

Iodothiophenes and Related Compounds as Coupling Partners in Copper-Mediated N-Arylation of Anilines

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Iodothiophenes and related compounds as coupling partners in copper-mediated *N*-arylation of anilines

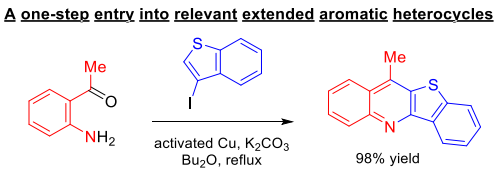
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Abstract *N*-arylation of various 2-acylated anilines with different electron-rich heteroaryl iodides (2- and 3-iodothiophenes, 2- and 3-iodobenzothiophenes, 2-iodobenzofuran) was achieved by using activated copper and potassium carbonate in dibutyl ether at reflux. The reactivity of the different heteroaryl iodides and anilines employed was discussed and rationalized on the basis of their electronic features. Subsequent cyclisation by aromatic electrophilic substitution easily took place in the case of remaining C2-free (benzo)thienyl or C3-free (benzo)furyl, affording original tri- and tetracycles. The antiproliferative activity of most of them was evaluated in A2058 melanoma cells and revealed four chlorinated tetracycles as effective growth inhibitors.

Key words aniline; thiophene; iodine; *N*-arylation; copper; antiproliferative activity; melanoma cells

Thiophenes and their benzo derivatives are aromatic heterocycles present in numerous bioactive compounds or in materials endowed with various electronic properties.[1] To access a wide variety of derivatives, functionalization of thiophenes is usually preferred over cyclization of suitable substrates.[2] However, while introducing aliphatic amines onto thiophenes has been developed by different ways,[3] the use of anilines and derivatives is less developed. Nucleophilic substitutions by anilines are only possible with activated thienyl halides under strong reaction conditions.[4] Thus, recourse to transition metal catalysts is mandatory in the case of unactivated thienyl halides.

Palladium-catalyzed reactions between bromothiophenes and diarylamines were documented by the groups of Watanabe[5] and Rasmussen[6] who used tri-*tert*-butylphosphine (ligand) and sodium *tert*-butoxide (base) in xylene at 120 °C. Luker[7] and Kirsch[8] employed bidentate BINAP and cesium carbonate in toluene at 110 °C for reacting arylamines with bromothiophenes bearing electron-withdrawing groups; interestingly, while the reactions worked well with the 2,3- and 2,5- isomers, they failed to deliver the products from the 2,4- ones.[7-8] Similarly, Queiroz's group documented the coupling of 3-bromobenzo[*b*]thiophene with 2-bromoanilines in moderate yields by using BINAP and sodium *tert*-butoxide in toluene at 120 °C;[9] the presence of an (electron-withdrawing) ester function at the 2-position of the benzothiophene ring proved to favor the reaction.[10] A close protocol was similarly reported by Buchwald and co-workers for the amination of 3-bromobenzo[*b*]thiophene with aniline, but using a bulky biaryl electron-rich ligand.[11]

By using reaction conditions close to those of Watanabe, Hartwig and co-workers observed that 3-bromothiophene reacts with anilines (diphenylamine < aniline < *N*-methylaniline) more rapidly than the 2- isomer does.[12] To rationalize the reactivity difference between 2- and 3-bromothiophenes, the results were compared with those from 2- and 3-bromofurans: the authors noticed higher yields from 2-bromofuran than from 2-bromothiophene, but higher yields from 3-bromothiophene than 3-bromofuran. Interestingly, a correlation was found between the yields recorded (2-furyl > 3-furyl and 3-thienyl > 2-thienyl) and those of the heteroarylamine reductive elimination from the corresponding dppf-chelated thienylpalladium amides (dppf = 1,1'-bis(diphenylphosphino)ferrocene).[13] The reactivity orders were further found to be related to the calculated Mulliken charges on carbons of thiophene and furan, with 2-furyl (C2: +0.16) and 3-thienyl (C3: -0.27) being less electron-rich (i.e. reductive elimination with C-N bond formation favored) than 3-furyl (C3: -0.34) and 2-thienyl (C2: -0.43), respectively. Reductive elimination with C-N bond formation was also reported as being favored in the case of more electron-donating amido groups.[12-13]

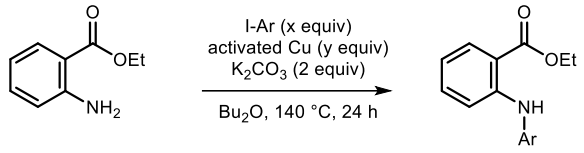
However, studies on the corresponding copper-mediated reactions remain, by far, less documented. In the course of the synthesis of inhibitors of platelet aggregation, Elslager and co-workers *N*-arylated potassium anthranilate by 3-bromobenzo[*b*]thiophene in the presence of *N*-ethylmorpholine and catalytic copper(II) bromide, albeit in a moderate 32% yield after 2 h in refluxing dimethylformamide.[14] A better result was

recorded by Zhu and co-workers who reacted 3-bromothiophene with aniline in water containing chitosan and copper(I) oxide, both catalytic, potassium hydroxide and tetrabutylammonium bromide (80% yield for the monoarylated product after 12 h reaction at 70 °C).[15] In contrast, Lu and Twieg hardly aminated 2-bromothiophene with *N*-(2-hydroxyethyl)aniline (employed as both reagent and solvent) in the presence of catalytic amounts of copper and copper(I) iodide, and potassium phosphate as base (15% yield after 2 days at 85 °C) while aniline and diphenylamine failed to react in *N*,*N*-dimethylethanolamine used as solvent.[16]

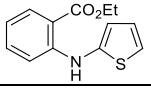
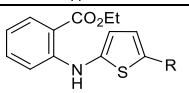
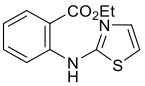
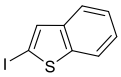
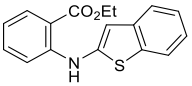
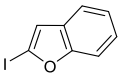
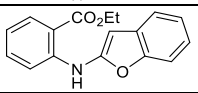
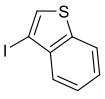
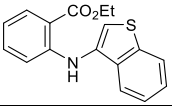
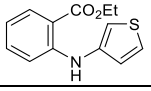
Within studies dedicated to copper-mediated C-N bond formation from aryl iodides,[3k,17] we successfully reacted 2-acylated anilines (2-aminoacetophenone and -benzophenone, 2-amino-3-benzoylpyridine and 1-amino-9-thioxanthone) with 2-iodothiophene and -benzothiophene.[17g,17h] In order to progress toward a better understanding of this reaction, here we initially compared the behavior of 2- and 3-iodothiophene, 2- and 3-iodobenzothiophene, and 2-iodobenzofuran in the *N*-arylation of ethyl anthranilate. Then, we prepared several thieno-, benzothieno- and benzofurano-fused quinolines from 2-aminoacetophenone, 2-aminobenzophenones and 2-aminobenzaldehydes by *N*-arylation and subsequent cyclization. To highlight the biological interest of these polycyclic heterocycles, they were evaluated for their antiproliferative activity in A2058 melanoma cells.

The few studies dedicated to the copper-catalyzed reactions of halogenated thiophenes with anilines suggest a reactivity order between 2- and 3-bromothiophenes similar to the one observed in palladium-catalyzed reactions; however, it is difficult to come to a clear conclusion due to the different reaction conditions employed. Thus, by starting from ethyl anthranilate (or 2-aminobenzoate; **1**), we decided to compare the reactivities of different thienyl and benzothienyl iodides (Table 1).

Table 1 *N*-arylation of ethyl anthranilate (**1**).



1 **2**

Entry	I-Ar		x equiv	y equiv	Product **2**, Yield (%)[a]	
1			1.0	0.2		**2a**, 43[b] (20)[c,d]
2			1.0	2.0		**2a**, 45[b]
3			1.5	1.0[e]		**2a**, 52[b] (48)[b,f]
4		R = Me	1.5	1.0[e]		traces[h]
5		R = COPh	1.5	1.0[e]		traces[h]
6		R = Cl	1.5	1.0[e]		traces[h]
7			1.5	1.0[e]		traces[h]
8			1.0	0.2		**2b**, 30[b]
9			1.0	1.0[e]		**2b**, 34[b]
10			1.5	1.0[e]		**2b**, 57[b] (53)[g]
11			1.5	1.0[e]		<20[h]
12			1.5	1.0[e]		**2c**, 96
13			1.0	1.0[e]		**2d**, 92

[a] After purification (see experimental part). [b] The rest is mainly recovered ethyl anthranilate and 2-iodothiophene. [c] After 57 h reaction time. [d] Degradation was noticed. [e] Added by portions of 0.2 equiv every 2 h. [f] The reaction was performed in the presence of CuI (1 equiv). [g] After 12 h reaction time. [h] Not possible to isolate the pure product from the reaction mixture.

Inspired by the conditions previously found to couple 2-acylated anilines with (benzo)thienyl iodides,[17g,17h] we first attempted the reaction between **1** and 2-iodothiophene in the presence of a catalytic amount of activated copper and 2 equivalents of potassium carbonate. The expected *N*-thienylated product **2a** was isolated in 43% yield after 24 h reaction time at 140 °C in dibutyl ether while lower yields were noticed after extended contact times due to increased unknown by-products formation (entry 1). By increasing the amount of copper to 2 equivalents, **2a** was obtained in a similar 45% yield (entry 2). However, by using 1 equivalent of copper, added by fractions of 0.2 equivalent every two hours, **2a** was isolated in a slightly improved 52% yield. Because copper(I) iodide is sometimes recommended as an additive in such *N*-arylations,[16] it was added with copper by fractions of 0.2 equivalent every two hours; however, no improvement was noticed (entry 3). It is worth noting that in the other conditions tested (either (i) copper(I) iodide (0.05 equiv), *N*,*N*'-dimethylethylenediamine

(0.1 equiv), potassium phosphate (2 equiv) in dioxane at 90 °C for 15 h,[18] or (ii) copper(I) iodide (0.05 equiv), potassium phosphate (2 equiv) in dimethylsulfoxide at 90 °C for 15 h),[17d] no reaction took place.

