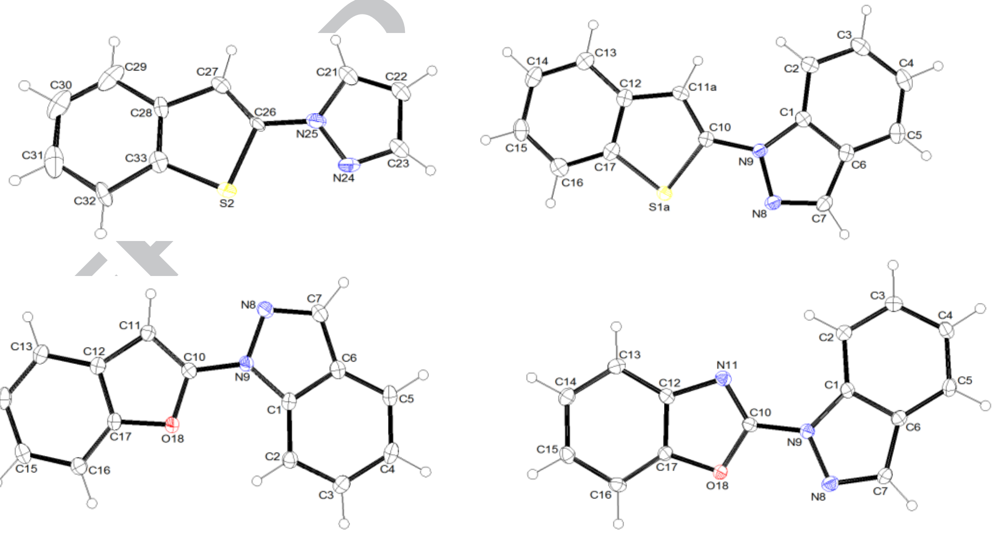
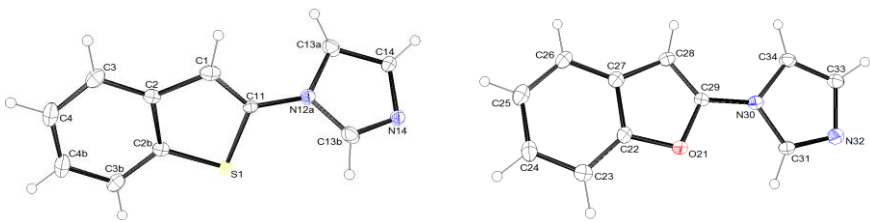


Figure 3. ORTEP diagrams (30% probability) of the compounds 1h, 2h and 2i.



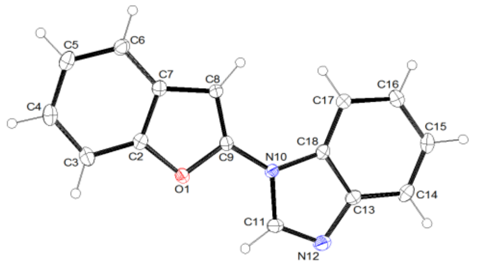
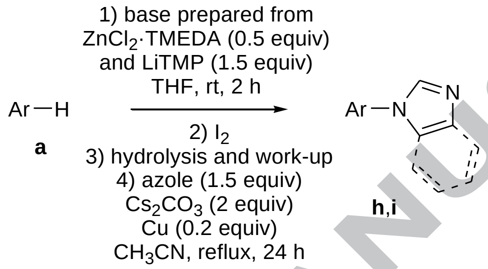
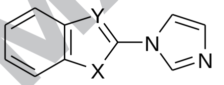
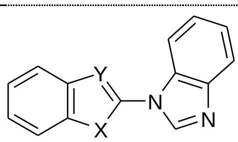


Table 4. Deprotometalation-iodination of the heterocycles 1a-4a followed by *N*-arylation of imidazole and benzimidazole with the crude iodides 1b-4b.

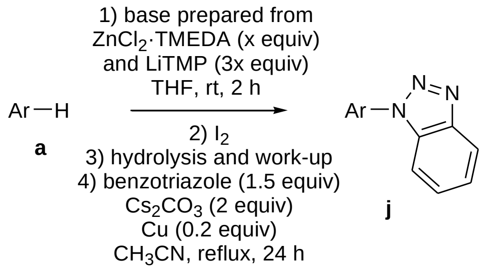


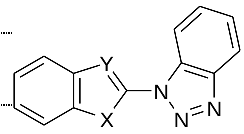
Entry	Ar-H	X, Y	Product, Overall yield (%)[a]	
1	**1a**	S, CH		**1h**, 36
2	**2a**	O, CH		**2h**, 81
3	**3a**	S, N		**3h**, 69
4	**4a**	O, N		**4h**, 66[b]
5	**1a**	S, CH		**1i**, 37
6	**2a**	O, CH		**2i**, 50
7	**3a**	S, N		**3i**, 56
8	**4a**	O, N		**4i**, 39

[a] After purification by column chromatography. [b] Using 0.5 equiv of azole.

When benzotriazole was employed as azole, yields for the compounds **1j**, **2j**, **3j** and **4j** dropped to 34, 39, 36 and 6%, respectively (Table 5, entries 1, 2, 4 and 6, Figure 4), a result that could be in relation with a lower reactivity of triazoles when compared with azoles and diazoles.[7] We thus decided to attempt the overall process from **2a** and **3a** by using $ZnCl_2$·TMEDA (1 equiv) and LiTMP (3 equiv) for the deprotometalation step. Under these conditions, bad results were obtained; indeed, 13 and 18% yields were respectively recorded (entries 3 and 5) against 39 and 36% before. These results show that the *N*-arylation efficiency is affected by compounds present in the crude iodide.

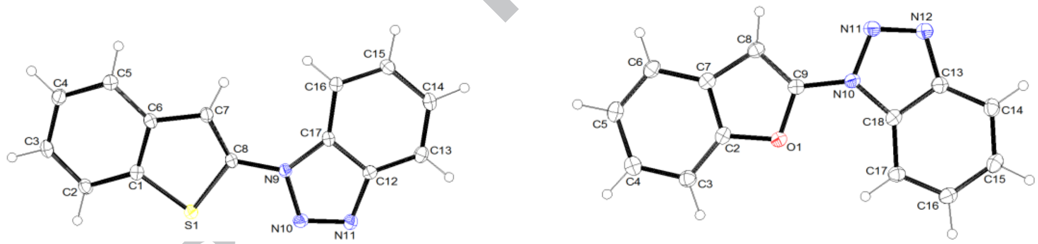
Table 5. Deprotometalation-iodination of the heterocycles 1a-4a followed by *N*-arylation of benzotriazole with the crude iodides 1b-4b.



Entry	Ar-H	X, Y	x	Product, Overall yield (%)[a]	Estimated *N*-arylation yield (%)[b]
1	**1a**	S, CH	0.5	 **1j**, 34	47
2	**2a**	O, CH	0.5	**2j**, 39	57
3			1	**2j**, 13	16
4	**3a**	S, N	0.5	**3j**, 36	63
5			1	**3j**, 18	27
6	**4a**	O, N	0.5	**4j**, 6[c]	12

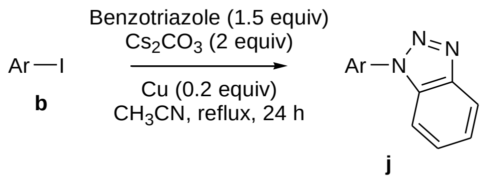
[a] After purification by column chromatography. [b] Calculated from Table 1. [c] Using 0.5 equiv of azole.

