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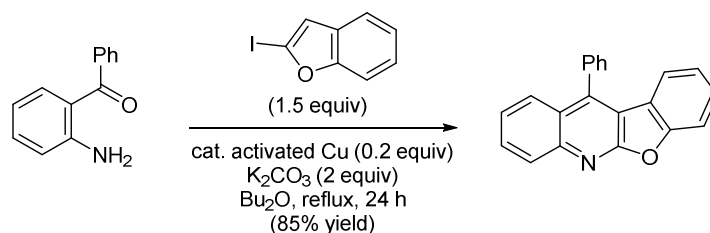
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Graphical Abstract



2-Aminophenones, a common precursor to *N*-aryl isatins and acridines endowed with bioactivities

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Keywords: isatin; acridin; *N*-arylation; copper; kinase inhibition; antiproliferative activity; melanoma cells

Abstract:

Because *N*-arylation of isatin only worked with iodoferrocene (and in low yield), we employed *N*-arylation of 2-aminophenones and subsequent oxidative cyclization to access various *N*-arylated isatins. In the course of this work, we observed that *N*-arylation using 2-iodofuran, 2-iodobenzofuran and 2-iodobenzothiophene did not lead to the expected derivatives, but to (benzo)furo- and (benzo)thieno[2,3-*b*]quinolines. Separate cyclization was also performed under acidic conditions on 2-(arylamino)phenones in order to obtain acridines and related compounds. Most of the synthesized compounds were screened for their antiproliferative activity in A2058 melanoma cells, and against a panel of disease-relevant kinases such as mammalian CDK5/p25, PIM1, CLK1, DYRK1A, GSK3 α/β , Haspin and leishmanial CK1. The biological results are reported.

1. Introduction

Heterocycles possessing an aromatic core are key entities in numerous molecules of pharmaceutical interest, as well as in organic materials for a wide range of applications. Among them, isatins and acridines are of the highest interest.

Isatins can be found in natural products,² pharmaceuticals³ and dyes.⁴ Due to their wide properties,¹ numerous procedures are reported to access them.⁵ We can for example cite oxidation of indoles,⁶ C-H functionalization of suitable *N*-substituted anilines,⁷ intramolecular oxidative cyclization,⁸ and double carbonylation followed by cyclization.⁹

Regarding acridines, they are present in compounds having versatile pharmacological activities (anticancer, antibacterial, etc) including alkaloids from natural plants and marine organisms. Moreover, they are used as pigments and dyes, as well as in fluorescent materials.¹⁰ Since the Bernthsen's synthesis of acridines,¹¹ gentler methods have been developed.¹² For instance, we can cite quinoline aminobenzannulation reaction,¹³ intramolecular Heck reaction,¹⁴ use of *in situ* generated arynes,¹⁵ palladium-catalyzed reaction between 1,2-dibromobenzenes and *N*-tosyl hydrazones,¹⁶ rhodium-catalyzed [3+3] annulation of aryl azides with azobenzenes,¹⁷ indium-catalyzed cyclization of 2-

(arylamino)benzaldehydes,¹⁸ palladium-catalyzed aniline arylation followed by cyclization and aromatization,¹⁹ copper salt-mediated cyclization of trityl amines,²⁰ zinc salt-promoted cyclization of 2-(arylamino)phenyl imines,²¹ copper-catalyzed reaction of 2-cyanoanilines with diaryliodonium salts,²² palladium-catalyzed reaction of 2-bromobenzaldehydes with anilines,²³ reaction of 2-acylanilines with cyclohexanones,²⁴ and rhodium-catalyzed bilateral cyclization of benzaldehydes with nitrosobenzenes.²⁵

We here report our efforts to combine copper-catalyzed *N*-arylation of 2-aminophenones with either intramolecular oxidative cyclization or cyclization of 2-(arylamino)phenones in order to get isatins and acridines, respectively.

Most of the compounds obtained were evaluated for their antiproliferative activity against melanoma cells. Indeed, if melanoma account for 2% of skin cancers, their mortality rate remains very high (80%) mainly due to the melanocyte intrinsic resistance to chemical agents and radiotherapy, a good ability to adapt and acquire resistance, and to develop distant metastases (e.g. in brain).²⁶ There is thus a need to identify other pharmacological targets and to develop new drugs. The selected cell lines, which have relevant mutations, are a suitable model to evaluate the cytotoxicity and the antiproliferative activity of original molecules due to their natural and acquired resistance to chemotherapy and radiotherapy.

The bioactivity of the small chemical compounds synthesized was also analyzed against a panel of disease-related kinases. Indeed, since the end of the nineties, this class of signaling biomolecules has become a major class of drug targets since they are often deregulated in diseases such as cancers and neurodegenerative disorders.²⁷ Today, 39 FDA-approved kinase inhibitors are on the market and more than 250 drug candidates are undergoing clinical evaluation.²⁸

2. Results and Discussion

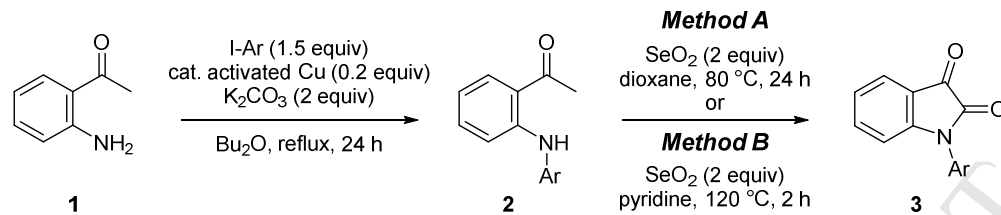
In the course of our studies dedicated to the generation of new aromatic heterocycles, we attempted to *N*-arylate isatins. Under the conditions reported by Chakraborty and co-workers from iodobenzene,²⁹ and by Moghaddam and co-workers from bromobenzene,³⁰ we failed in obtaining the *N*-arylated isatin