By reacting **1** with 2-iodo-5-methylthiophene under the conditions optimized for 2-iodothiophene, only traces of the expected product were detected (entry 4). Since it is known from the literature that such methyl-substituted products can be more prone to decomposition than their methyl-free analogs,[12] this result cannot be used to better understand the reaction. Introducing an electron-withdrawing ketone function or chloro group at the 5-position of thiophene similarly led to traces of the *N*-thienylated products (entries 5 and 6). In these cases, an intramolecular electron transfer from the nitrogen lone pair to the thienyl ring, facilitated by the presence of an electron-withdrawing group,[3k] could explain the low stability of the formed 2-(arylamino)thiophenes during both synthesis and purification. Note that using 2-iodothiazole as aryl iodide also led to a similar result, with traces of the expected product only detected in the crude (entry 7).

We next turned our attention to the reaction between **1** and 2-iodobenzothiophene. After optimization of the conditions (entries 8-10), the expected *N*-heteroarylated product **2b** was produced in a slightly higher 57% yield (entry 10; Figure 1). As far as 2-iodobenzofuran is concerned, the reaction worked to some extent but it proved impossible to isolate the pure product from the reaction mixture due to its low stability (entry 11).[19]

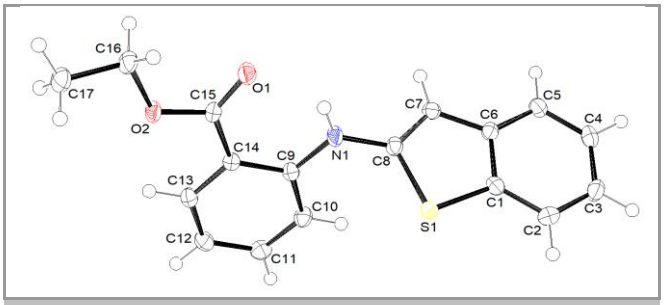


Figure 1 ORTEP diagram (50% probability) of the compound **2b**.

When compared with its 2-iodinated isomer, 3-iodobenzothiophene proved much more reactive, affording the *N*-arylated derivative **2c** in a nearly quantitative yield upon treatment by **1** as before (entry 12). A reactivity higher than that of the 2-iodinated isomer was also recorded in the case of 3-iodothiophene, which was converted into the derivative **2d** in high yield (entry 13).

For palladium-catalyzed coupling reactions in which oxidative addition is rate determining, literature provides approaches to predict the regioselectivity in the case of polyhalogenated substrates. In the case of two identical halogens, the reaction is generally favored at the most electron-deficient carbon.[20] In this vein, Fairlamb and co-workers proposed to employ the ^{13}C NMR chemical shifts as a measure of their electrophilicities, with the most deshielded carbon corresponding to the preferred coupling site.[21] We thus compared the ^{13}C NMR spectra of 2-iodothiophene (C2 at 72.8 ppm) and 3-iodothiophene (C3 at 76.8 ppm),[22] as well as those of 2-iodobenzothiophene (C2 at 78.5 ppm) and its 3-iodo isomer (C3 at 78.4 ppm).[23] All these C-I chemical shifts are below that of iodobenzene (94.4 ppm), in line with the lower reactivities noticed. The values are in accordance with an easier oxidative addition at C3 in the iodothiophene series. However, they alone cannot explain the discrepancy observed in the iodobenzothiophene series; therefore, inspired by the studies performed under palladium catalysis, we also looked at the reductive elimination step.

On the basis of the carbons Mulliken charges (see Figure 2), the obtained results show that the reactions are favored for less electron-rich 3-thienyl and 3-benzothienyl, when compared with 2-thienyl and 2-benzothienyl. Between thiophene and benzothiophene, charges for the carbons at C2 are close with a slightly less negative value for the latter. Less electron-rich aryl groups (that facilitate reductive elimination) seem to also favor this copper-mediated *N*-arylation, as proposed by Hartwig and co-workers for related palladium-catalyzed reactions in the thiophene and furan series.[12-13]

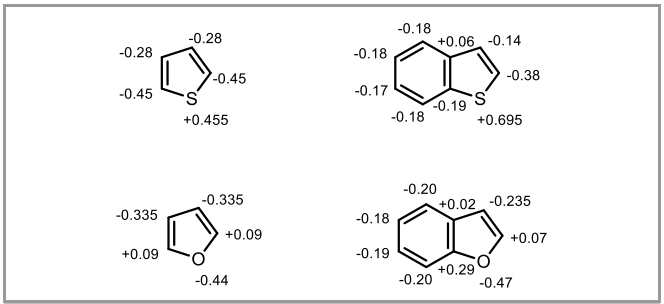
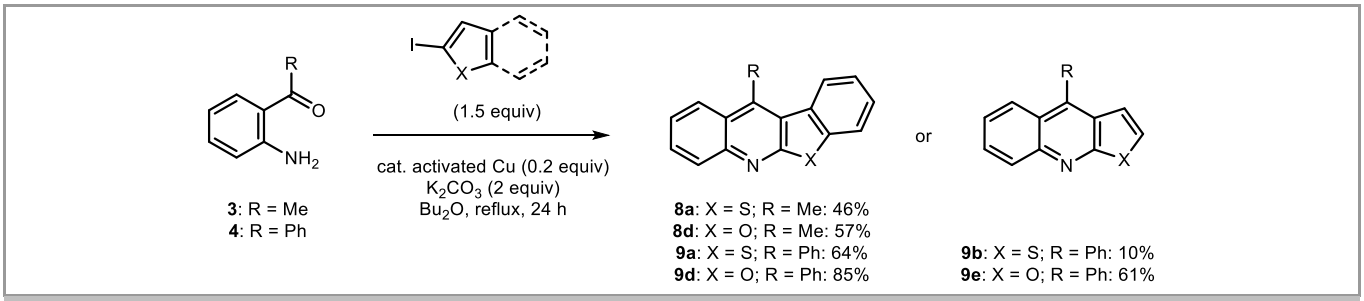


Figure 2 Mulliken charges on atoms calculated (MP2/6-31G(d)) by Belen'kii, Suslov and Chuvylkin for thiophene, benzo[*b*]thiophene, benzo[*b*]furan and furan.[24]

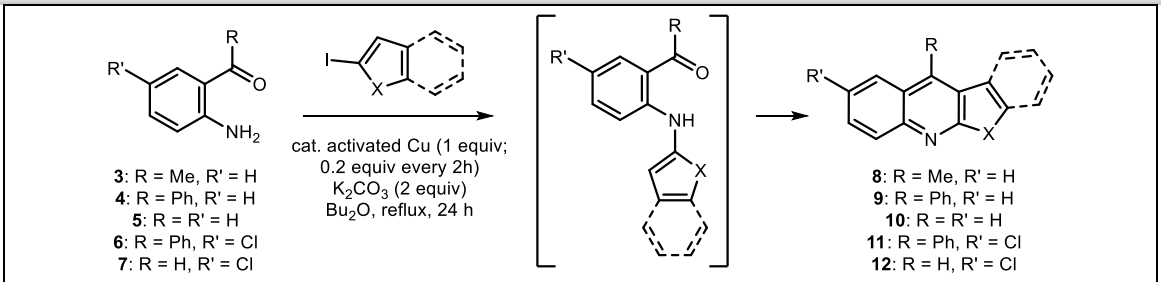
Due to the instability of some of the *N*-arylated ethyl anthranilates, it proved difficult to compare the reactivities of all the thienyl iodides and related compounds. We thought an alternative way could consist in trapping the formed *N*-thienyl derivatives as soon as they are formed by cyclisation, as documented in a previous study (Scheme 1).[17g]

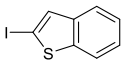
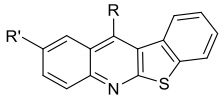
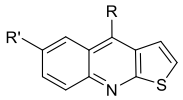
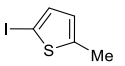
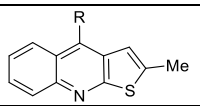
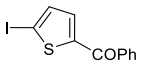
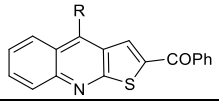
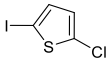
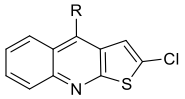
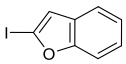
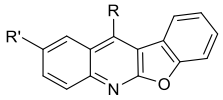
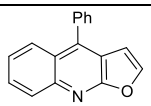
To this purpose, we replaced the ester **1** by more reactive aldehydes and ketones, and chose a wider range of reagents (2-aminoacetophenone (**3**), 2-aminobenzophenone (**4**), 2-aminobenzaldehyde (**5**), 2-amino-5-chlorobenzophenone (**6**) and 2-amino-5-chlorobenzaldehyde (**7**)) in order (i) to study the impact of the aniline on the course of the reaction, and (ii) to prepare a larger range of molecules for biological evaluation. Reactions were performed with 2-iodothiophene and related compounds (Table 2), as well as with 3-iodothiophene and its benzo analog (Table 3) under the optimized reaction conditions. Even if they were carried out by using only 0.2 equivalent of activated copper,[17g] in order to get a comprehensive view we decided to add in these tables the yields of the six reactions already published.



Scheme 1 Results obtained in the frame of a previous study.[17g]

Table 2 *N*-arylation-cyclization between **3**-**7** and 2-iodo(benzo)thiophenes/furans to afford tri- and tetracycles.



Entry	Aniline	Iodide	equiv	Product, Yield (%)[a]	
1[17g]	**3**		1.5		**8a** (R = Me, R′ = H), 46
2[17g]	**4**		1.5		**9a** (R = Ph, R′ = H), 64
3	**5**		1.5		**10a** (R = R′ = H), 78
4	**6**		1		**11a** (R = Ph, R′ = Cl), 59
5	**7**		1		**12a** (R = H, R′ = Cl), 42
6[17g]	**4**		1.5		**9b** (R = Ph, R′ = H), 10[b]
7	**6**		1		**11b** (R = Ph, R′ = Cl), 4
8	**7**		1		**12b** (R = H, R′ = Cl), 5
9	**3**		1.5		**8c** (R = Me), 22[c]
10	**4**		1.5		**9c** (R = Ph), 14
11	**5**		1.5		**10c** (R = H), 17
12	**3**		1.5		R = Me: traces
13	**4**		1.5		R = Ph: traces
14	**3**		1.5		R = Me: traces
15	**4**		1.5		R = Ph: traces
16	**3**		1.5		**8d** (R = Me, R′ = H), 94, 57[17g]
17	**4**		1.5		**9d** (R = Ph, R′ = H), 79, 85[17g]
18	**5**		[d]		**10d** (R = R′ = H), 82
19	**6**		1		**11d** (R = Ph, R′ = Cl), 85
20	**7**		1		**12d** (R = H, R′ = Cl), 59
21[17g]	**5**		1.5		**9e**, 61

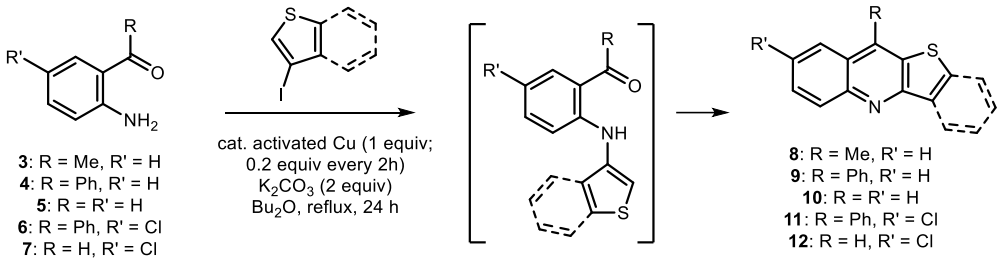
[a] After purification (see experimental part). [b] *N*-(2-thienyl)benzophenone (**9b′**) was also isolated in 50% yield. [c] *N*-(5-methyl-2-thienyl)acetophenone (**8c′**) was also isolated in 13% yield. [d] To improve the yield, 1.5 equiv of 2-aminobenzaldehyde and 1 equiv of 2-iodobenzofuran were used.