Figure 4. ORTEP diagrams (30% probability) of the compounds 1j and 2j.



In order to attempt a rationalization of these results, we performed the *N*-arylation step of benzotriazole using the purified iodides **1b**-**4b** (Table 6). Surprisingly, these reactions furnished the *N*-aryl benzotriazoles in yields in general lower than those observed using the process without purification (Table 5). From 2-iodobenzothiazole (**3a**), the best *N*-arylation yield was observed by carrying out the reaction in the presence of 1.5 equiv of 2,2,6,6-tetramethylpiperidine (Table 6, entry 3), an amount equivalent to that present after the deprotometalation-iodination sequence using $ZnCl_2$·TMEDA (0.5 equiv) and LiTMP (1.5 equiv). NMR spectra showing the presence of 2,2,6,6-tetramethylpiperidine in the crude iodides, it was suspected as having an effect on the course of the *N*-arylation.

Table 6. ***N*-arylation of benzotriazole with the purified iodides 1b-4b.**



Entry	Ar-I	X, Y	Product, Yield (%)[a]
1	**1b**	S, CH	**1j**, 10
2	**2b**	O, CH	**2j**, 28
3	**3b**	S, N	**3j**, 38 (47)[b] (35)[c]
4	**4b**	O, N	**4j**, 3

[a] After purification by column chromatography. [b] In the presence of TMPH (1.5 equiv). [c] In the presence of TMPH (3 equiv).

2.2. Antiproliferative activity of the bis-heterocycles in A2058 melanoma cells

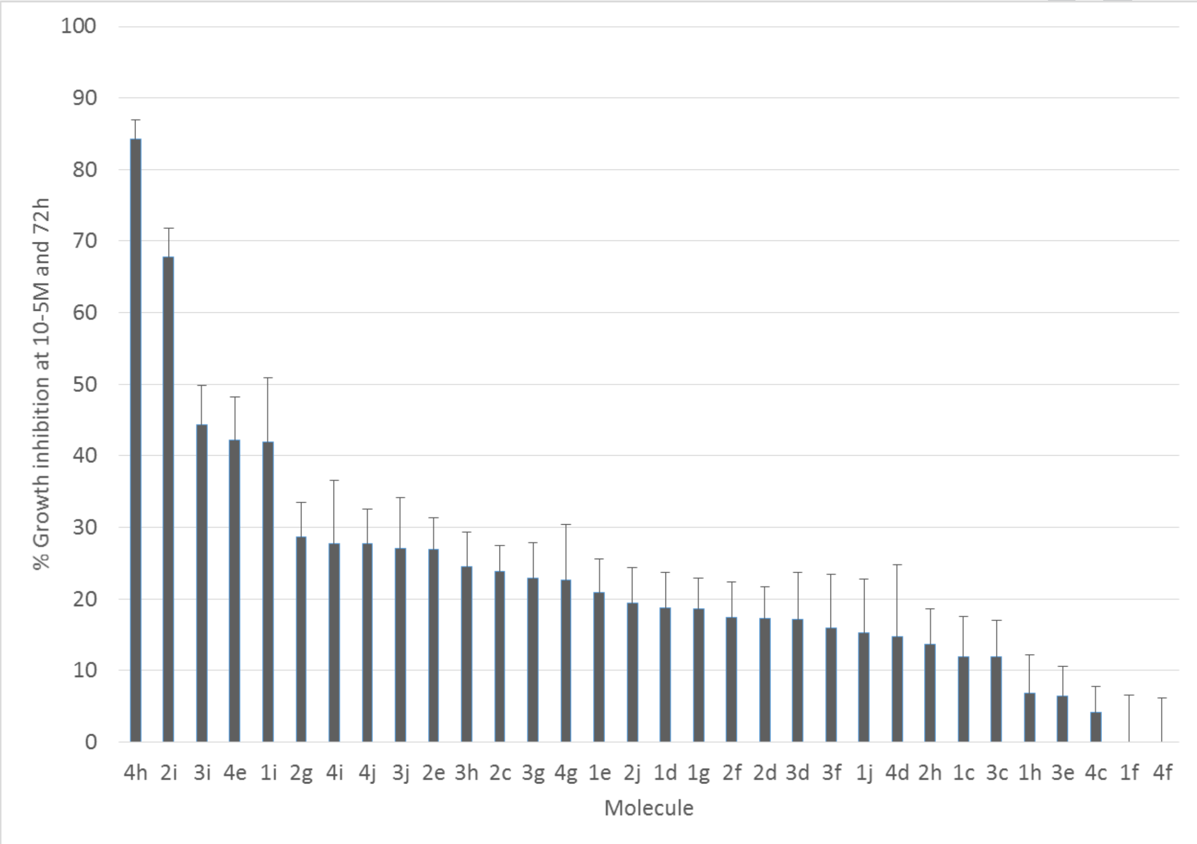
Most of the C,N'-linked bis-heterocycles induced a high growth inhibition of A2058 melanoma cells after a 72 h treatment at 10^{-5} M (Figure 5). Compound **4h** proved to be the most cytotoxic molecule, inducing a 84.3 ± 2.7% growth inhibition. By recording growth inhibition at different concentrations, an IC_{50} value of 7.1 μM was obtained for **4h**. In addition, the four bis-heterocycles containing benzimidazole (**1i**, **2i**, **3i** and **4i)** were among the seven most antiproliferative molecules, suggesting that this pharmacophore is involved in the inhibition of specific pharmacological targets in melanoma cells. Particularly, topoisomerase II was previously reported as a target of benzimidazoles derivatives,[8] and further studies should be considered to validate the activity of our derivatives on isolated topoisomerase II.

3. Conclusion

Thus, a large range of C,N'-linked bis-heterocycles have been synthesized from benzothiophene, benzofuran, benzothiazole or benzoxazole, on the one hand, and azoles or polyazoles, on the other hand, by using a deprotometalation-iodination-*N*-arylation sequence.

Most molecules show promising activity as antiproliferative drugs in human invasive melanoma cells, and should be further studied as potential Topoisomerase II inhibitors.

Figure 5. Growth inhibition of CRL 11147 human melanoma cells after 72 h in the presence of 10^{-5} M bis-heterocycle.



4. Experimental

4.1. General

All the reactions were performed 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 MHz 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.[9] The iodides **1b**, **2b**, **3b** and **4b** were previously described.[3c]

Crystallography. The samples were studied with graphite monochromatized Mo-Kα radiation (λ = 0.71073 Å). X-ray diffraction data were collected at T = 150(2) K using APEXII Bruker-AXS diffractometer. The structure was solved by direct methods using the SIR97 program,[10] and then refined with full-matrix least-square methods based on F^2 (SHELX-97)[11] with the aid of the WINGX program.[12] 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).[13]

4.2. General procedure: 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[14] (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. The structure of the new compounds was confirmed either by X-ray diffraction (see data below) or through microanalysis.

4.2.1. 2-(1-Pyrryl)benzothiophene (1c). The general procedure using benzothiophene (**1a**, 0.12 mL, 1.0 mmol) and pyrrole (0.10 mL, 1.5 mmol, 1.5 equiv) gave **1c** (eluent: heptane) in

43% yield as a beige powder: mp 168 °C; IR (ATR): 720, 773, 880, 956, 1024, 1065, 1207, 1254, 1354, 1371, 1454, 1470, 1481, 1574, 1620, 3123 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.38 (t, 2H, *J* = 2.2 Hz), 7.09 (d, 1H, *J* = 0.6 Hz), 7.13 (t, 2H, *J* = 2.1 Hz), 7.32 (td, 1H, *J* = 7.8 and 1.5 Hz), 7.39 (td, 1H, *J* = 7.5 and 1.2 Hz), 7.71 (dm, 1H, *J* = 7.5 Hz), 7.76 (dm, 1H, *J* = 7.8 Hz); ^{13}C NMR ($CDCl_3$) δ 119.8 (CH), 111.3 (2CH), 120.9 (2CH), 122.2 (CH), 123.2 (CH), 124.2 (CH), 125.1 (CH), 135.0 (C), 138.9 (C), 143.5 (C).