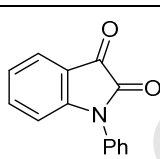
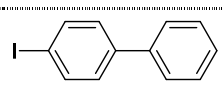
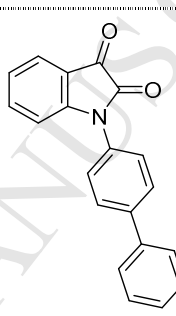
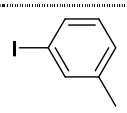
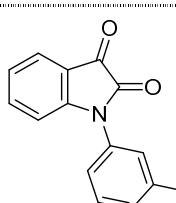
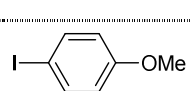
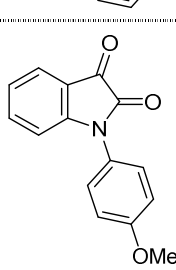
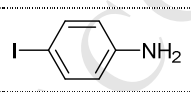
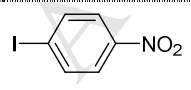
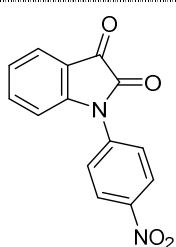
as described. The procedure of Shibata and co-workers on oxindole (0.2 equiv of *N,N'*-dimethylethylenediamine, 0.1 equiv of copper(I) iodide, 2.2 equiv of potassium carbonate in refluxing acetonitrile)³¹ did not allow isatin to be *N*-arylated by iodobenzene either. Recourse to catalytic copper(I) oxide (0.1 equiv) and iron(III) acetylacetonate (0.3 equiv), in the presence of cesium carbonate (2 equiv) as base, in dimethylformamide at 90 °C (30 h), as documented by Taillefer and co-workers from 2-pyrrolidinone,³² did not furnish the expected *N*-phenyl isatin from iodobenzene. Finally, by following conditions reported by Ranu and co-workers to couple amides with aryl iodides,³³ iodobenzene was treated by isatin (2 equiv) in the presence of nickel(II) acetylacetonate (0.1 equiv), copper(I) iodide (0.1 equiv) and cesium carbonate (2 equiv) in *N*-methyl-2-pyrrolidinone at 100 °C, but without success.

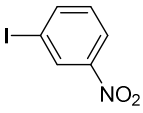
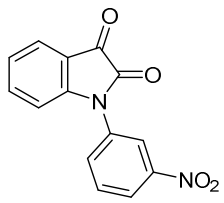
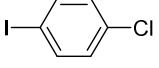
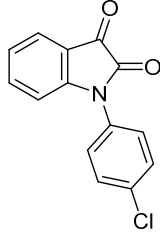
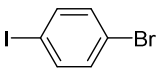
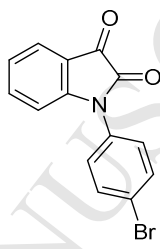
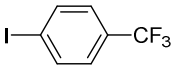
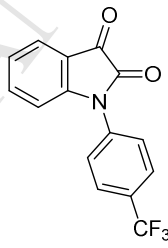

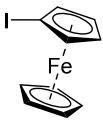
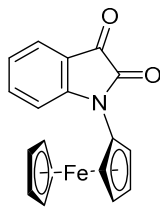
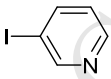
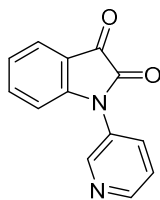
These disappointing results led us to consider an alternative way to synthesize *N*-arylated isatins. Intramolecular oxidative cyclization being largely developed,⁸ we decided to involve in the reaction various 2-(arylamino)acetophenones. For this purpose, *N*-arylation of 2-aminoacetophenone (**1**) to afford the derivatives **2** was achieved by reaction with iodides in the presence of catalytic activated Cu³⁴ and potassium carbonate (2 equiv) at the reflux temperature of dibutyl ether.^{8b} (Table 1, left). Oxidative cyclization was next performed by following the optimized procedure of Deng and co-workers using selenium dioxide in dioxane at 80 °C (Table 1, right, **Method A**).

The expected isatins were often produced in satisfying yields. Nevertheless, **3f** and **3g** proved difficult to isolate due to their low solubility (entries 6 and 7). The method being unsuitable to cyclize 2-(ferrocenylamino)acetophenone (**2l**) into **3l** (mainly recovery of **2l**), we attempted an alternative way using iodine (1.3 equiv) as oxidative agent in dimethylsulfoxide;^{8j} unfortunately, by slowly increasing the reaction temperature from 20 to 120 °C until disappearance of **2l**, only degradation was noticed (entry 12). In the case of **2m**, conversion to the expected product **3m** gave a better result by using pyridine as solvent at 120 °C instead of dioxane at 80 °C, either because of a higher solubility of **3m** in the former or since a higher temperature is used (entry 13, **Method A**; Figure 1, left).

Table 1. *N*-arylation of 2-aminoacetophenone (**1**) to afford the diarylamines **2**, and subsequent conversion to the isatins **3**.