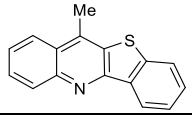
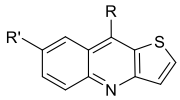
First of all, if *N*-arylation was readily followed by *in situ* cyclization in the case of 2-iodobenzothiophene (Table 2, entries 1-5; Figure 3), 2-iodobenzofuran (entries 16-20) and 2-iodofuran (entry 21), cyclization was delayed in the case of the different 2-iodothiophenes. Indeed, after 24 h reaction time, the intermediate *N*-(2-thienyl)benzophenone (**9b′**) and *N*-(5-methyl-2-thienyl)acetophenone (**8c′**) were, for example, isolated in 50 and 13% yield, respectively (entries 6 and 9). By using 2-iodo-5-methylthiophene, the cyclized products were obtained in slightly higher yields than from 2-iodothiophene (entries 9-11); on the contrary, from 2-iodothiophenes bearing electron-withdrawing groups at C5, they were only observed as traces (entries 12-15), a result probably due to instability issue as already observed with the 5-substituted iodothiophenes (Table 1, entries 4-6).

When compared with 2-iodobenzothiophene, 2-iodobenzofuran gave the tetracycles in higher yields, irrespective of the aniline employed (entries 16-20). These

results could be rationalized by a less electron-donating 2-benzofuryl, when compared with 2-benzothienyl, thus favoring the reductive elimination. If such was the case, 3-iodobenzothiophene should be more reactive than its 2-isomer on the basis of the Mulliken charges of carbons (see Figure 2). Indeed, 3-iodobenzothiophene reacted with 2-aminoacetophenone (**3**) in a quantitative yield (Table 3, entry 1). Concerning 3-iodothiophene, its reactivity toward the tested anilines proved in general to be very high, superior than that of its 2-isomer, a result still in good agreement with the reactivity predicted by Mulliken charges calculation. Moreover, cyclization by attack of the C2 carbon of thiophene is much more efficient than by attack of its less electron-rich C3 carbon (entries 2-6).

Table 3 *N*-arylation-cyclization between **3**-**7** and 3-iodo(benzo)thiophenes to afford tri- and tetracycles.



Entry	Aniline	Iodide	equiv	Product, Yield (%)[a]	
1	**3**		1.5		**8f**, 98
2 3 4 5 6	**3** **4** **5** **6** **7**		1.5 1.5 1.5 1 1		**8g** (R = Me, R' = H), 98 **9g** (R = Ph, R' = H), 96 **10g** (R = R' = H), 40 **11g** (R = Ph, R' = Cl), 89 **12g** (R = H, R' = Cl), 63

[a] After purification (see experimental part).

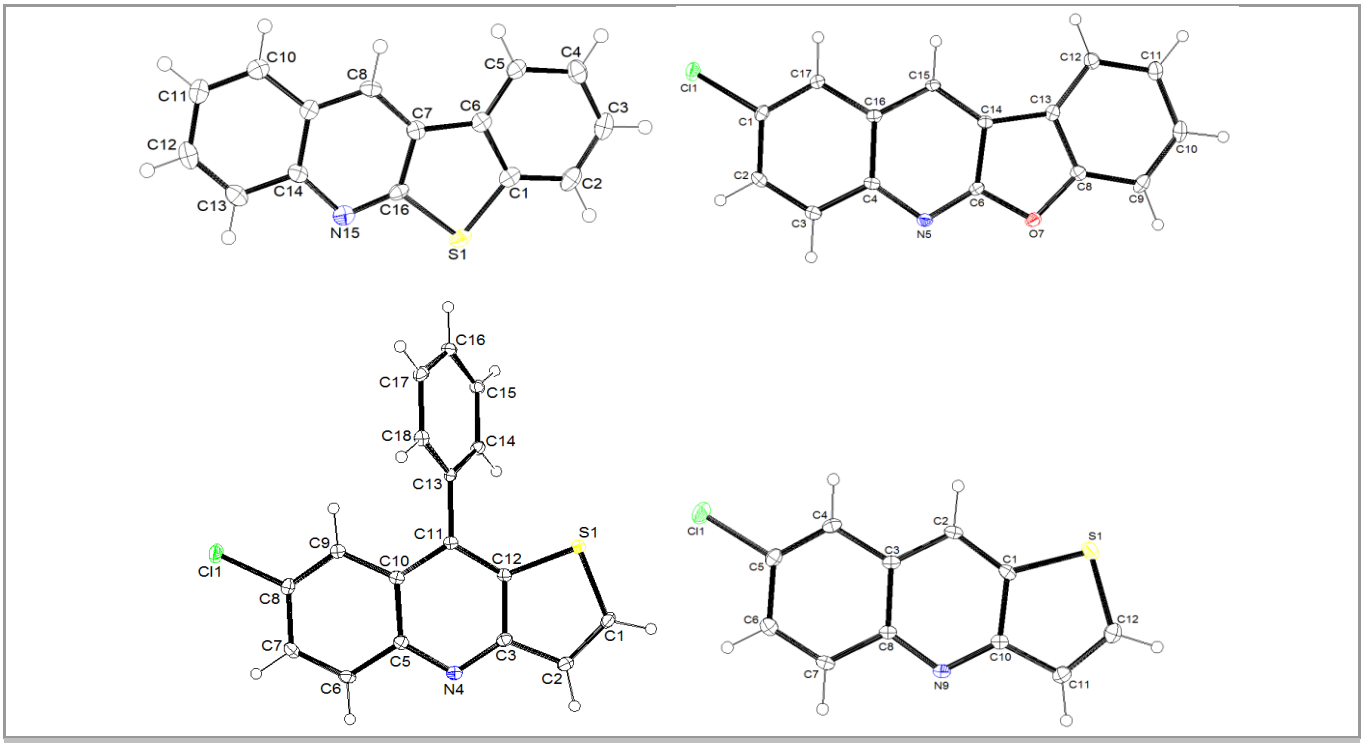


Figure 3 ORTEP diagrams (50% probability) of the compounds **10a**, **12d**, **11g** and **12g**.

The use of different anilines shows that their nature has an impact on the efficiency of the reaction. For example, under the optimized conditions, no reaction was observed between 2-iodothiophene and anilines such as 3,5-dimethoxyaniline and 4-fluoroaniline while degradation was noticed with 4-nitroaniline. Even the more reactive 3-iodothiophene did not react at all with 3,5-dimethoxyaniline and 4-fluoroaniline. The presence of the C=O group next to amino is required since 4-acetylaniline also

failed in reacting with 3-iodothiophene. However, for a currently unexplained reason, 2-amino-3-formylpyridine did not react.

Aldehyde functions gave generally lower yields than ketones, in particular when chlorine is present at the *para* position relative to the aniline. Thus, it seems that reactions are less favored in the presence of electron-withdrawing groups, as previously observed under palladium catalysis.[8]

In spite of a renewed interest for the synthesis of thieno[2,3-*b*]quinolines,[25] benzothieno[2,3-*b*]quinolines,[26] benzofuro[2,3-*b*]quinolines,[25d,27] thieno[3,2-*b*]quinolines[28] and benzothieno[3,2-*b*]quinolines,[29] biological activities of these compounds have been reported unevenly. While numerous studies have concerned bioactive thieno[2,3-*b*]quinolines[30] and furo[2,3-*b*]quinolines,[31] fewer works have been dedicated to the benzo-fused analogs, and specifically to benzothieno[2,3-*b*]quinolines[32] and benzofuro[2,3-*b*]quinolines.[32-33] The biological properties of thieno[3,2-*b*]quinolines[34] and benzothieno[3,2-*b*]quinolines[35] have not yet been extensively studied either.

In the course of our previous study,[17g] compounds **8a** and **8d** were tested against A2058 melanoma cells, and showed a significant antiproliferative activity (60-70% growth inhibition of 2000 cells at 10^{-5} M after 72 h); albeit less efficient, **9a** and **9d** also proved promising (45-55% at 10^{-5} M after 72 h) (Figure 4, left; Figure 5, top). Tsuchimoto and co-workers reported in 2018 an efficient approach to access such compounds in a similar scope by indium-catalyzed annulation of 2-acylanilines with suitably methoxy-substituted (benzo)furans or (benzo)thiophenes.[28] In the same paper, they also highlighted the similarity between 11-methylbenzothieno[3,2-*b*]quinoline (**8f**) and 11-methylcryptolepine (Figure 4, right), which is a submicromolar cytotoxic agent against KB cancer cells.[36] Furthermore, Bonjean, Bailly and co-workers showed in 1998 that cryptolepine selectively binds to DNA and acts both as a potent topoisomerase II inhibitor and a promising antitumor agent in melanoma cells.[37]

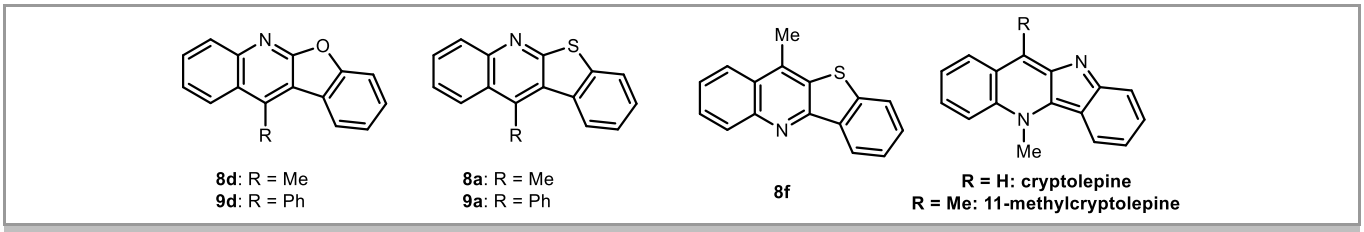


Figure 4 Compounds previously shown to inhibit melanoma cells growth (left). Similarity between **8f** and cryptolepines (right).