4.2.2. 2-(1-Pyrryl)benzofuran (2c). The general procedure using benzofuran (**2a**, 0.11 mL, 1.0 mmol) and pyrrole (0.10 mL, 1.5 mmol, 1.5 equiv) gave **2c** (eluent: heptane) in 48% yield as a whitish powder: mp 112 °C; IR (ATR): 721, 773, 880, 956, 1024, 1065, 1169, 1207, 1254, 1354, 1371, 1454, 1470, 1481, 1620, 3050, 3134 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.32 (d, 1H, *J* = 0.9 Hz), 6.38 (t, 2H, *J* = 2.2 Hz), 7.09-7.16 (m, 4H), 7.31-7.41 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 87.6 (CH), 110.9 (CH), 111.3 (2CH), 118.9 (2CH), 120.4 (CH), 123.3 (CH), 123.6 (CH), 129.0 (C), 150.3 (C), 151.4 (C).

4.2.3. 2-(1-Pyrryl)benzothiazole (3c). The general procedure using benzothiazole (**3a**, 0.11 mL, 1.0 mmol) and pyrrole (0.10 mL, 1.5 mmol, 1.5 equiv) gave **3c** (eluent: heptane-AcOEt 90:10) in 48% yield as a white powder: mp 146 °C; IR (ATR): 695, 722, 749, 911, 996, 1051, 1070, 1278, 1336, 1441, 1456, 1473, 1525, 1541, 1595, 2867, 2930, 3059, 3128 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.39 (t, 2H, *J* = 2.2 Hz), 7.33 (ddd, 1H, *J* = 8.7, 7.5 and 1.2 Hz), 7.43-7.49 (m, 3H), 7.78 (ddd, 1H, *J* = 8.1, 1.2 and 0.6 Hz), 7.88 (ddd, 1H, *J* = 8.1, 1.2 and 0.6 Hz); ^{13}C NMR ($CDCl_3$) δ 112.7 (2CH), 120.1 (2CH), 121.4 (CH), 122.1 (CH), 124.6 (CH), 126.7 (CH), 132.0 (C), 151.2 (C), 159.5 (C). The NMR data are analogous to those previously described.[15] **Crystal data for 3c.** $C_{11}H_8N_2S$, M = 200.25, monoclinic, $P2_1/a$, a = 11.3079(9), b = 6.4758(5), c = 12.6883(10) Å, β = 90.263(3) °, V = 929.13(13) $Å^3$, Z = 4, d = 1.432 g cm^{-3}, μ = 0.303 mm^{-1}. A final refinement on F^2 with 2122 unique intensities and 128 parameters converged at $\omega R(F^2) = 0.1279$ ($R(F) = 0.0528$) for 1924 observed reflections with $I > 2\sigma(I)$. CCDC 985374.

4.2.4. 2-(1-Pyrryl)benzoxazole (4c). The general procedure using benzoxazole (**4a**, 0.12 g, 1.0 mmol) and pyrrole (0.10 mL, 1.5 mmol, 1.5 equiv) gave **4c** (eluent: heptane-AcOEt 90:10) in 40% yield as a whitish powder: mp 136 °C; IR (ATR): 727, 748, 761, 949, 973, 1000, 1056, 1077, 1315, 1399, 1438, 1446, 1491, 1538, 1597, 3059 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.41 (t, 2H, J = 2.2 Hz), 7.28 (td, 1H, J = 7.5 and 1.5 Hz), 7.33 (td, 1H, J = 7.5 and 1.5 Hz), 7.50 (dd, 1H, J = 7.8 and 1.5 Hz), 7.54 (t, 2H, J = 2.4 Hz), 7.63 (dd, 1H, J = 7.5 and 1.5 Hz); ^{13}C NMR ($CDCl_3$) δ 110.1 (CH), 113.1 (2CH), 119.1 (CH), 119.6 (2CH), 124.1 (CH), 125.1 (CH), 141.4 (C), 149.1 (C), 154.8 (C).

4.2.5. 2-(1-Indolyl)benzothiophene (1d). The general procedure using benzothiophene (**1a**, 0.12 mL, 1.0 mmol) and indole (0.12 g, 1.5 mmol, 1.5 equiv) gave **1d** (eluent: heptane) in 33% yield as a green powder: mp 56-58 °C; IR (ATR): 744, 782, 798, 876, 909, 1008, 1045, 1145, 1158, 1246, 1301, 1438, 1471, 1523, 1738, 3064, 3131 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.79 (dd, 1H, J = 3.3 and 0.8 Hz), 7.28-7.51 (m, 4H), 7.34 (d, 1H, J = 0.6 Hz), 7.45 (d, 1H, J = 3.3 Hz), 7.75-7.89 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 105.2 (CH), 111.1 (CH), 115.1 (CH), 121.4 (CH), 121.4 (CH), 122.3 (CH), 123.3 (CH), 123.6 (CH), 124.5 (CH), 125.1 (CH), 128.9 (CH), 129.5 (C), 136.3 (C), 136.6 (C), 138.5 (C), 141.6 (C).

4.2.6. 2-(1-Indolyl)benzofuran (2d). The general procedure using benzofuran (**2a**, 0.11 mL, 1.0 mmol) and indole (0.12 g, 1.5 mmol, 1.5 equiv) gave **2d** (eluent: heptane) in 31% yield as a white powder: mp 64 °C; IR (ATR): 697, 723, 748, 912, 1071, 1208, 1337, 1443, 1456, 1475, 1524, 1542, 1596, 3059, 3128 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.58 (d, 1H, J = 0.9 Hz), 6.75 (dd, 1H, J = 3.3 and 0.6 Hz), 7.23-7.33 (m, 3H), 7.36 (td, 1H, J = 7.6 and 1.2 Hz), 7.51-7.55 (m, 1H), 7.57-7.61 (m, 2H), 7.70 (d, 1H, J = 7.8 Hz), 7.87 (dd, 1H, J = 8.1 and 0.9 Hz) ; ^{13}C NMR ($CDCl_3$) δ 90.8 (CH), 106.0 (CH), 111.0 (CH), 111.9 (CH), 120.5 (CH), 121.5

(CH), 121.8 (CH), 123.6 (CH), 123.6 (CH), 123.7 (CH), 126.0 (CH), 129.0 (C), 129.7 (C), 135.2 (C), 149.4 (C), 151.4 (C).

4.2.7. 2-(1-Indolyl)benzothiazole (3d). The general procedure using benzothiazole (**3a**, 0.11 mL, 1.0 mmol) and indole (0.12 g, 1.5 mmol, 1.5 equiv) gave **3d** (eluent: heptane-AcOEt 90:10) in 53% yield as a pale pink powder: mp 110 °C (lit.[16] 107-108 °C); IR (ATR): 699, 726, 746, 907, 974, 1001, 1056, 1078, 1290, 1315, 1398, 1446, 1539, 1577, 1596, 3058 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.77 (dd, 1H, *J* = 3.6 and 0.8 Hz), 7.30-7.37 (m, 2H), 7.43-7.53 (m, 2H), 7.66-7.70 (m, 2H), 7.80 (ddd, 1H, *J* = 8.0, 1.2 and 0.6 Hz), 7.98 (ddd, 1H, *J* = 8.1, 1.1 and 0.6 Hz), 8.65 (ddd, 1H, *J* = 8.3, 1.6 and 0.7 Hz); ^{13}C NMR ($CDCl_3$) δ 108.2 (CH), 114.4 (CH), 121.2 (CH), 121.4 (CH), 122.1 (CH), 122.9 (CH), 124.3 (CH), 124.5 (CH), 126.5 (CH), 126.7 (CH), 130.5 (C), 131.6 (C), 135.5 (C), 151.3 (C), 158.9 (C).