Entry	I-Ar	2 , Yield (%) ^a	<i>Method</i>	Product 3 , Yield (%) ^a
1	I-Ph	2a , 71	<i>A</i>	3a , 90 
2		2b , 60	<i>A</i>	3b , 67 
3		2c , 88	<i>A</i>	3c , 68 
4		2d , 94	<i>A</i>	3d , 71 
5		2e , 70	^{-b}	^{-b}
6		2f , 66	<i>A</i>	3f , 20 ^c 

7		2g , 71	A		3g , 13 ^c
8		2h , 63	A		3h , 45
9		2i , 94	A		3i , 80
10		2j , 90	A		3j , 62
11		2k , 69	-	-	-
12		2l , 87	A		3l , 0 ^d
13		2m , 62	B		3m , 89

^a After purification (see experimental part). ^b Not attempted. ^c These compounds proved difficult to isolate due to solubility issues. ^d Mainly recovery of **2l**.

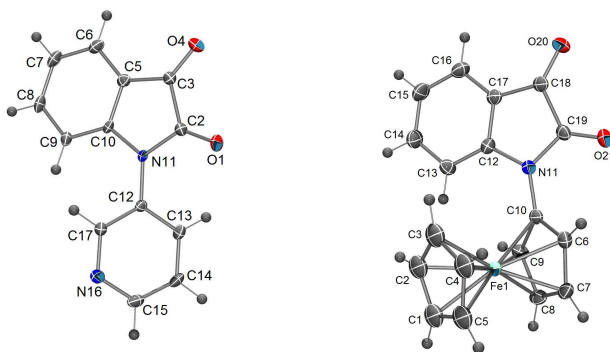
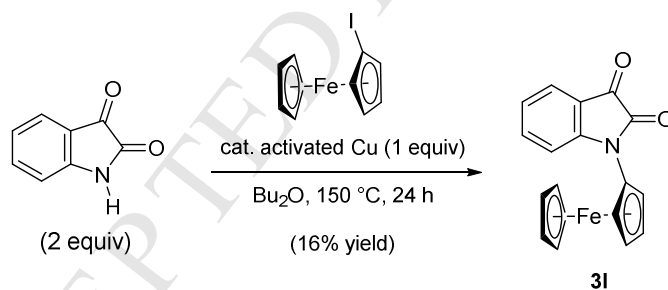


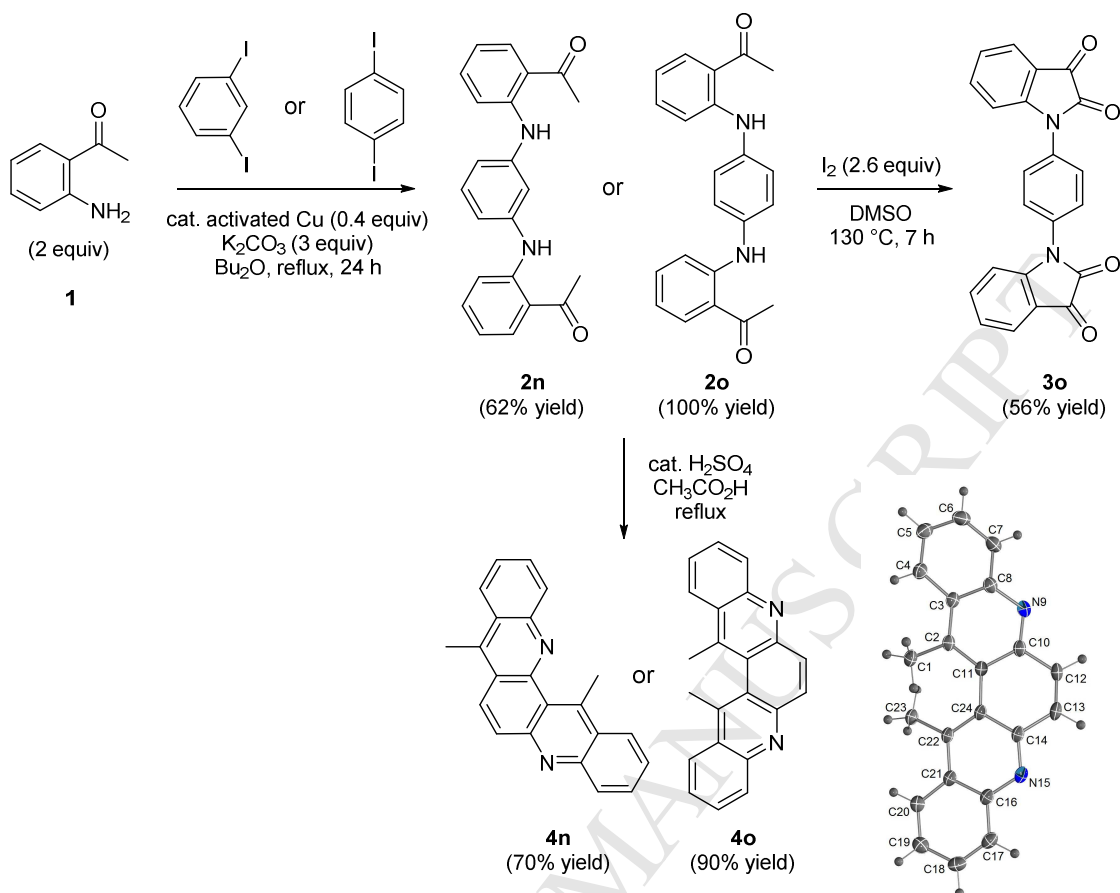
Figure 1. ORTEP diagrams (50% probability) of the isatins **3m** and **3l**.

Because we could not convert **2l** into the corresponding *N*-ferrocenylisatin (**3l**) (entry 12), we tried again to arylate isatin but this time using iodoferrocene. Using activated copper (1 equiv) and tripotassium phosphate (2 equiv) in dimethylformamide at 145 °C for several days did not lead to any conversion (iodoferrocene recovered). *N*-ferrocenylisatin (**3l**) was only obtained, albeit in a moderate 16% yield, when isatin and iodoferrocene were treated by activated copper in dibutyl ether at 150 °C for 24 h (Scheme 1; Figure 1, right).