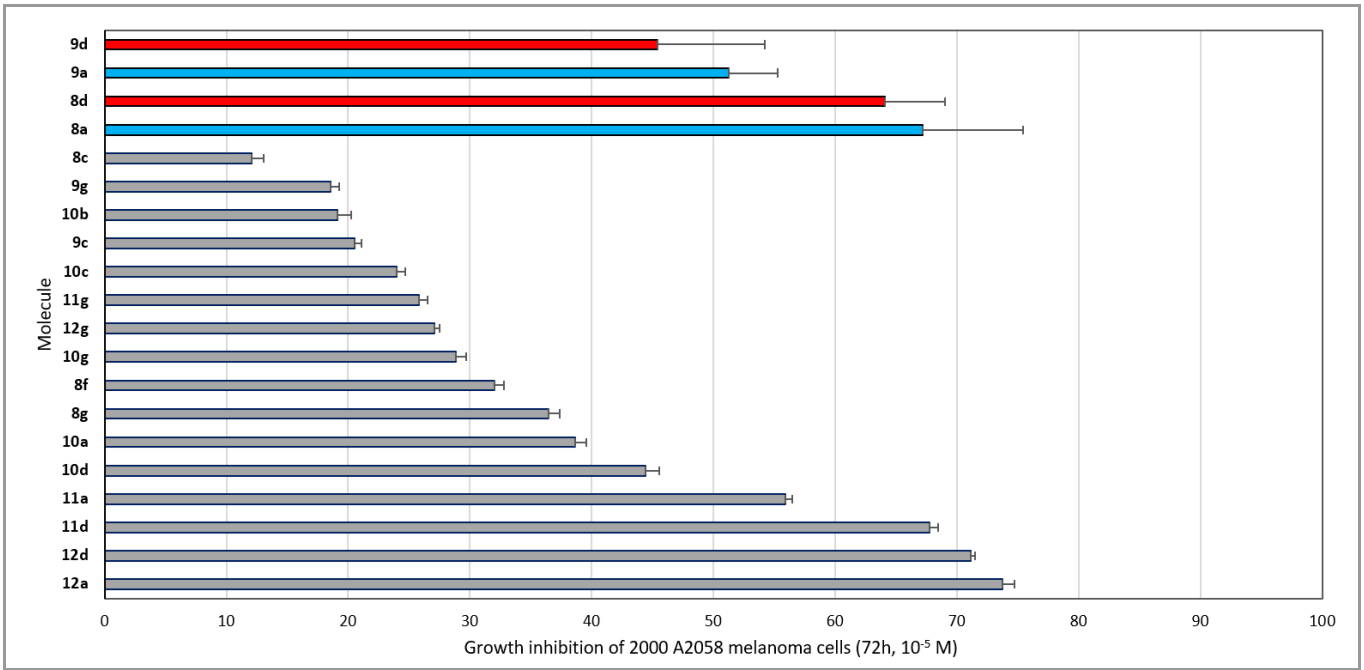


Figure 5 Antiproliferative activity of four compounds previously evaluated (top, colored) and of 16 of the compounds here synthesized (bottom, grey) at 10^{-5} M after 72 h in A2058 human melanoma cells.

Consequently, some of the tri- and tetracycles obtained in the frame of this study were tested for their antiproliferative activity against melanoma cells (Figure 5, bottom). Most of the tested compounds showed an activity against A2058 cell lines, selected because of their natural and acquired resistance to chemotherapy and radiotherapy. However, while **8f** only exerted a moderate antiproliferative activity, other compounds proved more promising. In particular, the tetracyclic compounds **12a** and **12d** possessing no methyl group but a chlorine atom at the 9-position showed stronger activity as antiproliferative drugs in human invasive melanoma cells. The compounds **11a** and **11d** which are the 9-chloro analogs of **9a** and **9d**, respectively, also exhibited activities superior than their non-chlorinated analogs.

Through this copper-mediated *N*-arylation of anilines using five-membered heteroaromatic iodides such as 2- and 3-iodothiophenes and their benzo-fused analogs, we could evidence the impact of the electronic features of both the heteroaryl group of the iodide and the aryl group of the aniline.

When *N*-arylation is *in situ* followed by aromatic electrophilic substitution (a combination that easily takes place from 3-iodo(benzo)thiophene or 2-iodo(benzo)furan), this reaction offers a general one-step entry into relevant extended aromatic heterocycles. On the model of the previously tested compounds **8a** and **8d**, the molecules **12a** and **12d** showed promising activity as antiproliferative drugs in human invasive melanoma cells. It would be of interest to evaluate the 9-chloro analogs of **8a** and **8d** for their antiproliferative activity against such cells. In addition, due to their structural analogy with cryptolepines, this original family of compounds could be subjected to further biological activity studies in search of valuable antibacterial and antimalarial properties.

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General Considerations. All the reactions were performed under an argon atmosphere. 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 either on a Bruker Avance III spectrometer at 300 MHz and 75 MHz respectively, on a Bruker Avance III spectrometer at 400 MHz and 100 MHz respectively, or on a Bruker Avance III HD spectrometer at 500 MHz and 126 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.[38] Mass spectra (HRMS) were recorded in ASAP mode on a Maxis 4G apparatus. Activated copper,[39] 2-iodobenzothiophene,[17a,40] 2-iodobenzofuran,[17a,40] 2-iodothiazole,[41] 3-iodobenzothiophene,[23] 2-chloro-5-iodothiophene,[42] 2-benzoyl-5-iodothiophene[17e,43] and 2-aminobenzaldehyde[44] were prepared as described previously. Dibutyl ether was degassed prior to use. All reagents not listed in the publication were obtained from commercial sources.

Crystallography. The samples were studied with monochromatized Mo-Kα radiation (λ = 0.71073 Å, multilayered monochromator). The X-ray diffraction data of **2b**, **10a**, **12d**, **11g** and **12g** were collected at 150 K by using D8 VENTURE Bruker AXS diffractometer equipped with a (CMOS) PHOTON 100 detector. The structures were solved by dual-space algorithm using the *SHELXT* program,[45] and then refined with full-matrix least-square methods based on F^2 (*SHELXL-2014*).[46] All non-hydrogen atoms were refined with anisotropic atomic displacement parameters. Except H1 that was introduced in the structural model through Fourier difference maps analysis in the case of **2b**, H atoms were finally included in their calculated positions and treated as riding on their parent atom with constrained thermal parameters. The molecular diagrams were generated by ORTEP-3 (version 2.02).[47]

Procedures

General procedure 1 / *N*-arylation of ethyl anthranilate (1): To the required iodide (1.5 mmol) in Bu_2O (1.5 mL) were successively added activated Cu (13 mg, 0.2 mmol), ethyl anthranilate (**1**, 0.15 mL, 1.0 mmol) and K_2CO_3 (0.28 g, 2.0 mmol). The reaction mixture was degassed and refluxed under argon for 24 h. Activated Cu (4 x 13 mg, 4 x 0.2 mmol) was added after 2, 4, 6 and 8 h of heating. After cooling to room temperature, the reaction mixture was concentrated. Addition of H_2O (25 mL), extraction with AcOEt (3x10 mL), drying over Na_2SO_4, removal of the solvent and purification by chromatography on silica gel (the eluent is given in the product description) led to the expected compound.

General procedure 2 / *N*-arylation of 2-aminoacetophenone (3): To the required iodide (1.5 mmol) in Bu_2O (1.5 mL) were successively added activated Cu (13 mg, 0.2 mmol), 2-aminoacetophenone (**3**, 0.12 g, 1.0 mmol) and K_2CO_3 (0.28 g, 2.0 mmol). The reaction mixture was degassed and refluxed under argon for 24 h. Activated Cu (4 x 13 mg, 4 x 0.2 mmol) was added after 2, 4, 6 and 8 h of heating. After cooling to room temperature, the reaction mixture was concentrated. Addition of H_2O (25 mL), extraction with AcOEt (3x10 mL), drying over Na_2SO_4, removal of the solvent and purification by chromatography on silica gel (the eluent is given in the product description) led to the expected compound.

General procedure 3 / *N*-arylation of 2-aminobenzophenone (4): To the required iodide (1.5 mmol) in Bu_2O (1.5 mL) were successively added activated Cu (13 mg, 0.2 mmol), 2-aminobenzophenone (**4**, 0.20 g, 1.0 mmol) and K_2CO_3 (0.28 g, 2.0 mmol). The reaction mixture was degassed and refluxed under argon for 24 h. Activated Cu (4 x 13 mg, 4 x 0.2 mmol) was added after 2, 4, 6 and 8 h of heating. After cooling to room temperature, the reaction mixture was concentrated. Addition of H_2O (25 mL), extraction with AcOEt (3x10 mL), drying over Na_2SO_4, removal of the solvent and purification by chromatography on silica gel (the eluent is given in the product description) led to the expected compound.

General procedure 4 / *N*-arylation of 2-aminobenzaldehyde (5): To the required iodide (1.5 mmol) in Bu_2O (1.5 mL) were successively added activated Cu (13 mg, 0.2 mmol), freshly prepared 2-aminobenzaldehyde (**5**, 0.12 g, 1.0 mmol) and K_2CO_3 (0.28 g, 2.0 mmol). The reaction mixture was degassed and refluxed under argon for 24 h. Activated Cu (4 x 13 mg, 4 x 0.2 mmol) was added after 2, 4, 6 and 8 h of heating. After cooling to room temperature, the reaction mixture was concentrated. Addition of H_2O (25 mL), extraction with AcOEt (3x10 mL), drying over Na_2SO_4, removal of the solvent and purification by chromatography on silica gel (the eluent is given in the product description) led to the expected compound.