4.2.8. 2-(1-Indolyl)benzoxazole (4d). The general procedure using benzoxazole (**4a**, 0.12 g, 1.0 mmol) and indole (0.12 g, 1.5 mmol, 1.5 equiv) gave **4d** (eluent: heptane-AcOEt 90:10) in 45% yield as a pale pink powder: mp 134 °C; IR (ATR): 695, 723, 778, 956, 1066, 1207, 1254, 1372, 1454, 1481, 1616, 1948, 3121 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.78 (dd, 1H, *J* = 3.6 and 0.8 Hz), 7.25-7.39 (m, 3H), 7.47 (ddd, 1H, *J* = 8.3, 7.3 and 1.1 Hz), 7.53 (ddd, 1H, *J* = 7.8, 1.3 and 0.6 Hz), 7.65-7.68 (m, 1H), 7.71 (ddd, 1H, *J* = 7.8, 1.4 and 0.6 Hz), 7.86 (d, 1H, *J* = 3.6 Hz), 8.58 (ddd, 1H, *J* = 8.3, 1.6 and 0.7 Hz); ^{13}C NMR ($CDCl_3$) δ 108.6 (CH), 110.0 (CH), 114.7 (CH), 118.9 (CH), 121.3 (CH), 123.1 (CH), 123.6 (CH), 124.7 (CH), 128.4 (CH), 124.9 (CH), 130.2 (C), 134.8 (C), 141.6 (C), 148.5 (C), 154.8 (C).

4.2.9. 2-(9-Carbazolyl)benzothiophene (1e). The general procedure using benzothiophene (**1a**, 0.12 mL, 1.0 mmol) and carbazole (0.17 g, 1.5 mmol, 1.5 equiv) gave **1e** (eluent: heptane-AcOEt 70:30) in 32% yield as a pale yellow powder: mp 96 °C; IR (ATR): 717, 738, 790, 981, 1174, 1219, 1228, 1297, 1319, 1333, 1365, 1451, 1479, 1580, 1594, 1609, 3026 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.37 (ddd, 2H, *J* = 7.7, 7.2 and 1.0 Hz), 7.45-7.53 (m, 5H), 7.66 (td, 2H, J = 8.2 and 0.8 Hz), 7.87-7.92 (m, 2H), 8.17 (ddd, 2H, J = 7.7, 1.2 and 0.7 Hz); ^{13}C NMR ($CDCl_3$) δ 110.5 (2CH), 120.4 (2CH), 121.0 (CH), 121.0 (2CH), 122.7 (CH), 123.9 (2C), 124.0 (CH), 124.9 (CH), 125.1 (CH), 126.5 (2CH), 138.1 (C), 138.2 (C), 139.1 (C), 141.6 (2C). **Crystal data for 1e.** 2($C_{20}H_{13}NS$), M = 598.75, monoclinic, $P2_1/c$, a = 22.0832(5), b = 6.1505(2), c = 23.8915(6) Å, β = 117.3650(10) °, V = 2881.88(14) Å^3, Z = 4, d = 1.38 g cm^{-3}, μ = 0.219 mm^{-1}. A final refinement on F^2 with 6561 unique intensities and 397 parameters converged at $\omega R(F^2)$ = 0.121 ($R(F)$ = 0.0445) for 5254 observed reflections with $I > 2\sigma(I)$. CCDC 985365.

4.2.10. 2-(9-Carbazolyl)benzofuran (2e). The general procedure using benzofuran (**2a**, 0.11 mL, 1.0 mmol) and carbazole (0.17 g, 1.5 mmol, 1.5 equiv) gave **2e** (eluent: heptane-AcOEt 70:30) in 45% yield as a white powder: mp 152 °C; IR (ATR): 726, 748, 974, 1000, 1056, 1078, 1290, 1315, 1398, 1438, 1446, 1539, 1596, 3060 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.84 (d, 1H, J = 0.9 Hz), 7.36-7.46 (m, 4H), 7.54 (ddd, 2H, J = 8.3, 7.3 and 1.3 Hz), 7.62-7.66 (m, 1H), 7.70-7.74 (m, 1H), 7.79 (td, 2H, J = 8.2 and 0.7 Hz), 8.17 (ddd, 2H, J = 7.8, 1.1 and 0.7 Hz); ^{13}C NMR ($CDCl_3$) δ 97.0 (CH), 111.3 (CH), 111.4 (2CH), 120.4 (2CH), 120.9 (CH), 121.6 (2CH), 123.5 (CH), 124.3 (2C), 124.3 (CH), 126.7 (2CH), 128.5 (C), 139.9 (2C), 147.7 (C), 152.1 (C).

4.2.11. 2-(9-Carbazolyl)benzothiazole (3e). The general procedure using benzothiazole (**3a**, 0.11 mL, 1.0 mmol) and carbazole (0.17 g, 1.5 mmol, 1.5 equiv) gave **3e** (eluent: heptane-AcOEt 70:30) in 50% yield as a yellow powder: mp 140 °C; IR (ATR): 694, 719, 801, 956, 1016, 1067, 1208, 1253, 1331, 1373, 1440, 1454, 1476, 1516, 1571, 1622, 3125 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.38-7.45 (m, 3H), 7.53-7.61 (m, 3H), 7.89 (dd, 1H, J = 7.9 and 0.6 Hz), 8.10 (d, 3H, J = 7.8 Hz), 8.52 (d, 2H, J = 8.4 Hz); ^{13}C NMR ($CDCl_3$) δ 113.4 (2CH), 120.2 (2CH), 121.2 (CH), 122.3 (CH), 122.8 (2CH), 124.6 (CH), 125.3 (2C), 126.7 (CH), 127.1 (2CH), 132.1 (C), 139.3 (2C), 150.3 (C), 157.8 (C). The NMR data are in accordance with those previously reported.[17]

4.2.12. 2-(9-Carbazolyl)benzoxazole (4e). The general procedure using benzoxazole (**4a**, 0.12 g, 1.0 mmol) and carbazole (0.17 g, 1.5 mmol, 1.5 equiv) gave **4e** (eluent: heptane-AcOEt 70:30) in 42% yield as a pale yellow powder: mp 206 °C; IR (ATR): 726, 763, 881, 987, 1129, 1176, 1211, 1345, 1375, 1456, 1476, 1523, 1542, 1576, 1604, 3056, 3143 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.26-7.45 (m, 4H), 7.55-7.63 (m, 3H), 7.75 (ddd, 1H, *J* = 7.8, 1.3 and 0.6 Hz), 8.06 (ddd, 1H, *J* = 7.7, 1.1 and 0.6 Hz), 8.67 (d, 1H, *J* = 8.4 Hz); ^{13}C NMR ($CDCl_3$) δ 110.0 (CH), 115.2 (2CH), 118.9 (CH), 120.1 (2CH), 123.3 (2CH), 123.6 (CH), 125.0 (CH), 125.7 (2C), 127.4 (2CH), 138.0 (2C), 141.3 (C), 148.3 (C), 155.6 (C).