Scheme 1. *N*-arylation of isatin with iodoferrocene to afford **3l**.

Double *N*-arylation starting from 1,3- and 1,4-diiodobenzene similarly worked to furnish the *N,N*-diarylated phenylenediamines **2n** and **2o**. From **2o**, our attempt to generate the corresponding bis-isatin **3o** as previously (4 equiv selenium dioxide in dioxane at 80 °C) failed; nevertheless, **3o** could be isolated in 56% yield using iodine in dimethylsulfoxide.^{8j} Both **2n** and **2o** were converted to pentacycles as described previously,³⁵ and the structure of **4o** could be confirmed by X-ray diffraction (Scheme 2).



Scheme 2. *N*-arylation of 2-aminoacetophenone (**1**) to afford the diarylamines **2n** and **2o**, formation of the bis-isatin **3o** from **2o**, and cyclization to the pentacycles **4n** (from **2n**) and **4o** (from **2o**); ORTEP diagram (50% probability level) of the pentacycle **4o**.

As shown in Table 1, it is possible to prepare 2-(2-thienylamino)acetophenone (**2k**). Nevertheless, this compound proved sensitive to degradation, and our attempts to make the corresponding isatin, by using either selenium dioxide in dioxane at 80 °C (complex mixture obtained including dearylated isatin) or iodine in dimethylsulfoxide at 130 °C (degradation), failed. Replacing 2-iodothiophene by 2-iodobenzothiophene in the *N*-arylation of 2-aminoacetophenone (**1**) was even more striking. Indeed, under the conditions used (0.2 equiv of activated copper, 2 equiv of potassium carbonate, reflux of dibutyl ether), the expected 2-(2-benzothieryl-amino)acetophenone was not isolated but instead the benzothieno[2,3-*b*]quinoline **4p** resulting from subsequent reaction of the benzothieryl ring with the nearby ketone and dehydration (Table 2, entry 1; Figure 2, left).

Because very few efficient methods are reported to access benzothieno[2,3-*b*]quinolines³⁶ and benzofuro[2,3-*b*]quinolines,³⁷ we decided to extend the scope of the reaction (Table 2). For this purpose, 2-aminoacetophenone (**1**) was similarly *N*-arylated with 2-iodobenzofuran and cyclized to furnish the benzofuro[2,3-*b*]quinoline **4q** (entry 2). 2-Aminobenzophenone (**5**) and 2-amino-3-benzoylpyridine (**7**) were next successfully employed to afford the derivatives **6p**, **6q**, **8p** and **8q** (entries 3-6; Figure 2, right). Furan being more suitable than thiophene to undergo such cyclizations, as shown by higher yields in all the attempted reactions, the use of 2-iodofuran was tested: unlike 2-iodothiophene (entry 7), it allowed the expected tricycle to be formed in 61% yield (entry 8).

Table 2. *N*-arylation-cyclization from 2-aminoketones to afford tri- and tetracycles.

1: X = CH; R = Me
5: X = CH; R = Ph
7: X = N; R = Ph

4: X = CH; R = Me
6: X = CH; R = Ph
8: X = N; R = Ph

Entry	Aminoketone	Iodide	Product, Yield (%) ^a
1	1		4p , 46
2			4q , 57
3	5		6p , 64
4			6q , 85
5	7		8p , 63
6			8q , 70
7	5		6k , 10
8			6r , 61

^a After purification (see experimental part). ^b The rest is mainly **9k**.

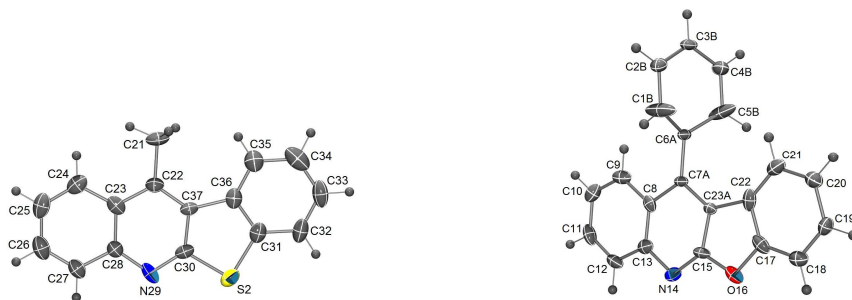
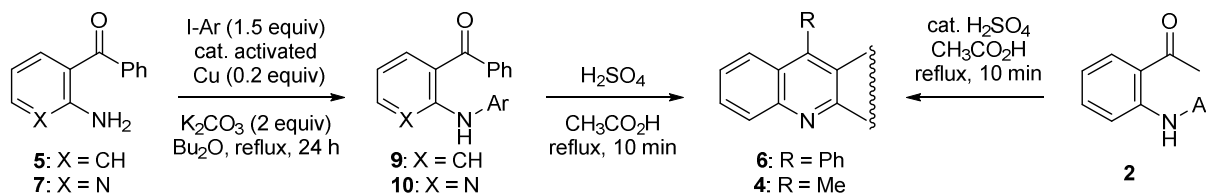
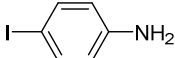
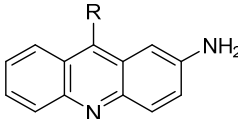
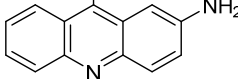
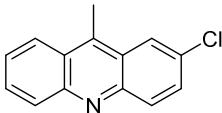
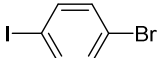
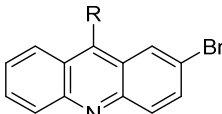
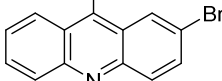
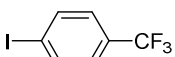
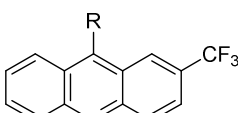
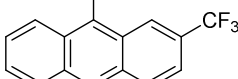

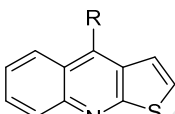
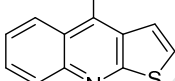


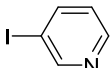
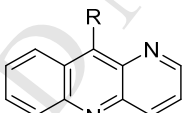
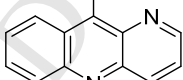


Figure 2. ORTEP diagrams (50% probability) of the tetracycles **4p** and **6q**.