General procedure 5 / *N*-arylation of 2-amino-5-chlorobenzophenone (6): To the required iodide (1.5 mmol) in Bu_2O (1.5 mL) were successively added activated Cu (13 mg, 0.2 mmol), 2-amino-5-chlorobenzophenone (**6**, 0.23 g, 1.0 mmol) and K_2CO_3 (0.28 g, 2.0 mmol). The reaction mixture was degassed and refluxed under argon for 24 h. Activated Cu (4 x 13 mg, 4 x 0.2 mmol) was added after 2, 4, 6 and 8 h of heating. After cooling to room temperature, the reaction mixture was concentrated. Addition of H_2O (25 mL), extraction with AcOEt (3x10 mL), drying over Na_2SO_4, removal of the solvent and purification by chromatography on silica gel (the eluent is given in the product description) led to the expected compound.

General procedure 6 / *N*-arylation of 2-amino-5-chlorobenzaldehyde (7): To the required iodide (1.5 mmol) in Bu_2O (1.5 mL) were successively added activated Cu (13 mg, 0.2 mmol), 2-amino-5-chlorobenzaldehyde (**7**, 0.16 g, 1.0 mmol) and K_2CO_3 (0.28 g, 2.0 mmol). The reaction mixture was degassed and refluxed under argon for 24 h. Activated Cu (4 x 13 mg, 4 x 0.2 mmol) was added after 2, 4, 6 and 8 h of heating. After cooling to room temperature, the reaction mixture was concentrated. Addition of H_2O (25 mL), extraction with AcOEt (3x10 mL), drying over Na_2SO_4, removal of the solvent and purification by chromatography on silica gel (the eluent is given in the product description) led to the expected compound.

Ethyl 2-(2-thienylamino)benzoate (2a)

The general procedure 1 using 2-iodothiophene (0.17 mL) gave **2a** (eluent: heptane-AcOEt 95:5; R_f = 0.45) in 52% yield (129 mg) as a yellow oil.

IR (ATR): 689, 746, 848, 1018, 1045, 1078, 1138, 1160, 1236, 1309, 1368, 1442, 1496, 1543, 1582, 1678, 2981, 3075, 3301 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.39 (t, 3H, *J* = 7.1 Hz, CH_3), 4.35 (q, 2H, *J* = 7.1 Hz, CH_2), 6.73 (ddd, 1H, *J* = 8.1, 7.0 and 1.1 Hz, H_4 or H_5), 6.80 (dt, 1H, *J* = 3.7 and 1.2 Hz, $H_{3'}$), 6.91 (dd, 1H, *J* = 5.7 and 3.5 Hz, $H_{4'}$), 6.99-7.07 (m, 2H, H_3 and $H_{5'}$), 7.30 (ddd, 1H, *J* = 8.6, 7.0 and 1.7 Hz, H_4 or H_5), 7.97 (dd, 1H, *J* = 8.0 and 1.7 Hz, H_6), 9.48 (s, 1H, NH).

^{13}C NMR (75 MHz, $CDCl_3$) δ 14.3 (CH_3), 60.7 (CH_2), 111.5 (C), 113.7 (CH), 117.2 (CH), 120.9 (CH), 121.5 (CH), 125.9 (CH), 131.2 (CH), 134.3 (CH), 143.7 (C), 149.7 (C), 168.5 (C).

HRMS, *m/z* 248.3196 (1 ppm) found (calcd for $C_{13}H_{14}NO_2S$, $[M+H]^+$, requires 248.31945).

Ethyl 2-(2-benzothienylamino)benzoate (2b)

The general procedure 1 using 2-iodobenzothiophene (0.39 g) gave **2b** (eluent: heptane-AcOEt 95:5; R_f = 0.56) in 57% yield (170 mg) as a beige powder.

Mp 86 °C.

IR (ATR): 707, 725, 750, 860, 1020, 1083, 1139, 1162, 1185, 1237, 1299, 1368, 1438, 1453, 1477, 1494, 1540, 1579, 1682, 2983, 3282 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$) δ 1.44 (t, 3H, *J* = 7.1 Hz, CH_3), 4.40 (q, 2H, *J* = 7.1 Hz, CH_2), 6.83 (sept, 1H, *J* = 4.1 Hz), 7.02 (s, 1H, $H_{3'}$), 7.27 (td, 1H, *J* = 7.5 and 1.3 Hz), 7.34 (td, 1H, *J* = 7.5 and 1.3 Hz), 7.38-7.41 (m, 2H), 7.65 (d, 1H, *J* = 7.3 Hz), 7.72 (d, 1H, *J* = 7.8 Hz), 8.02 (d, 1H, *J* = 8.0 Hz, H_6), 9.85 (s, 1H, NH).

^{13}C NMR (75 MHz, $CDCl_3$) δ 14.4 (CH_3), 61.0 (CH_2), 112.3 (C), 114.5 (CH), 114.6 (CH), 118.2 (CH), 122.2 (CH), 122.7 (CH), 123.7 (CH), 124.6 (CH), 131.5 (CH), 134.5 (CH), 136.0 (C), 139.1 (C), 144.1 (C), 148.2 (C), 168.6 (C).

HRMS, *m/z* 298.0897 (0 ppm) found (calcd for $C_{17}H_{16}NO_2S$, $[M+H]^+$, requires 298.08962).

Crystal data for **2b**. $C_{17}H_{15}NO_2S$, *M* = 297.36, triclinic, *P* -1, *a* = 7.5861(6), *b* = 10.5280(8), *c* = 10.7427(8) Å, α = 115.185(2), β = 108.486(3), γ = 93.901(3) °, *V* = 715.47(10) $Å^3$, *Z* = 2, *d* = 1.380 g cm^{-3}, μ = 0.230 mm^{-1}. A final refinement on F^2 with 3258 unique intensities and 201 parameters converged at $\omega R(F^2)$ = 0.0839 ($R(F)$ = 0.0333) for 2901 observed reflections with $I > 2\sigma(I)$. CCDC 2015229.

Ethyl 2-(3-benzothienylamino)benzoate (2c)

The general procedure 1 using 3-iodobenzothiophene (0.39 g) gave **2c** (eluent: heptane-AcOEt 95:5; R_f = 0.65) in 96% yield (285 mg) as a yellow powder.

Mp 58 °C.

IR (ATR): 657, 697, 719, 744, 755, 792, 858, 896, 1024, 1053, 1083, 1106, 1149, 1186, 1186, 1233, 1252, 1308, 1326, 1365, 1434, 1453, 1466, 1520, 1572, 1588, 1676, 2912, 2993, 3064, 3112, 3302 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$) δ 1.48 (t, 3H, *J* = 7.1 Hz, CH_3), 4.46 (q, 2H, *J* = 7.1 Hz, CH_2), 6.79 (t, 1H, *J* = 7.5 Hz, H_4 or H_5), 7.18 (d, 1H, *J* = 8.5 Hz, H_3), 7.22 (s, 1H, $H_{2'}$), 7.35 (ddd, 1H, *J* = 8.4, 7.3 and 1.0 Hz), 7.40-7.44 (m, 2H), 7.81 (dd, 1H, *J* = 6.1 and 3.2 Hz, $H_{4'}$ or $H_{7'}$), 7.88 (dd, 1H, *J* = 6.2 and 2.9 Hz, $H_{4'}$ or $H_{7'}$), 8.09 (dd, 1H, *J* = 8.0 and 1.2 Hz, H_6), 9.90 (s, 1H, NH).

^{13}C NMR (75 MHz, $CDCl_3$) δ 14.4 (CH_3), 60.8 (CH_2), 111.9 (C), 113.0 (CH), 114.3 (CH), 117.1 (CH), 121.2 (CH), 123.1 (CH), 124.2 (CH), 125.0 (CH), 131.6 (CH), 133.3 (C), 134.4 (CH), 135.3 (C), 138.7 (C), 148.7 (C), 168.8 (C).

HRMS, *m/z* 298.0898 (1 ppm) found (calcd for $C_{17}H_{16}NO_2S$, $[M+H]^+$, requires 298.08962).

Ethyl 2-(3-thienylamino)benzoate (2d)

The general procedure 1 using 3-iodothiophene (0.15 mL) gave **2d** (eluent: heptane-AcOEt 95:5; R_f = 0.80) in 92% yield (228 mg) as a yellow oil.

IR (ATR): 698, 745, 771, 834, 958, 1018, 1045, 1078, 1140, 1160, 1216, 1236, 1316, 1367, 1454, 1503, 1544, 1583, 1677, 2980, 3108, 3314 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$) δ 1.43 (t, 3H, *J* = 7.1 Hz, CH_3), 4.38 (q, 2H, *J* = 7.1 Hz, CH_2), 6.74 (ddd, 1H, *J* = 8.1, 7.0 and 1.1 Hz, H_4 or H_5), 6.94-6.97 (m, 1H, $H_{2'}$), 7.03 (dd, 1H, *J* = 5.1 and 1.4 Hz, $H_{4'}$ or $H_{5'}$), 7.21 (dd, 1H, *J* = 8.5 and 0.8 Hz, H_3), 7.29 (dd, 1H, *J* = 5.1 and 3.1 Hz, $H_{4'}$ or $H_{5'}$), 7.34 (ddd, 1H, *J* = 8.6, 7.0 and 1.6 Hz, H_4 or H_5), 8.02 (dd, 1H, *J* = 8.0 and 1.6 Hz, H_6), 9.61 (s, 1H, NH).

^{13}C NMR (75 MHz, $CDCl_3$) δ 14.3 (CH_3), 60.5 (CH_2), 111.4 (C), 111.7 (CH), 113.7 (CH), 116.7 (CH), 124.5 (CH), 125.1 (CH), 131.5 (CH), 134.2 (CH), 139.4 (C), 148.6 (C), 168.4 (C).

HRMS, *m/z* 248.3195 (0 ppm) found (calcd for $C_{13}H_{14}NO_2S$, $[M+H]^+$, requires 248.31945).

2,4-Dimethylthieno[2,3-*b*]quinoline (8c)

[CAS Reg. No. 2245159-23-1]

The general procedure 2 using 2-iodo-5-methylthiophene (crude; prepared from thiophene (0.12 mL, 1.5 mmol) by treatment with butyllithium (1.8 mmol) in THF (2 mL) at -20 °C for 30 min, iodomethane (0.11 mL, 1.8 mmol) at 0 °C for 1 h, butyllithium (1.6 mmol) in THF (2 mL) at -20 °C for 30 min, and iodine (0.41 g, 1.6 mmol) in THF (2 mL)) gave **8c** (eluent: heptane-AcOEt 90:10; R_f = 0.475) in 22% yield (47 mg) as a beige powder.