4.2.13. 2-(1-Pyrazolyl)benzothiophene (1f). The general procedure using benzothiophene (**1a**, 0.12 mL, 1.0 mmol) and pyrazole (0.10 mL, 1.5 mmol, 1.5 equiv) gave **1f** (eluent: heptane) in 47% yield as a whitish powder: mp 102 °C; IR (ATR): 727, 748, 761, 973, 1000, 1056, 1077, 1236, 1289, 1315, 1398, 1438, 1446, 1491, 1538, 1597, 3059 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.46 (dd, 1H, *J* = 2.4 and 2.0 Hz), 7.21 (s, 1H), 7.31 (td, 1H, *J* = 7.2 and 1.4 Hz), 7.36 (td, 1H, *J* = 7.5 and 1.3 Hz), 7.67-7.70 (m, 1H), 7.72 (d, 1H, *J* = 1.5 Hz), 7.75-7.78 (m, 1H), 7.90 (d, 1H, *J* = 2.7 Hz); ^{13}C NMR ($CDCl_3$) δ 108.4 (CH), 108.6 (CH), 122.2 (CH), 123.4 (CH), 124.3 (CH), 125.0 (CH), 127.9 (CH), 135.5 (C), 138.5 (C), 141.6 (CH), 143.0 (C). **Crystal data for 1f.** $3(C_{11}H_8N_2S)$, M = 600.76, monoclinic, $P\ c$, a = 7.3675(4), b = 7.8206(4), c = 25.5774(13) Å, β = 93.082(3) °, V = 1471.59(13) $Å^3$, Z = 2, d = 1.356 g cm^{-3}, μ = 0.287 mm^{-1}. A final refinement on F^2 with 6115 unique intensities and 338 parameters converged at $\omega R(F^2)$ = 0.1322 ($R(F)$ = 0.0577) for 4010 observed reflections with $I > 2\sigma(I)$. CCDC 985366.

4.2.14. 2-(1-Pyrazolyl)benzofuran (2f). The general procedure using benzofuran (**2a**, 0.11 mL, 1.0 mmol) and pyrazole (0.10 mL, 1.5 mmol, 1.5 equiv) gave **2f** (eluent: heptane) in 54%

yield as a beige powder: mp 74 °C; IR (ATR): 737, 763, 881, 1017, 1129, 1172, 1212, 1344, 1376, 1455, 1476, 1575, 1608, 1622, 1928, 3056, 3143 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.48 (dd, 1H, *J* = 2.5 and 1.8 Hz), 6.74 (d, 1H, *J* = 0.8 Hz), 7.24-7.31 (m, 2H), 7.46-7.51 (m, 1H), 7.54-7.59 (m, 1H), 7.79 (d, 1H, *J* = 1.4 Hz), 8.06 (d, 1H, *J* = 2.5 Hz); ^{13}C NMR ($CDCl_3$) δ 90.0 (CH), 107.8 (CH), 111.0 (CH), 121.0 (CH), 123.8 (CH), 124.0 (CH), 127.8 (CH), 128.6 (C), 142.6 (CH), 149.4 (C), 151.6 (C).

4.2.15. 2-(1-Pyrazolyl)benzothiazole (3f). The general procedure using benzothiazole (**3a**, 0.11 mL, 1.0 mmol) and pyrazole (0.10 mL, 1.5 mmol, 1.5 equiv) gave **3f** (eluent: heptane-AcOEt 90:10) in 48% yield as a white powder: mp 146 °C; IR (ATR): 727, 749, 762, 973, 1000, 1056, 1077, 1288, 1315, 1398, 1438, 1446, 1491, 1538, 1597, 1793, 1832, 1975, 3058 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.52 (dd, 1H, *J* = 2.7 and 1.8 Hz), 7.35 (td, 1H, *J* = 7.6 and 1.2 Hz), 7.47 (td, 1H, *J* = 7.6 and 1.2 Hz), 7.78 (d, 1H, *J* = 1.2 Hz), 7.83 (dd, 1H, *J* = 7.8 and 1.2 Hz), 7.89 (dd, 1H, *J* = 8.1 and 1.2 Hz), 8.48 (d, 1H, *J* = 2.7 Hz); ^{13}C NMR ($CDCl_3$) δ 109.4 (CH), 121.7 (CH), 122.4 (CH), 125.0 (CH), 126.7 (CH), 128.0 (CH), 133.2 (C), 143.4 (CH), 151.0 (C), 160.5 (C). The NMR data are analogous to those previously described.[18]

4.2.16. 2-(1-Pyrazolyl)benzoxazole (4f). The general procedure using benzoxazole (**4a**, 0.12 g, 1.0 mmol) and pyrazole (0.10 mL, 1.5 mmol, 1.5 equiv) gave **4f** (eluent: heptane-AcOEt 90:10) in 41% yield as a pale orange powder: mp 146 °C; IR (ATR): 727, 749, 761, 973, 1000, 1056, 1077, 1117, 1288, 1315, 1398, 1438, 1446, 1491, 1538, 1597, 1793, 1832, 3059 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.55 (dd, 1H, *J* = 2.7 and 1.5 Hz), 7.31 (td, 1H, *J* = 7.5 and 1.8 Hz), 7.35 (td, 1H, *J* = 7.5 and 1.8 Hz), 7.54-7.57 (m, 1H), 7.65-7.69 (m, 1H), 7.86 (d, 1H, *J* = 1.2 Hz), 8.37 (d, 1H, *J* = 2.7 Hz); ^{13}C NMR ($CDCl_3$) δ 109.8 (CH), 110.8 (CH), 119.7 (CH), 124.8 (CH), 125.3 (CH), 129.9 (CH), 140.8 (C), 144.6 (CH), 149.5 (C), 153.8 (C).

4.2.17. 2-(1-Indazolyl)benzothiophene (1g). The general procedure using benzothiophene (**1a**, 0.12 mL, 1.0 mmol) and indazole (0.11 g, 1.5 mmol, 1.5 equiv) gave **1g** (eluent: heptane) in 46% yield as a beige powder: mp 94 °C; IR (ATR): 700, 724, 745, 770, 902, 937, 1003, 1110, 1184, 1350, 1385, 1426, 1443, 1539, 1597, 1612, 1744, 3050 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.26-7.41 (m, 3H), 7.43 (d, 1H, J = 0.5 Hz), 7.53 (ddd, 1H, J = 8.4, 7.0 and 1.1 Hz), 7.76-7.84 (m, 3H), 7.93 (ddd, 1H, J = 8.5, 1.6 and 0.7 Hz), 8.23 (d, 1H, J = 0.9 Hz); ^{13}C NMR ($CDCl_3$) δ 110.0 (CH), 110.9 (CH), 121.6 (CH), 122.1 (CH), 122.4 (CH), 123.4 (CH), 124.2 (CH), 124.9 (CH), 125.7 (C), 128.1 (CH), 135.6 (C), 136.7 (CH), 138.8 (C), 138.9 (C), 142.8 (C). **Crystal data for 1g.** $C_{15}H_{10}N_2S$, M = 250.31, orthorhombic, $P\ 2_1\ 2_1\ 2_1$, a = 4.9340(2), b = 11.8093(4), c = 20.1488(6) Å, V = 1174.01(7) $Å^3$, Z = 4, d = 1.416 g cm^{-3}, μ = 0.256 mm^{-1}. A final refinement on F^2 with 2694 unique intensities and 170 parameters converged at $\omega R(F^2)$ = 0.0748 ($R(F)$ = 0.0323) for 2459 observed reflections with $I > 2\sigma(I)$. CCDC 985367.