This one-pot *N*-arylation-cyclization reaction, albeit very useful as shown in Table 2, cannot be extended to all the aryl iodides. Thus, in order to access a larger range of tricycles, we combined *N*-arylation of different 2-aminophenones (Table 3, left; Figure 3, left) with acid-mediated cyclization (Table 3, right; Figure 3, right). By using sulfuric acid in boiling acetic acid for 10 min,³⁸ the expected heterocycles of acridine-type were obtained satisfactorily in most cases. From **5**, formation of the expected thieno[2,3-*b*]quinoline **6k** was already detected after the *N*-arylation step. The electron-rich ferrocenyl derivatives **2l** and **9l** did not lead to the expected tricycles; instead, either unidentified products were formed (with no more unsubstituted cyclopentadienyl ring in the case of **9l**) or the starting materials **9l** (entry 10) and **2l** (result not shown) were recovered. In the case of **9m** and **2m**, lower yields were observed for the cyclized products **6m** and **4m** (entries 12 and 13); this could be due to lower reactivity of the π -deficient pyridine toward the ketone function. Moreover, even if the reactions appear as being regioselective with isolated **6m** and **4m**, the NMR spectra of the crudes show that other products are formed. Extending the reaction time from **2m** led to degradation (formation of a 4-substituted acetophenone was suspected).

Table 3. *N*-arylation of the 2-aminoketones **5** and **7** to respectively afford **9** and **10**, and cyclization of the 2-(arylamino)ketones **2** and **9** to respectively afford the acridines and related compounds **4** and **6**.



Entry	I-Ar	9 , Yield (%) ^a	Product, Reaction time, Yield (%) ^a
1		9e (from 5), 42	 6e (R = Ph; from 9e), 15 min, 59
2			 4e (R = Me; from 2e), 10 min, 94
3	-	-	 4h (from 2h), 10 min, 92
4		9i (from 5), 74	 6i (R = Ph; from 9i), 15 min, 46
5			 4i (R = Me; from 2i), 10 min, 95
6		9j (from 5), 81	 6j (R = Ph; from 9j), 10 min, 96
7			 4j (R = Me; from 2j), 30 min, 98
8		9k (from 5), 50 ^b	 6k (R = Ph; from 9k), 30 min, 80
9			 4k (R = Me; from 2k), 10 min, 61
10		9l (from 5), 85	-
11		10l (from 7), 82	-
12		9m (from 5), 88	 6m (R = Ph; from 9m), 2 h, 54 ^c
13		10m (from 7) ^d	 4m (R = Me; from 2m), 30 min, 57 ^c

^a After purification (see experimental part). ^b Further cyclization to 4-phenylthieno[2,3-*b*]quinoline (**6k**) was also noticed in 10% yield. ^c Starting material and unidentified products were also present in the crude. ^d **10m** also formed but proved to have a very low solubility in organic solvents.

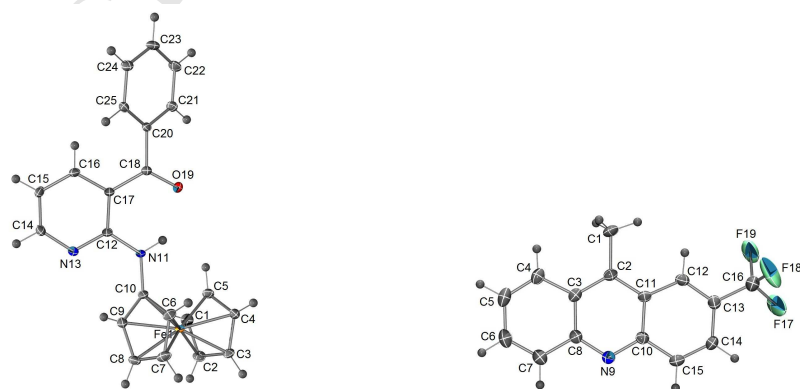


Figure 3. ORTEP diagrams (50% probability) of the compounds **10l** and **4j**.

3. Antiproliferative activity in A2058 melanoma cells

Most of the synthesized compounds were tested and exerted a significant antiproliferative activity in A2058 melanoma cells (Figure 4). The best result was obtained with the acridine **6i** which induced $95.97\% \pm 2.56\%$ growth inhibition at 10^{-5} M. Nevertheless, other heterocyclic products such as the pentacycle **4o**, its precursor **2o**, the ferrocene- and pyridine-containing isatins **3l** and **3m**, and the tetracycles **4p** and **4q** also exhibited high antiproliferative activity.