Mp 92 °C (lit.[28] mp 91-92 °C).

IR (ATR): 549, 584, 610, 664, 754, 806, 954, 1090, 1262, 1370, 1435, 1552, 1666, 2956 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$) δ 2.63 (s, 3H), 2.87 (s, 3H), 7.05 (q, 1H, *J* = 1.3 Hz), 7.52 (ddd, 1H, *J* = 8.3, 6.8 and 1.2 Hz), 7.68 (ddd, 1H, *J* = 8.2, 6.7 and 1.4 Hz), 8.08 (dd, 2H, *J* = 8.5 and 1.4 Hz).

^{13}C NMR (75 MHz, $CDCl_3$) δ 15.3 (CH_3), 17.5 (CH_3), 117.4 (CH), 124.2 (CH), 125.1 (CH), 125.2 (C), 128.5 (CH), 129.0 (CH), 132.4 (C), 136.6 (C), 141.9 (C), 146.0 (C), 163.6 (C).

The analyses are as described previously.[28]

2-(5-Methyl-2-thienylamino)acetophenone (**8c'**) was also isolated (eluent: heptane-AcOEt 90:10; R_f = 0.62) in 13% yield (30 mg) as an orange oil.

IR (ATR): 594, 612, 750, 796, 955, 1019, 1038, 1092, 1151, 1242, 1311, 1357, 1398, 1419, 1450, 1504, 1572, 1604, 1638, 1678, 2914, 2965, 3236 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$) δ 2.45 (s, 3H), 2.64 (s, 3H), 6.57-6.61 (m, 2H), 6.73 (t, 1H, *J* = 7.5 Hz), 7.06 (dd, 1H, *J* = 8.6 and 1.0 Hz), 7.32 (ddd, 1H, *J* = 8.6, 6.9 and 1.5 Hz), 7.79 (dd, 1H, *J* = 8.0 and 1.5 Hz), 10.3 (br s, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 15.3 (CH_3), 28.1 (CH_3), 114.4 (CH), 116.7 (CH), 118.5 (C), 122.6 (CH), 123.7 (CH), 132.3 (CH), 135.0 (CH), 136.2 (C), 140.4 (C), 150.2 (C), 201.3 (C).

11-Methylbenzofuro[2,3-*b*]quinoline (8d)

[CAS Reg. No. 70751-32-5]

The general procedure 2 using 2-iodobenzofuran (0.37 g) gave **8d** (eluent: heptane-AcOEt 90:10; R_f = 0.47) in 94% yield (219 mg) as a white powder.

Mp 194 °C (lit.[48] 189-190.5 °C).

IR (ATR): 698, 720, 745, 756, 852, 895, 1022, 1039, 1084, 1103, 1149, 1191, 1209, 1253, 1310, 1342, 1365, 1388, 1454, 1513, 1592, 1606, 1676, 2992, 3064, 3302 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$) δ 3.15 (s, 3H), 7.41 (td, 1H, *J* = 7.6 and 1.1 Hz), 7.55 (td, 1H, *J* = 7.8 and 1.3 Hz), 7.59 (ddd, 1H, *J* = 8.3, 6.9 and 1.3 Hz), 7.64 (br d, 1H, *J* = 8.1 Hz), 7.76 (ddd, 1H, *J* = 8.3, 6.8 and 1.4 Hz), 8.12-8.17 (m, 2H), 8.21 (dd, 1H, *J* = 8.5 and 0.9 Hz).

^{13}C NMR (75 MHz, $CDCl_3$) δ 15.3 (CH_3), 112.1 (CH), 116.1 (C), 123.3 (CH), 123.4 (C), 123.5 (CH), 124.0 (CH), 124.9 (CH), 126.2 (C), 128.7 (CH), 129.2 (CH), 129.5 (CH), 140.8 (C), 146.0 (C), 155.7 (C), 162.2 (C).

The analyses are as described previously.[17g]

11-Methylbenzothieno[3,2-*b*]quinoline (8f)

[CAS Reg. No. 2035-00-9]

The general procedure 2 using 3-iodobenzothiophene (0.39 g) gave **8f** (eluent: heptane-AcOEt 90:10; R_f = 0.55) in 98% yield (244 mg) as a yellow powder.

Mp 150 °C.

IR (ATR): 709, 736, 752, 766, 789, 854, 1013, 1108, 1167, 1229, 1261, 1337, 1441, 1455, 1497, 1553, 1590, 1673, 2920 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$) δ 2.63 (s, 3H, CH_3), 7.40-7.53 (m, 3H), 7.62-7.72 (m, 2H), 7.83 (dd, 1H, *J* = 8.5 and 1.4 Hz), 8.23 (dd, 1H, *J* = 8.5 and 1.2 Hz), 8.54-8.59 (m, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 17.0 (CH_3), 122.6 (CH), 122.8 (CH), 123.9 (CH), 124.8 (CH), 125.6 (CH), 125.8 (C), 128.2 (CH), 129.5 (CH), 129.9 (CH), 131.8 (C), 134.9 (C), 136.7 (C), 140.6 (C), 146.5 (C), 152.9 (C).

The NMR data are as described previously.[28]

9-Methylthieno[3,2-*b*]quinoline (8g)

[CAS Reg. No. 1450739-76-0]

The general procedure 2 using 3-iodothiophene (0.15 mL) gave **8g** (eluent: petrol-AcOEt 80:20; R_f = 0.32) in 98% yield (195 mg) as a beige powder.

Mp 84 °C.

IR (ATR): 683, 700, 744, 797, 860, 1014, 1079, 1224, 1259, 1367, 1406, 1439, 1506, 1552, 1579, 2962 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$) δ 2.74 (s, 3H, CH_3), 7.42 (ddd, 1H, *J* = 8.1, 6.6 and 1.2 Hz), 7.51 (d, 1H, *J* = 5.7 Hz), 7.63 (ddd, 1H, *J* = 8.4, 6.6 and 1.4 Hz), 7.76 (d, 1H, *J* = 5.7 Hz), 7.89 (dd, 1H, *J* = 8.5, 1.3 Hz), 8.11 (dd, 1H, *J* = 8.6 and 1.2 Hz).

^{13}C NMR (75 MHz, $CDCl_3$) δ 17.1 (CH_3), 122.9 (CH), 124.0 (C), 125.2 (CH), 125.4 (CH), 128.6 (CH), 129.6 (CH), 131.5 (C), 133.7 (CH), 137.7 (C), 147.0 (C), 156.6 (C).

The NMR data are as described previously.[49]

2-Methyl-4-phenylthieno[2,3-*b*]quinoline (9c)

The general procedure 3 using 2-iodo-5-methylthiophene (crude; prepared from thiophene (0.12 mL, 1.5 mmol) by treatment with butyllithium (1.8 mmol) in THF (2 mL) at -20 °C for 30 min, iodomethane (0.11 mL, 1.8 mmol) at 0 °C for 1 h, butyllithium (1.6 mmol) in THF (2 mL) at -20 °C for 30 min, and iodine (0.41 g, 1.6 mmol) in THF (2 mL)) gave **9c** (eluent: petrol-AcOEt 90:10; R_f = 0.57) in 14% yield (39 mg) as a beige powder.

Mp 174 °C.

IR (ATR): 550, 611, 643, 662, 703, 739, 754, 773, 820, 1059, 1132, 1267, 1440, 1546, 3056 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$) δ 2.56 (s, 3H), 6.73 (d, 1H, *J* = 1.4 Hz), 7.40-7.60 (m, 6H), 7.69 (ddd, 1H, *J* = 8.4, 6.7 and 1.4 Hz), 7.80 (dd, 1H, *J* = 8.6 and 1.3 Hz), 8.16 (d, 1H, *J* = 8.5 Hz).

^{13}C NMR (75 MHz, $CDCl_3$) δ 17.4 (CH_3), 118.4 (CH), 124.4 (C), 125.3 (CH), 126.3 (CH), 128.5 (CH), 128.6 (CH), 128.6 (CH), 128.7 (2CH), 130.1 (2CH), 131.9 (C), 136.5 (C), 140.9 (C), 142.7 (C), 146.4 (C), 163.6 (C).

HRMS, *m/z* 276.0845 (1 ppm) found (calcd for $C_{18}H_{14}NS$, $[M+H]^+$, requires 276.08415).

11-Phenylbenzofuro[2,3-*b*]quinoline (9d)

[CAS Reg. No. 129190-65-4]

The general procedure 3 using 2-iodobenzofuran (0.37 g) gave **9d** (eluent: heptane-AcOEt 90:10; R_f = 0.70) in 79% yield (233 mg) as a white powder.

Mp 211 °C (lit.[17g] mp 208 °C).

IR (ATR): 700, 718, 740, 816, 879, 934, 1018, 1100, 1145, 1192, 1219, 1307, 1336, 1349, 1387, 1455, 1591, 2972 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$) δ 7.06-7.11 (m, 1H), 7.12 (td, 1H, *J* = 7.8 and 1.0 Hz), 7.43-7.50 (m, 2H), 7.54-7.57 (m, 2H), 7.61 (d, 1H, *J* = 8.2 Hz), 7.63-7.69 (m, 3H), 7.77 (ddd, 1H, *J* = 8.3, 6.9 and 1.4 Hz), 7.82 (dd, 1H, *J* = 8.6 and 0.8 Hz), 8.22 (dd, 1H, *J* = 8.3 and 1.2 Hz).

^{13}C NMR (75 MHz, $CDCl_3$) δ 111.9 (CH), 115.7 (C), 122.5 (C), 123.0 (CH), 123.2 (CH), 125.1 (CH), 125.7 (C), 126.3 (CH), 128.7 (CH), 129.1 (CH), 129.1 (CH), 129.2 (2CH), 129.4 (2CH), 129.7 (CH), 135.5 (C), 144.1 (C), 146.3 (C), 156.0 (C), 162.2 (C).

The analyses are as described previously.[17g]

9-Phenylthieno[3,2-*b*]quinoline (9g)

[CAS Reg. No. 2245159-24-2]

The general procedure 3 using 3-iodothiophene (0.15 mL) gave **9g** (eluent: heptane-AcOEt 80:20; R_f = 0.47) in 96% yield (251 mg) as a beige powder.

Mp 194 °C.