4.2.18. 2-(1-Indazolyl)benzofuran (2g). The general procedure using benzofuran (**2a**, 0.11 mL, 1.0 mmol) and indazole (0.11 g, 1.5 mmol, 1.5 equiv) gave **2g** (eluent: heptane) in 40% yield as a pale pink powder: mp 100 °C; IR (ATR): 700, 725, 746, 770, 902, 939, 1003, 1110, 1145, 1205, 1350, 1386, 1426, 1443, 1539, 1597, 1612, 1745, 3063 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.78 (d, 1H, J = 0.9 Hz), 7.27-7.34 (m, 3H), 7.52-7.63 (m, 3H), 7.81 (dt, 1H, J = 8.0 and 1.0 Hz), 8.08 (dq, 1H, J = 8.5 and 0.9 Hz), 8.27 (d, 1H, J = 0.9 Hz); ^{13}C NMR ($CDCl_3$) δ 91.4 (CH), 111.2 (CH), 111.9 (CH), 120.8 (CH), 121.4 (CH), 122.8 (CH), 123.8 (CH), 123.8 (CH), 125.1 (C), 128.4 (CH), 128.6 (C), 137.9 (CH), 138.9 (C), 150.0 (C), 151.8 (C). **Crystal data for 2g.** $C_{15}H_{10}N_2O$, M = 234.25, monoclinic, $C\ 2/c$, a = 24.6806(12), b = 6.7281(3), c = 14.0318(6) Å, β = 105.777(2) °, V = 2242.25(18) $Å^3$, Z = 8, d = 1.388 g cm^{-3}, μ = 0.089 mm^{-1}. A final refinement on F^2 with 2543 unique intensities and 163 parameters converged at $\omega R(F^2)$ = 0.0929 ($R(F)$ = 0.0379) for 2096 observed reflections with $I > 2\sigma(I)$. CCDC 985370.

4.2.19. 2-(1-Indazolyl)benzothiazole (3g). The general procedure using benzothiazole (**3a**, 0.11 mL, 1.0 mmol) and indazole (0.11 g, 1.5 mmol, 1.5 equiv) gave **3g** (eluent: heptane-AcOEt 90:10) in 53% yield as a whitish powder: mp 146 °C; IR (ATR): 724, 752, 938, 1110, 1171, 1184, 1350, 1385, 1426, 1443, 1539, 1597, 1612, 1743, 2924, 3051 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.30-7.38 (m, 2H), 7.47 (ddd, 1H, *J* = 8.5, 7.3 and 1.3 Hz), 7.62 (ddd, 1H, *J* = 7.6 and 1.2 Hz), 7.77 (dt, 1H, *J* = 8.1 and 0.8 Hz), 7.83 (dd, 1H, *J* = 7.9 and 0.7 Hz), 7.96 (ddd, 1H, *J* = 8.1, 1.0 and 0.5 Hz), 8.21 (d, 1H, *J* = 0.7 Hz), 8.81 (dd, 1H, *J* = 8.5 and 0.8 Hz); ^{13}C NMR ($CDCl_3$) δ 114.5 (CH), 121.2 (CH), 121.3 (CH), 122.2 (CH), 123.9 (CH), 124.3 (CH), 126.2 (C), 126.3 (CH), 129.2 (CH), 132.3 (C), 138.7 (C), 138.9 (CH), 151.8 (C), 161.1 (C).

4.2.20. 2-(1-Indazolyl)benzoxazole (4g). The general procedure using benzoxazole (**4a**, 0.12 g, 1.0 mmol) and indazole (0.11 g, 1.5 mmol, 1.5 equiv) gave **4g** (eluent: heptane-AcOEt 90:10) in 44% yield as a whitish powder: mp 148 °C; IR (ATR): 700, 724, 746, 770, 937, 1003, 1110, 1184, 1350, 1385, 1426, 1443, 1539, 1597, 1612, 1743, 2924, 3051 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.32-7.44 (m, 3H), 7.62-7.70 (m, 2H), 7.78 (dm, 1H, *J* = 7.3 Hz), 7.83 (dt, 1H, *J* = 8.0 and 0.8 Hz), 8.34 (d, 1H, *J* = 0.9 Hz), 8.63 (dd, 1H, *J* = 8.5 and 0.8 Hz); ^{13}C NMR ($CDCl_3$) δ 110.5 (CH), 113.9 (CH), 119.3 (CH), 121.3 (CH), 124.0 (CH), 124.2 (CH), 125.0 (CH), 125.7 (C), 129.3 (CH), 138.9 (C), 140.1 (CH), 141.3 (C), 148.8 (C), 154.4 (C). **Crystal data for 4g.** $C_{14}H_9N_3O$, M = 235.24, monoclinic, $P2_1/a$, a = 8.2690(15), b = 14.389(3), c = 9.7013(17) Å, β = 110.499(8) °, V = 1081.2(4) Å^3, Z = 4, d = 1.445 g cm^{-3}, μ = 0.095 mm^{-1}. A final refinement on F^2 with 2428 unique intensities and 163 parameters converged at $\omega R(F^2)$ = 0.1239 ($R(F)$ = 0.0596) for 1550 observed reflections with $I > 2\sigma(I)$. CCDC 985375.

4.2.21. 2-(1-Imidazolyl)benzothiophene (1h). The general procedure using benzothiophene (**1a**, 0.12 mL, 1.0 mmol) and imidazole (0.10 g, 1.5 mmol, 1.5 equiv) gave **1h** (eluent: heptane-AcOEt 20:80) in 36% yield as a whitish powder: mp 128 °C; IR (ATR): 723, 750, 809, 822, 1038, 1066, 1103, 1231, 1438, 1457, 1481, 1575, 1660, 3112 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.23 (br s, 2H), 7.32 (br s, 1H), 7.34-7.44 (m, 2H), 7.74-7.80 (m, 2H), 7.94 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 113.5 (CH), 119.5 (CH), 122.2 (CH), 123.7 (CH), 125.1 (CH), 125.3 (CH), 130.6 (CH), 135.7 (C), 136.6 (CH), 138.0 (C), 138.3 (C). **Crystal data for 1h.**

$C_{11}H_8N_2S$, *M* = 200.25, orthorhombic, *F d 2 d*, *a* = 9.3280(7), *b* = 12.0169(10), *c* = 16.2272(11) Å, *V* = 1819.0(2) Å^3, *Z* = 8, *d* = 1.462 g cm^{-3}, μ = 0.309 mm^{-1}. A final refinement on F^2 with 772 unique intensities and 71 parameters converged at $\omega R(F^2)$ = 0.0751 ($R(F)$ = 0.0279) for 752 observed reflections with $I > 2\sigma(I)$. CCDC 985368.

4.2.22. 2-(1-Imidazolyl)benzofuran (2h). The general procedure using benzofuran (**2a**, 0.11 mL, 1.0 mmol) and imidazole (0.10 g, 1.5 mmol, 1.5 equiv) gave **2h** (eluent: heptane-AcOEt 20:80) in 81% yield as a whitish powder: mp 60 °C; IR (ATR): 749, 783, 813, 995, 1058, 1102, 1205, 1253, 1330, 1453, 1472, 1485, 1512, 1623, 1644, 3114 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.56 (s, 1H), 7.26-7.35 (m, 3H), 7.48-7.58 (m, 3H), 8.18 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 91.0 (CH), 111.0 (CH), 120.8 (CH), 123.8 (CH), 124.4 (CH), 127.9 (C), 130.6 (CH), 146.5 (C), 151.6 (C), 2 CH not seen. **Crystal data for 2h.** 6($C_{11}H_8N_2O$), *M* = 1105.16, monoclinic, *P 2$_1$/n*, *a* = 18.6374(10), *b* = 13.8711(6), *c* = 22.2273(11) Å, β = 113.7840(10) °, *V* = 5258.2(4) Å^3, *Z* = 4, *d* = 1.396 g cm^{-3}, μ = 0.093 mm^{-1}. A final refinement on F^2 with 12028 unique intensities and 758 parameters converged at $\omega R(F^2)$ = 0.153 ($R(F)$ = 0.0653) for 5680 observed reflections with $I > 2\sigma(I)$. CCDC 985371.