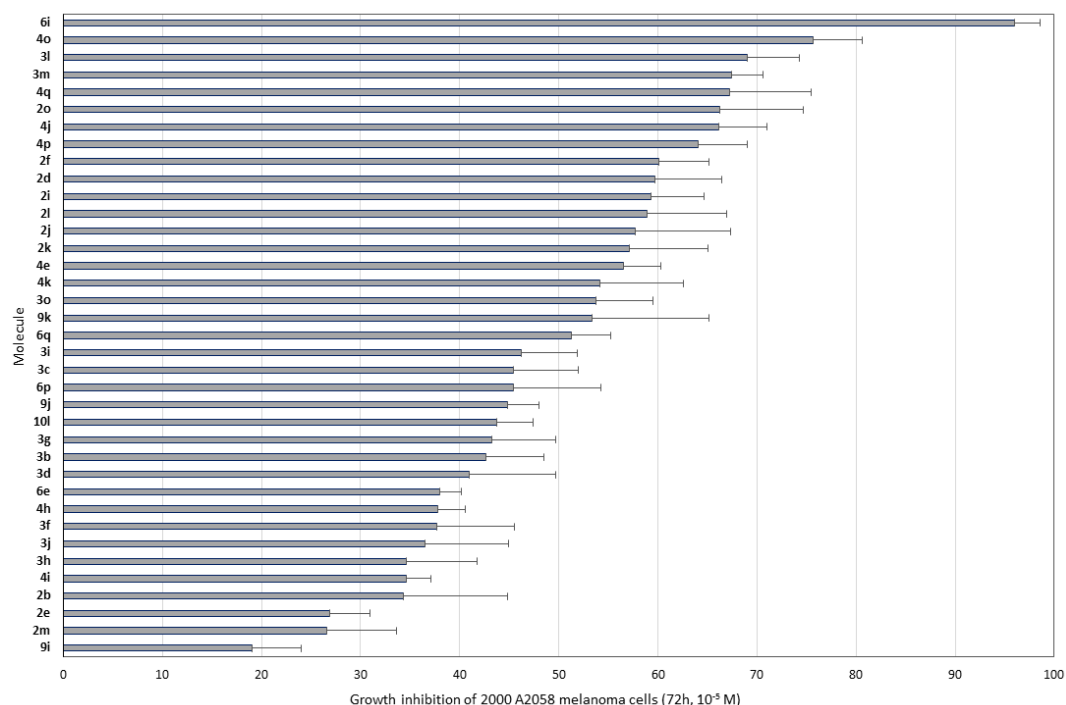


Figure 4: Antiproliferative activity of most of the synthesized compounds at 10^{-5} M after 72 h in A2058 human melanoma cells.

Most of the synthesized compounds were also evaluated³⁹ against a short panel of disease-related protein kinases: cyclin-dependent kinases 2 (CDK2/Cyclin A), 5 (CDK5/p25) and 9 (CDK9/Cyclin T); proto-oncogene kinase PIM1; CDC2-like kinase 1 (CLK1), dual specificity tyrosine phosphorylation regulated kinase 1A (DYRK1A); glycogen-synthase kinase-3 (GSK-3 α/β); casein kinase 1 (CK1

isoforms δ/ϵ); mitotic kinases Haspin and Aurora B; and leishmanial casein kinase 1 (*LmCK1*) (Table 4).

Table 4. Inhibitory activities of synthesized compounds against a short panel of disease-related protein kinases. The table displays the remaining kinase activities detected after treatment with 10 μ M of the tested compounds. The values obtained after treatment with 1 μ M are given in brackets. Results are expressed in % of maximal activity, i.e. measured in the absence of inhibitor but with an equivalent dose of DMSO (solvent of the tested compounds). ATP concentration used in the kinase assays was 15 μ mol/L (values are means, n = 2). Kinases are from human origin unless specified: *Mm*, *Mus musculus*; *Rn*, *Rattus norvegicus*; *Ssc*, *Sus scrofa domesticus*; *Lm*, *Leishmania major*.