IR (ATR): 708, 742, 760, 807, 1074, 1405, 2972 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$) δ 7.45 (ddd, 1H, *J* = 8.4, 6.8 and 1.3 Hz), 7.53-7.60 (m, 5H), 7.66 (d, 1H, *J* = 5.7 Hz), 7.73 (ddd, 1H, *J* = 8.5, 6.7 and 1.5 Hz), 7.84 (d, 1H, *J* = 8.6 Hz), 7.87 (d, 1H, *J* = 5.9 Hz), 8.25 (d, 1H, *J* = 8.6 Hz).

^{13}C NMR (75 MHz, $CDCl_3$) δ 123.5 (C), 125.2 (CH), 125.3 (CH), 125.7 (CH), 129.0 (2CH), 129.0 (CH), 129.1 (CH), 129.5 (CH), 129.5 (2CH), 131.7 (C), 135.2 (CH), 136.6 (C), 142.4 (C), 147.8 (C), 157.2 (C).

The NMR data are as described previously.[28]

Benzothieno[2,3-*b*]quinoline (10a)[50]

[CAS Reg. No. 243-47-0]

The general procedure 4 using 2-iodobenzothiophene (0.39 g) gave **10a** (eluent: heptane-AcOEt 95:5; R_f = 0.75) in 78% yield (184 mg) as a beige powder.

Mp 126 °C.

IR (ATR): 734, 761, 780, 909, 1066, 1377, 2972 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$) δ 7.42-7.55 (m, 3H), 7.73 (t, 1H, *J* = 7.7 Hz), 7.80 (d, 1H, *J* = 7.9 Hz), 7.94 (d, 1H, *J* = 8.1 Hz), 8.10-8.14 (m, 2H), 8.65 (s, 1H, H_{11}).

^{13}C NMR (75 MHz, $CDCl_3$) δ 122.3 (CH), 123.2 (CH), 125.1 (CH), 125.5 (C), 125.7 (CH), 127.9 (CH), 128.2 (CH), 128.4 (CH), 128.5 (CH), 128.8 (C), 129.8 (CH), 132.5 (C), 138.5 (C), 147.8 (C), 163.3 (C).

Crystal data for **10a**. $C_{15}H_9NS$, *M* = 235.29, orthorhombic, *P c a* 2_1, *a* = 22.6342(15), *b* = 5.9707(4), *c* = 16.1450(12) Å, *V* = 2181.9(3) $Å^3$, *Z* = 8, *d* = 1.433 g cm^{-3}, μ = 0.268 mm^{-1}. A final refinement on F^2 with 4798 unique intensities and 308 parameters converged at $\omega R(F^2)$ = 0.0979 ($R(F)$ = 0.0426) for 4092 observed reflections with $I > 2\sigma(I)$. CCDC 2015230.

2-Methylthieno[2,3-*b*]quinoline (10c)

The general procedure 4 using 2-iodo-5-methylthiophene (crude; prepared from thiophene (0.12 mL, 1.5 mmol) by treatment with butyllithium (1.8 mmol) in THF (2 mL) at -20 °C for 30 min, iodomethane (0.11 mL, 1.8 mmol) at 0 °C for 1 h, butyllithium (1.6 mmol) in THF (2 mL) at -20 °C for 30 min, and iodine (0.41 g, 1.6 mmol) in THF (2 mL)) gave **10c** (eluent: petrol-AcOEt 80:20; R_f = 0.65) in 17% yield (34 mg) as a beige solid.

Mp 97 °C.

IR (ATR): 475, 505, 522, 598, 655, 704, 782, 823, 862, 912, 1051, 1136, 1219, 1339, 1392, 1435, 1488, 1597, 2918 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$) δ 2.62 (s, 3H, CH_3), 6.95 (t, 1H, *J* = 1.4 Hz, H_3), 7.50 (ddd, 1H, *J* = 8.0, 6.7 and 1.2 Hz, H_6 or H_7), 7.69 (ddd, 1H, *J* = 8.4, 6.7 and 1.5 Hz, H_6 or H_7), 7.89 (dd, 1H, *J* = 8.3 and 1.4 Hz, H_5 or H_8), 8.11 (d, 1H, *J* = 8.6 Hz, H_5 or H_8), 8.29 (s, 1H, H_4).

^{13}C NMR (75 MHz, $CDCl_3$) δ 17.4 (CH_3), 118.5 (CH), 125.4 (CH), 126.0 (C), 128.2 (CH), 128.3 (CH), 128.4 (CH), 128.8 (CH), 133.2 (C), 143.2 (C), 146.1 (C), 164.0 (C).

HRMS, *m/z* 200.0528 (0 ppm) found (calcd for $C_{12}H_{10}NS$, $[M+H]^+$, requires 200.05285).

Benzofuro[2,3-*b*]quinoline (10d)

[CAS Reg. No. 19960-29-3]

The general procedure 4 using 2-iodobenzofuran (0.25 g, 1.0 mmol) gave **10d** (eluent: heptane-AcOEt 90:10; R_f = 0.375) in 82% yield (180 mg) as a white powder.

Mp 198 °C (lit.[48] mp 188-189 °C).

IR (ATR): 480, 557, 574, 619, 715, 743, 786, 864, 907, 937, 985, 1014, 1100, 1173, 1198, 1261, 1336, 1350, 1389, 1454, 1509, 1596, 2922 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$) δ 7.33 (t, 1H, *J* = 7.4 Hz), 7.46-7.58 (m, 3H), 7.71 (ddd, 1H, *J* = 8.3, 6.9 and 1.2 Hz), 7.92 (dd, 2H, *J* = 7.5 and 3.0 Hz), 8.11 (d, 1H, *J* = 8.5 Hz, H_7), 8.53 (s, 1H, H_{11}).

^{13}C NMR (75 MHz, $CDCl_3$) δ 112.0 (CH), 117.7 (C), 121.7 (CH), 122.2 (C), 123.5 (CH), 125.1 (CH), 126.1 (C), 128.2 (CH), 128.5 (CH), 129.0 (CH), 129.3 (CH), 129.6 (CH), 146.0 (C), 155.9 (C), 162.6 (C).

Thieno[3,2-*b*]quinoline (10g)

[CAS Reg. No. 269-62-5]

The general procedure 4 using 3-iodothiophene (0.15 mL) gave **10g** (eluent: petrol-AcOEt 80:20; R_f = 0.40) in 40% yield (74 mg) as a beige powder.

Mp 120 °C.

IR (ATR): 742, 1066, 1225, 1394, 2972 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49 (ddd, 1H, *J* = 8.0, 6.6 and 1.1 Hz), 7.60 (d, 1H, *J* = 5.7 Hz), 7.71 (ddd, 1H, *J* = 8.5, 6.7 and 1.5 Hz), 7.84 (dd, 1H, *J* = 8.3 and 1.4 Hz), 7.88 (d, 1H, *J* = 5.7 Hz), 8.18 (d, 1H, *J* = 8.6 Hz), 8.58 (s, 1H, H_9).

^{13}C NMR (75 MHz, $CDCl_3$) δ 124.7 (CH), 125.0 (C), 125.7 (CH), 127.4 (CH), 129.2 (CH), 129.3 (CH), 129.7 (CH), 131.0 (C), 134.7 (CH), 147.0 (C), 157.5 (C).

The NMR data are as described previously.[49]

9-Chloro-11-phenylbenzothieno[2,3-*b*]quinoline (11a)

[CAS Reg. No. 320590-06-5]

The general procedure 5 using 2-iodobenzothiophene (0.39 g) gave **11a** (eluent: petrol-AcOEt 90:10; R_f = 0.53) in 59% yield (204 mg) as a beige powder.

Mp 250 °C (lit.[51] 239-241 °C).

IR (ATR): 658, 672, 701, 718, 749, 772, 808, 869, 894, 918, 949, 1075, 1103, 1149, 1178, 1236, 1317, 1408, 1445, 1490, 1510, 1570, 1612, 2162, 3058 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.77 (d, 1H, *J* = 8.1 Hz, H_1), 7.09 (ddd, 1H, *J* = 8.2, 7.7 and 1.0 Hz, H_2 or H_3), 7.38-7.43 (m, 3H), 7.56 (d, 1H, *J* = 2.3 Hz, H_{10}), 7.64-7.70 (m, 4H), 7.79 (d, 1H, *J* = 7.9 Hz, H_4), 8.10 (d, 1H, *J* = 9.0 Hz, H_7).

^{13}C NMR (75 MHz, $CDCl_3$) δ 123.0 (CH), 124.8 (CH), 125.3 (CH), 125.7 (CH), 126.3 (C), 126.7 (C), 128.2 (CH), 129.0 (2CH), 129.3 (CH), 129.8 (CH), 129.8 (2CH), 130.5 (CH), 131.4 (C), 132.8 (C), 135.7 (C), 138.8 (C), 142.8 (C), 145.5 (C), 163.5 (C).

6-Chloro-4-phenylthieno[2,3-*b*]quinoline (11b)

[CAS Reg. No. 62452-41-9]

The general procedure 5 using 2-iodothiophene (0.17 mL) gave **11b** (eluent: petrol-AcOEt 90:10) in 4% yield (12 mg) as an orange oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.11 (d, 1H, *J* = 6.3 Hz, H_3), 7.47-7.64 (m, 5H, Ph), 7.55 (d, 1H, *J* = 6.3 Hz, H_2), 7.68 (dd, 1H, *J* = 9.0 and 2.3 Hz, H_7), 7.82 (d, 1H, *J* = 2.3 Hz, H_5), 8.17 (d, 1H, *J* = 9.1 Hz, H_8).

These data are as reported previously.[52]

9-Chloro-11-phenylbenzofuro[2,3-*b*]quinoline (11d)

The general procedure 5 using 2-iodobenzofuran (0.37 g) gave **11d** (eluent: petrol-AcOEt 90:10; R_f = 0.52) in 85% yield (280 mg) as a yellowish powder.

Mp 260 °C.

IR (ATR): 658, 700, 719, 749, 808, 869, 894, 949, 1077, 1100, 1148, 1176, 1236, 1318, 1407, 1443, 1490, 1509, 1571, 1611, 2989 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.08 (td, 1H, *J* = 7.5 and 1.2 Hz, H_2), 7.14 (dd, 1H, *J* = 7.8 and 0.9 Hz, H_1), 7.48 (ddd, 1H, *J* = 8.4, 7.1 and 1.6 Hz, H_3), 7.52-7.55 (m, 2H), 7.59 (d, 1H, *J* = 8.2 Hz, H_4), 7.65-7.71 (m, 4H), 7.74 (d, 1H, *J* = 2.2 Hz, H_{10}), 8.12 (d, 1H, *J* = 8.9 Hz, H_7).