4.2.23. 2-(1-Imidazolyl)benzothiazole (3h). The general procedure using benzothiazole (**3a**, 0.11 mL, 1.0 mmol) and imidazole (0.10 g, 1.5 mmol, 1.5 equiv) gave **3h** (eluent: heptane-AcOEt 20:80) in 69% yield as a beige powder: mp 138 °C; IR (ATR): 695, 722, 761, 844, 935, 1033, 1090, 1240, 1312, 1372, 1442, 1472, 1541, 1594, 1695, 3112 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.22 (br s, 1H), 7.39 (t, 1H, *J* = 7.6 Hz), 7.50 (t, 1H, *J* = 7.6 Hz), 7.62 (s, 1H), 7.81 (d, 1H, *J* = 7.8 Hz), 7.92 (d, 1H, *J* = 8.1 Hz); ^{13}C NMR ($CDCl_3$) δ 117.7 (CH), 121.4 (CH), 122.7 (CH), 125.4 (CH), 127.0 (CH), 131.1 (CH), 132.0 (C), 135.8 (CH), 150.3 (C), 155.7 (C). The NMR data are analogous to those previously described.[15]

4.2.24. 2-(1-Imidazolyl)benzoxazole (4h). The general procedure using benzoxazole (**4a**, 0.12 g, 1.0 mmol) but imidazole (33 mg, **0.5** mmol, **0.5** equiv) gave **4h** (eluent: heptane-

AcOEt 90:10) in 66% yield as a yellow powder: mp 112 °C; IR (ATR): 709, 739, 755, 990, 1006, 1051, 1094, 1239, 1318, 1408, 1456, 1486, 1583, 1634, 2924, 2955, 3115 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.15 (s, 1H), 7.21-7.30 (m, 2H), 7.41-7.45 (m, 1H), 7.55-7.59 (m, 1H), 7.62 (br s, 1H), 8.29 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 110.5 (CH), 117.2 (CH), 119.6 (CH), 125.0 (CH), 125.4 (CH), 131.4 (CH), 140.4 (C), 148.9 (C), 152.0 (C), one CH not seen.

4.2.25. 2-(1-Benzimidazolyl)benzothiophene (1i). The general procedure using benzothiophene (**1a**, 0.12 mL, 1.0 mmol) and benzimidazole (0.12 g, 1.5 mmol, 1.5 equiv) gave **1i** (eluent: heptane) in 37% yield as a beige powder: mp 122 °C; IR (ATR): 725, 764, 987, 1017, 1071, 1129, 1210, 1241, 1338, 1375, 1457, 1475, 1523, 1542, 1596, 1621, 3057, 3143 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.39-7.50 (m, 5H), 7.73-7.76 (m, 1H), 7.83-7.93 (m, 3H), 8.25 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 110.9 (CH), 117.1 (CH), 120.8 (CH), 122.5 (CH), 123.5 (CH), 124.1 (CH), 124.4 (CH), 125.4 (CH), 125.4 (CH), 136.8 (C), 137.1 (C), 137.9 (C), 1 CH and 2C not seen.

4.2.26. 2-(1-Benzimidazolyl)benzofuran (2i). The general procedure using benzofuran (**2a**, 0.11 mL, 1.0 mmol) and benzimidazole (0.12 g, 1.5 mmol, 1.5 equiv) gave **2i** (eluent: heptane) in 50% yield as a whitish powder: mp 118 °C; IR (ATR): 726, 763, 987, 1018, 1129, 1211, 1345, 1375, 1457, 1475, 1523, 1543, 1576, 1599, 1621, 1928, 3055, 3143 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.69 (d, 1H, J = 0.8 Hz), 7.28-7.45 (m, 4H), 7.52-7.56 (m, 1H), 7.60-7.63 (m, 1H), 7.77 (d, 1H, J = 7.2 Hz), 7.91 (d, 1H, J = 8.1 Hz), 8.39 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 93.0 (CH), 111.2 (CH), 111.5 (CH), 120.9 (CH), 121.0 (CH), 123.8 (CH), 124.0 (CH), 124.6 (CH), 124.7 (CH), 128.1 (C), 132.5 (C), 140.9 (CH), 143.9 (C), 145.9 (C), 151.7 (C). **Crystal data for 2i.** 2($C_{15}H_{10}N_2O$), M = 468.5, monoclinic, $C\ 2/c$, a = 24.8998(14), b = 10.4891(6), c = 19.2261(11) Å, β = 118.094(2) °, V = 4429.8(4) Å^3, Z = 8, d = 1.405 g cm^{-3}, μ = 0.090 mm^{-1}. A final refinement on F^2 with 5074 unique intensities and 325 parameters converged at $\omega R(F^2)$ = 0.1043 ($R(F)$ = 0.0479) for 3471 observed reflections with $I > 2\sigma(I)$. CCDC 985372.

4.2.27. 2-(1-Benzimidazolyl)benzothiazole (3i). The general procedure using benzothiazole (**3a**, 0.11 mL, 1.0 mmol) and benzimidazole (0.12 g, 1.5 mmol, 1.5 equiv) gave **3i** (eluent: heptane-AcOEt 90:10) in 56% yield as a beige powder: mp 120 °C; IR (ATR): 695, 724, 735, 765, 957, 1066, 1119, 1207, 1221, 1253, 1305, 1370, 1452, 1480, 1516, 1615, 3055, 3125 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.35-7.54 (m, 4H), 7.82-7.89 (m, 2H), 7.98 (ddd, 1H, J = 8.1, 1.1 and 0.6 Hz), 8.30 (ddd, 1H, J = 8.1, 1.3 and 0.8 Hz), 8.59 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 113.4 (CH), 121.0 (CH), 121.5 (CH), 122.8 (CH), 124.6 (CH), 125.4 (CH), 125.4 (CH), 127.1 (CH), 131.8 (C), 132.0 (C), 141.3 (CH), 144.3 (C), 150.5 (C), 155.6 (C).

4.2.28. 2-(1-Benzimidazolyl)benzoxazole (4i). The general procedure using benzoxazole (**4a**, 0.12 g, 1.0 mmol) and benzimidazole (0.12 g, 1.5 mmol, 1.5 equiv) gave **4i** (eluent: heptane-AcOEt 90:10) in 39% yield as a white powder: mp 160 °C; IR (ATR): 695, 723, 749, 912, 996, 1051, 1070, 1110, 1240, 1278, 1336, 1394, 1442, 1456, 1474, 1525, 1541, 1595, 1907, 3059, 3127 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.29-7.43 (m, 3H), 7.48 (td, 1H, J = 8.0 and 1.2 Hz), 7.52-7.56 (m, 1H), 7.68-7.72 (m, 1H), 7.86 (d, 1H, J = 7.6 Hz), 8.36 (d, 1H, J = 8.2 Hz), 8.67 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 110.4 (CH), 114.0 (CH), 119.6 (CH), 120.9 (CH), 124.8 (CH), 124.8 (CH), 125.4 (CH), 125.7 (CH), 131.0 (C), 140.1 (C), 140.8 (CH), 143.8 (C), 148.6 (C), 152.3 (C).