Compound	CDK5/p25	PIM1	<i>Mm</i> CLK1	<i>Rn</i> DYRK1A	<i>Ssc</i> GSK3 α/β	<i>Lm</i> CK1	Haspin
2b	91 (100)	97 (103)	97 (84)	94 (80)	73 (87)	130 (70)	149 (107)
2e	- ^a	95 (95)	105 (108)	94 (87)	107 (92)	- ^a	92 (90)
2j	101 (93)	106 (109)	106 (94)	99 (86)	63 (104)	126 (74)	131 (119)
2k	99 (129)	64 (120)	104 (125)	70 (75)	121 (77)	99 (80)	93 (75)
2l	114 (127)	140 (134)	127 (116)	128 (130)	110 (110)	107 (77)	79 (125)
2m	113 (125)	128 (132)	112 (115)	129 (125)	141 (107)	84 (86)	88 (123)
3b	100 (87)	83 (90)	90 (99)	123 (90)	84 (103)	31 (108)	87 (111)
3c	95 (87)	94 (109)	101 (108)	39 (89)	36 (90)	85 (77)	85 (114)
3d	95 (100)	101 (115)	93 (111)	112 (111)	101 (95)	144 (105)	87 (117)
3f	102 (93)	82 (102)	94 (108)	94 (87)	55 (116)	52 (79)	85 (110)
3g	98 (101)	89 (111)	89 (116)	159 (160)	41 (104)	32 (93)	58 (98)
3h	91 (105)	89 (113)	102 (138)	96 (121)	65 (126)	79 (98)	87 (93)
3i	111 (129)	89 (114)	106 (128)	88 (83)	52 (82)	43 (63)	84 (88)
3j	117 (128)	79 (113)	109 (78)	66 (86)	103 (65)	84 (67)	117 (77)
3l	124 (142)	91 (134)	109 (134)	92 (84)	80 (73)	55 (65)	119 (105)
3m	128 (120)	65 (106)	105 (112)	67 (61)	60 (66)	93 (70)	135 (85)
3o	74 (102)	88 (120)	107 (113)	91 (70)	140 (73)	57 (64)	168 (101)
4e	- ^a	27 (90)	58 (97)	32 (108)	108 (100)	- ^a	26 (79)
4h	- ^a	68 (96)	60 (99)	58 (102)	123 (104)	- ^a	75 (100)
4i	- ^a	58 (93)	69 (94)	57 (90)	99 (75)	- ^a	74 (90)
4j	88 (107)	73 (87)	55 (90)	80 (103)	88 (85)	72 (92)	77 (90)
4k	80 (100)	78 (88)	69 (91)	52 (89)	113 (77)	97 (71)	55 (89)
4m	89 (97)	80 (100)	43 (80)	72 (67)	50 (104)	82 (143)	44 (77)
4n	108 (95)	81 (84)	130 (96)	143 (136)	150 (95)	97 (61)	99 (90)
4o	101 (110)	65 (112)	57 (102)	92 (101)	137 (86)	85 (81)	72 (109)
4p	88 (126)	56 (108)	66 (131)	56 (82)	81 (77)	98 (82)	49 (80)
4q	73 (130)	69 (109)	62 (120)	68 (96)	72 (94)	79 (76)	89 (120)
6e	- ^a	60 (87)	51 (96)	84 (103)	106 (96)	- ^a	77 (92)
6i	- ^a	61 (109)	91 (104)	101 (135)	98 (95)	- ^a	101 (107)
6k	87 (110)	74 (91)	90 (101)	85 (111)	104 (88)	96 (78)	81 (104)
6p	77 (126)	46 (104)	64 (116)	52 (84)	39 (73)	73 (69)	71 (73)
6q	92 (127)	96 (107)	92 (117)	94 (124)	122 (87)	98 (88)	77 (85)
8q	- ^a	13 (44)	24 (73)	47 (65)	22 (44)	- ^a	104 (197)
9i	- ^a	107 (103)	117 (106)	119 (142)	115 (110)	- ^a	106 (104)
9j	- ^a	104 (111)	118 (106)	126 (133)	116 (107)	- ^a	106 (100)
9k	27 (113)	87 (111)	100 (120)	78 (75)	133 (85)	61 (76)	96 (90)

9l	100 (101)	103 (104)	76 (76)	100 (70)	84 (135)	149 (183)	77 (74)
10l	- ^a	90 (109)	114 (107)	132 (108)	107 (104)	- ^a	114 (107)

^a Not performed.

None of the tested compounds inhibits significantly CDK2/Cyclin A, CDK9/Cyclin T, CK1 δ/ϵ and Aurora B (data not shown). Nevertheless, positive results were recorded with CDK5/p25 (compound **9k**), PIM1 (compounds **4e**, **6p** and **8q**), CLK1 (compounds **4m** and **8q**), DYRK1A (compounds **3c** and **4e**), GSK-3 α/β (compounds **3c**, **3g**, **6p** and **8q**), *Lm*CK1 (compounds **3b**, **3g** and **3i**) and Haspin (compounds **4e**, **4m** and **4p**) at 10 μ M. At 1 μ M, **8q** remains active, but unselectively inhibits PIM1 and GSK-3 α/β .

4. Conclusion

Thus, whereas *N*-arylation of isatin only worked with iodoferrocene, various *N*-arylated isatins were synthesized by combining copper-catalyzed *N*-arylation of 2-aminoacetophenone and oxidative cyclization. With 2-iodofuran, 2-iodobenzofuran and 2-iodobenzothiophene, the corresponding 2-(arylamino)phenones cyclized under the *N*-arylation conditions, affording relevant furo- and thieno[2,3-*b*]quinolines in only one step. Finally, cyclization of other 2-(arylamino)phenones was performed under acidic conditions to furnish acridines and related compounds.

Because of their promising activity as antiproliferative drugs in human invasive melanoma cells, some of the synthesized molecules should be further elaborated. Moreover, there is a growing interest on PIM1 kinase for development of new targeted therapy against triple-negative breast tumors.⁴⁰ The inhibitors of PIM1 detected in this study should be improved in order to be evaluated as sensitizing agents for chemotherapy using pro-apoptotic drugs.

5. Experimental

5.1. General

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. ^1H and ^{13}C Nuclear Magnetic Resonance (NMR) spectra were recorded either on a Bruker Avance III spectrometer at 300 MHz and 75 MHz respectively, or on a Bruker Avance III HD spectrometer at 500 MHz and 126 MHz respectively. ^1H 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.⁴¹ Microanalyses were performed on a Flash 1112 Thermo Fisher elemental analyzer. Iodoferrocene,⁴² 2-iodobenzothiophene,⁴³ 2-iodobenzofuran⁴³ and 2-iodofuran⁴⁴ were prepared as described previously.

Crystallography. The samples were studied with monochromatized Mo-K α radiation ($\lambda = 0.71073$ Å). The X-ray diffraction data were collected at the temperature given in the product description by using either D8 VENTURE Bruker AXS diffractometer (multilayered monochromator; compounds **3l**, **3m**, **10l**, **4o**, **4p** and **6q**), or APEXII Bruker AXS diffractometer (graphite monochromator; compound **4j**). The structure was 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 the nitrogen linked hydrogen atom that was introduced in the structural model through Fourier difference maps analysis in the case of **10l**, H atoms were finally included in their calculated positions and, in the case of **3m**, **10l**, **4o** and **4j**, treated as riding on their parent atom with constrained thermal parameters. The molecular diagrams were generated by ORTEP-3 (version 2.02).⁴⁷

5.2. *N*-arylation of 2-aminoacetophenone (**1**)

5.2.1. General procedure 1: The *N*-arylated substrates were prepared by slightly modifying a literature procedure.^{8b} To the required iodide (9.0 mmol) in Bu_2O (3 mL) were successively added activated Cu^{34} (76 mg, 1.2 mmol), 2-aminoacetophenone (**1**, 0.73 mL, 6.0 mmol) and K_2CO_3 (1.7 g, 12 mmol). The mixture was degassed and refluxed under argon for 24 h. After cooling to room

temperature, the mixture was concentrated. Addition of H₂O (25 mL), extraction with AcOEt (3x10 mL), drying over Na₂SO₄, removal of the solvent and purification by chromatography on silica gel (the eluent is given in the product description) led to the expected compound.