^{13}C NMR (75 MHz, $CDCl_3$) δ 112.0 (CH), 116.6 (C), 122.2 (C), 123.2 (CH), 123.4 (CH), 125.0 (CH), 126.5 (C), 129.3 (2CH), 129.4 (CH), 129.4 (2CH), 129.6 (CH), 130.3 (CH), 130.4 (CH), 131.0 (C), 134.8 (C), 143.1 (C), 144.6 (C), 156.2 (C), 162.3 (C).

HRMS, *m/z* 330.0679 (0 ppm) found (calcd for $C_{21}H_{13}{}^{35}ClNO$, $[M+H]^+$, requires 330.06802).

7-Chloro-9-phenylthieno[3,2-*b*]quinoline (11g)

The general procedure 5 using 3-iodothiophene (0.15 mL) gave **11g** (eluent: petrol-AcOEt 80:20; R_f = 0.35) in 89% yield (263 mg) as a beige powder.

Mp 140 °C.

IR (ATR): 658, 699, 719, 746, 808, 869, 949, 1075, 1148, 1241, 1317, 1407, 1444, 1490, 1510, 1570, 2902, 2989, 3676 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52-7.65 (m, 7H), 7.78 (d, 1H, *J* = 2.2 Hz, H_8), 7.87 (d, 1H, *J* = 5.7 Hz, H_2 or H_3), 8.15 (d, 1H, *J* = 9.1 Hz, H_5).

^{13}C NMR (75 MHz, $CDCl_3$) δ 123.8 (CH), 124.0 (C), 125.2 (CH), 129.2 (2CH), 129.4 (CH), 129.4 (2CH), 130.0 (CH), 131.1 (CH), 131.5 (C), 132.6 (C), 135.7 (CH), 135.9 (C), 141.5 (C), 146.1 (C), 157.3 (C).

HRMS, *m/z* 296.0298 (1 ppm) found (calcd for $C_{17}H_{11}{}^{35}ClNS$, $[M+H]^+$, requires 296.02952).

Crystal data for **11g**. $C_{17}H_{10}ClNS$, *M* = 295.77, monoclinic, *P* $2_1/c$, *a* = 13.8767(8), *b* = 6.0408(3), *c* = 32.0906(19) Å, *β* = 100.996(2) °, *V* = 2640.7(3) Å^3, *Z* = 8, *d* = 1.488 g cm^{-3}, *μ* = 0.434 mm^{-1}. A final refinement on F^2 with 5970 unique intensities and 361 parameters converged at $\omega R(F^2)$ = 0.0887 ($R(F)$ = 0.0393) for 4588 observed reflections with $I > 2\sigma(I)$. CCDC 2015226.

9-Chlorobenzothieno[2,3-*b*]quinoline (12a)

[CAS Reg. No. 2387308-69-0]

The general procedure 6 using 2-iodobenzothiophene (0.39 g) gave **12a** (eluent: heptane-AcOEt 95:5; R_f = 0.27) in 42% yield (113 mg) as a pale yellow powder.

Mp 230 °C (lit.[26b] 230-232 °C).

IR (ATR): 706, 728, 749, 768, 802, 820, 916, 1021, 1070, 1220, 1260, 1338, 1385, 1452, 1480, 1585, 2961 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49-7.59 (m, 2H, H_2 and H_3), 7.70 (dd, 1H, *J* = 9.0 and 2.1 Hz, H_8), 7.86 (dd, 1H, *J* = 6.9 and 1.1 Hz, H_1 or H_4), 7.99 (d, 1H, *J* = 1.9 Hz, H_{10}), 8.10 (d, 1H, *J* = 9.0 Hz, H_7), 8.20 (d, 1H, *J* = 7.2 Hz, H_1 or H_4), 8.67 (s, 1H, H_{11}).

^{13}C NMR (75 MHz, $CDCl_3$) δ 122.6 (CH), 123.4 (CH), 125.4 (CH), 126.2 (C), 127.0 (CH), 127.0 (CH), 129.1 (CH), 129.7 (C), 129.7 (CH), 130.8 (CH), 131.5 (C), 132.2 (C), 138.8 (C), 145.9 (C), 163.6 (C).

These data are as reported previously.[26b]

6-Chlorothieno[2,3-*b*]quinoline (12b)

[CAS Reg. No. 65038-83-7]

The general procedure 6 using 2-iodothiophene (0.17 mL) gave **12b** (eluent: petrol-AcOEt 70:30; R_f = 0.50) in 5% yield (11 mg) as an orange powder.

Mp 164 °C (lit.[53] 167-168 °C).

IR (ATR): 740, 758, 803, 823, 926, 961, 1045, 1071, 1089, 1133, 1206, 1259, 1283, 1335, 1390, 1474, 1545, 1591, 1670, 2920 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 (d, 1H, *J* = 6.2 Hz, H_3), 7.64 (d, 1H, *J* = 6.2 Hz, H_2), 7.68 (dd, 1H, *J* = 9.2 and 2.3 Hz, H_7), 7.95 (d, 1H, *J* = 2.1 Hz, H_5), 8.12 (d, 1H, *J* = 9.1 Hz, H_8), 8.47 (s, 1H, H_4).

These data are as reported previously.[53]

^{13}C NMR (75 MHz, $CDCl_3$) δ 121.2 (CH), 126.2 (C), 126.8 (CH), 129.5 (CH), 129.8 (CH), 129.8 (CH), 130.6 (CH), 131.4 (C), 132.3 (C), 144.7 (C), 163.3 (C).

9-Chlorobenzofuro[2,3-*b*]quinoline (12d)

[CAS Reg. No. 124028-51-9]

The general procedure 6 using 2-iodobenzofuran (0.25 g, 1.0 mmol) gave **12d** (eluent: petrol-AcOEt 95:5; R_f = 0.32) in 59% yield (150 mg) as a yellow powder.

Mp 254 °C (lit.[54] mp 245-247 °C).

IR (ATR): 726, 739, 779, 816, 881, 917, 927, 1075, 1178, 1192, 1258, 1350, 1389, 1462, 1498, 1596, 2961 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$) δ 7.42 (td, 1H, *J* = 7.6 and 1.1 Hz, H_2 or H_3), 7.59 (ddd, 1H, *J* = 8.4, 7.7 and 1.2 Hz, H_2 or H_3), 7.64 (d, 1H, *J* = 8.0 Hz, H_1 or H_4), 7.69 (dd, 1H, *J* = 9.0 and 2.3 Hz, H_8), 7.99 (d, 1H, *J* = 2.3 Hz, H_{10}), 8.03 (d, 1H, *J* = 7.7 Hz, H_1 or H_4), 8.09 (d, 1H, *J* = 9.0 Hz, H_7), 8.57 (s, 1H, H_{11}).

^{13}C NMR (75 MHz, $CDCl_3$) δ 112.3 (CH), 118.8 (C), 122.0 (C), 122.1 (CH), 123.8 (CH), 126.8 (C), 126.8 (CH), 128.1 (CH), 130.0 (CH), 130.1 (CH), 130.5 (CH), 130.9 (C), 144.5 (C), 156.2 (C), 162.8 (C).

These data are as reported previously.[27b]

Crystal data for **12d**. $C_{15}H_8ClNO$, *M* = 253.67, monoclinic, *C c*, *a* = 23.719(4), *b* = 3.7644(8), *c* = 12.327(2) Å, *β* = 94.558(7) °, *V* = 1097.2(4) $Å^3$, *Z* = 4, *d* = 1.536 g cm^{-3}, *μ* = 0.331 mm^{-1}. A final refinement on F^2 with 2305 unique intensities and 163 parameters converged at $\omega R(F^2)$ = 0.1096 (*R*(*F*) = 0.0402) for 2160 observed reflections with $I > 2\sigma(I)$. CCDC 2015227.

7-Chlorothieno[3,2-*b*]quinoline (12g)

The general procedure 6 using 3-iodothiophene (0.15 mL) gave **12g** (eluent: petrol-AcOEt 70:30; R_f = 0.60) in 63% yield (138 mg) as a beige powder.

Mp 162 °C.

IR (ATR): 748, 784, 816, 831, 901, 927, 1019, 1076, 1172, 1286, 1347, 1387, 1468, 1508, 1545, 1579, 1608, 3039 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$) δ 7.61 (d, 1H, *J* = 5.6 Hz, H_2 or H_3), 7.66 (dd, 1H, *J* = 9.1 and 2.1 Hz, H_6), 7.87 (d, 1H, *J* = 2.1 Hz, H_8), 7.95 (d, 1H, *J* = 5.6 Hz, H_2 or H_3), 8.12 (d, 1H, *J* = 9.1 Hz, H_5), 8.56 (s, 1H, H_9).

^{13}C NMR (75 MHz, $CDCl_3$) δ 124.8 (CH), 125.5 (C), 125.9 (CH), 128.8 (CH), 130.4 (CH), 130.9 (CH), 131.4 (C), 132.1 (C), 135.2 (CH), 145.3 (C), 157.8 (C).

HRMS, *m/z* 219.9980 (1 ppm) found (calcd for $C_{11}H_7{}^{35}ClNS$, $[M+H]^+$, requires 219.99822).

Crystal data for **12g**. $C_{11}H_6ClNS$, *M* = 219.68, monoclinic, *P* $2_1/n$, *a* = 12.8017(8), *b* = 5.8980(3), *c* = 13.1896(8) Å, *β* = 112.039(3) °, *V* = 923.10(9) $Å^3$, *Z* = 4, *d* = 1.581 g cm^{-3}, *μ* = 0.589 mm^{-1}. A final refinement on F^2 with 2106 unique intensities and 127 parameters converged at $\omega R(F^2)$ = 0.0883 (*R*(*F*) = 0.0342) for 1821 observed reflections with $I > 2\sigma(I)$. CCDC 2015228.

Antiproliferative activity

The antiproliferative activity on melanoma cell line A2058 (ATCC® CRL-11147) was studied as reported previously.[17g] A2058 are known to be highly invasive human epithelial adherent melanoma cells. They are derived from lymph nodes metastatic cells obtained from a 43 years male patient and are tumorigenic at 100% frequency in nude mice. They are considered as very resistant to anticancer drugs. All cell culture experiments were performed at 37 °C. Cells were grown to confluence in 75 cm^2 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 4.104 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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Supporting Information

YES (this text will be updated with links prior to publication)

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