4.2.29. 2-(1-Benzotriazolyl)benzothiophene (1j). The general procedure using benzothiophene (**1a**, 0.12 mL, 1.0 mmol) and benzotriazole (0.12 g, 1.5 mmol, 1.5 equiv) gave **1j** (eluent: heptane-AcOEt 20:80) in 34% yield as a beige powder: mp 136 °C; IR (ATR): 699, 727, 749, 762, 948, 973, 1000, 1056, 1077, 1117, 1236, 1275, 1289, 1300, 1315, 1398, 1438, 1446, 1491, 1538, 1597, 3058 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.40-7.51 (m, 3H), 7.63 (d, 1H, J = 0.3 Hz), 7.64 (ddd, 1H, J = 8.1, 7.2 and 1.2 Hz), 7.84-7.89 (m, 2H), 7.92 (dt, 1H, J

= 8.4 and 0.9 Hz), 8.17 (dt, 1H, J = 8.4 and 0.9 Hz); ^{13}C NMR ($CDCl_3$) δ 110.6 (CH), 114.1 (CH), 120.7 (CH), 122.4 (CH), 124.2 (CH), 125.1 (CH), 125.4 (CH), 125.5 (CH), 129.1 (CH), 132.4 (C), 136.5 (C), 137.7 (C), 138.0 (C), 146.6 (C). **Crystal data for 1j.** $C_{14}H_9N_3S$, M = 251.3, orthorhombic, $Pc2_1b$, a = 5.42050(10), b = 8.1997(2), c = 25.1666(7) Å, V = 1118.57(5) Å^3, Z = 4, d = 1.492 g cm^{-3}, μ = 0.271 mm^{-1}. A final refinement on F^2 with 2454 unique intensities and 163 parameters converged at $\omega R(F^2)$ = 0.0881 ($R(F)$ = 0.0363) for 2308 observed reflections with $I > 2\sigma(I)$. CCDC 985369.

4.2.30. 2-(1-Benzotriazolyl)benzofuran (2j). The general procedure using benzofuran (**2a**, 0.11 mL, 1.0 mmol) and benzotriazole (0.12 g, 1.5 mmol, 1.5 equiv) gave **2j** (eluent: heptane-AcOEt 20:80) in 39% yield as a pale pink powder: mp 102 °C; IR (ATR): 695, 721, 742, 957, 1054, 1068, 1118, 1208, 1249, 1331, 1372, 1455, 1476, 1516, 1615, 1947, 3056, 3127 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.05 (d, 1H, J = 0.9 Hz), 7.32 (td, 1H, J = 7.3 and 1.4 Hz), 7.36 (td, 1H, J = 7.3 and 1.7 Hz), 7.45 (ddd, 1H, J = 8.2, 7.0 and 1.0 Hz), 7.56-7.67 (m, 3H), 8.00 (dt, 1H, J = 8.4 and 0.9 Hz), 8.13 (dt, 1H, J = 8.4 and 0.9 Hz); ^{13}C NMR ($CDCl_3$) δ 95.0 (CH), 111.4 (CH), 111.4 (CH), 120.4 (CH), 121.5 (CH), 124.1 (CH), 125.0 (CH), 125.1 (CH), 127.7 (C), 129.3 (CH), 131.7 (C), 145.8 (C), 146.4 (C), 152.3 (C). **Crystal data for 2j.** $C_{14}H_9N_3O$, M = 235.24, orthorhombic, $P2_12_12_1$, a = 4.6488(3), b = 12.9438(7), c = 18.0315(10) Å, V = 1085.01(11) Å^3, Z = 4, d = 1.44 g cm^{-3}, μ = 0.095 mm^{-1}. A final refinement on F^2 with 1471 unique intensities and 163 parameters converged at $\omega R(F^2)$ = 0.0825 ($R(F)$ = 0.0311) for 1390 observed reflections with $I > 2\sigma(I)$. CCDC 985373.

4.2.31. 2-(1-Benzotriazolyl)benzothiazole (3j). The general procedure using benzothiazole (**3a**, 0.11 mL, 1.0 mmol) and benzotriazole (0.12 g, 1.5 mmol, 1.5 equiv) gave **3j** (eluent: heptane-AcOEt 90:10 to 50:50) in 36% yield as a pale beige powder: mp 166 °C (lit.[19] 174 °C); IR (ATR): 698, 727, 749, 762, 973, 1000, 1056, 1077, 1117, 1274, 1288, 1300, 1315, 1398, 1438, 1446, 1538, 1597, 3059 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.38 (td, 1H, J = 7.6 and 1.2

Hz), 7.45-7.52 (m, 2H), 7.67 (ddd, 1H, *J* = 8.2, 7.1 and 1.0 Hz), 7.85 (dd, 1H, *J* = 7.9 and 0.7 Hz), 7.98 (dd, 1H, *J* = 8.1 and 0.6 Hz), 8.12 (dt, 1H, *J* = 8.3 and 0.9 Hz), 8.59 (dt, 1H, *J* = 8.3 and 0.9 Hz); ^{13}C NMR ($CDCl_3$) δ 114.0 (CH), 120.3 (CH), 121.7 (CH), 123.1 (CH), 125.7 (CH), 126.0 (CH), 126.9 (CH), 130.1 (CH), 131.2 (C), 132.4 (C), 146.9 (C), 150.9 (C), 157.4 (C).

4.2.32. 2-(1*H*-1-benzotriazolyl)benzoxazole (4j).[20] The general procedure using benzoxazole (**4a**, 0.12 g, 1.0 mmol) but benzotriazole (40 mg, **0.5** mmol, **0.5** equiv) gave **4j** (eluent: heptane-AcOEt 90:10 to 50:50) in 6% yield as a red powder: mp 190 °C; IR (ATR): 739, 808, 938, 952, 1014, 1158, 1257, 1448, 1475, 1584, 1761, 2924 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.42-7.47 (m, 2H), 7.57 (ddd, 1H, *J* = 8.1, 7.2 and 0.9 Hz), 7.68-7.72 (m, 1H), 7.77 (ddd, 1H, *J* = 8.4, 7.2 and 0.9 Hz), 7.81-7.85 (m, 1H), 8.22 (d, 1H, *J* = 8.4 Hz), 8.51 (d, 1H, *J* = 8.4 Hz); ^{13}C NMR ($CDCl_3$) δ 111.1 (CH), 113.2 (CH), 120.3 (CH), 120.7 (CH), 125.7 (CH), 125.7 (CH), 126.2 (CH), 130.5 (CH), 131.4 (C), 139.5 (C), 140.7 (C), 146.2 (C), 149.2 (C).

4.3. Antiproliferative activity of the bis-heterocycles in human melanoma cells. The antiproliferative activity of the synthesized bis-heterocycles 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. The bis-heterocycles 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 bis-heterocycle 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 bis-heterocycle. At t = 72 h, 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:

$$GI\ (\%) = 100 - ((A_{550\ nm}\ sample - A_{550\ nm}\ BG) / (A_{550\ nm}\ control - A_{550\ nm}\ BG)) \times 100,$$

with:

- $A_{550\ nm}$ sample: median absorbance of 8 wells containing cells and 10^{-5} M bis-heterocycle,
- $A_{550\ nm}$ BG: median background absorbance of 8 wells containing control cell culture medium + 1% DMSO,
- $A_{550\ nm}$ control: median absorbance of 8 wells containing cells and 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/xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx.

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