5.2.2. 2-(Phenylamino)acetophenone (2a). The general procedure 1 using iodobenzene (1.0 mL) gave **2a** (eluent: heptane-AcOEt 80:20) in 71% yield (0.90 g) as a yellow oil: ¹H NMR (CDCl₃) δ 2.65 (s, 3H), 6.74 (ddd, 1H, *J* = 8.1, 6.6 and 1.5 Hz), 7.12 (tt, 1H, *J* = 7.2 and 1.3 Hz), 7.23-7.39 (m, 6H), 7.82 (ddd, 1H, *J* = 8.1, 1.6 and 0.5 Hz), 10.55 (br s, 1H); ¹³C NMR (CDCl₃) δ 28.3 (CH₃), 114.3 (CH), 116.6 (CH), 119.1 (C), 123.3 (2CH), 124.1 (CH), 129.5 (2CH), 132.6 (CH), 134.7 (CH), 140.5 (C), 148.1 (C), 201.3 (C). The spectral data are analogous to those described previously.⁴⁸

5.2.3. 2-(4-(Phenyl)phenylamino)acetophenone (2b).^{8b} The general procedure 1 using 1-iodo-4-phenylbenzene (2.5 g) gave **2b** (eluent: heptane-AcOEt 80:20) in 60% yield (1.0 g) as a pale yellow powder: mp 92 °C; ¹H NMR (CDCl₃) δ 2.67 (s, 3H), 6.78 (ddd, 1H, *J* = 8.1, 5.0 and 3.1 Hz), 7.32-7.38 (m, 5H), 7.42-7.49 (m, 2H), 7.59-7.64 (m, 4H), 7.85 (ddd, 1H, *J* = 8.1, 1.4 and 0.7 Hz), 10.65 (br s, 1H); ¹³C NMR (CDCl₃) δ 28.2 (CH₃), 114.5 (CH), 116.8 (CH), 119.4 (C), 123.1 (2CH), 126.9 (2CH), 127.1 (CH), 128.1 (2CH), 128.9 (2CH), 132.7 (CH), 134.7 (CH), 136.7 (C), 139.8 (C), 140.7 (C), 147.8 (C), 201.3 (C).

5.2.4. 2-(3-Tolylamino)acetophenone (2c).^{8b} The general procedure 1 using 3-iodotoluene (1.2 mL) gave **2c** (eluent: heptane-AcOEt 80:20) in 88% yield (1.2 g) as a yellow oil: ¹H NMR (CDCl₃) δ 2.35 (d, 1H, *J* = 0.35 Hz), 2.64 (s, 3H), 6.72 (ddd, 1H, *J* = 8.1, 6.6 and 1.5 Hz), 6.93 (br d, 1H, *J* = 7.5 Hz), 7.06-7.08 (m, 2H), 7.20-7.33 (m, 3H), 7.81 (dd, 1H, *J* = 8.0 and 1.4 Hz), 10.50 (br s, 1H); ¹³C NMR (CDCl₃) δ 21.6 (CH₃), 28.2 (CH₃), 114.4 (CH), 116.5 (CH), 119.1 (C), 120.3 (CH), 124.0 (CH), 124.9 (CH), 129.2 (CH), 132.6 (CH), 134.6 (CH), 139.4 (C), 140.4 (C), 148.2 (C), 201.2 (C).

5.2.5. 2-(4-Methoxyphenylamino)acetophenone (2d). The general procedure 1 using 4-iodoanisole (2.1 g) gave **2d** (eluent: heptane) in 94% yield (1.4 g) as a yellow powder: mp 68 °C (lit.⁴⁹ 65.5-66.5 °C); ¹H NMR (CDCl₃) δ 2.64 (s, 3H), 3.82 (s, 3H), 6.67 (ddd, 1H, *J* = 8.1, 7.0 and 1.2 Hz), 6.88-6.94

(m, 2H), 6.99 (dd, 1H, $J = 8.5$ and 1.2 Hz), 7.14-7.21 (m, 2H), 7.24 (ddd, 1H, $J = 8.9$, 6.9 and 1.6 Hz), 7.79 (dd, 1H, $J = 8.1$ and 1.6 Hz), 10.37 (br s, 1H); ^{13}C NMR (CDCl_3) δ 28.2 (CH_3), 55.6 (CH_3), 113.8 (CH), 114.8 (2CH), 115.7 (CH), 118.3 (C), 126.4 (2CH), 132.6 (CH), 133.1 (C), 134.7 (CH), 149.7 (C), 157.0 (C), 201.2 (C). The spectral data are analogous to those described previously.⁴⁸

5.2.6. 2-(4-Aminophenylamino)acetophenone (2e). The general procedure 1 using 4-iodoaniline (2.0 g) gave **2e** (eluent: heptane-AcOEt 90:10; Rf (heptane-AcOEt 80:20) 0.08) in 70% yield (0.95 g) as an orange powder: mp 143 °C; IR (ATR): 705, 741, 795, 815, 842, 958, 1022, 1043, 1067, 1163, 1228, 1252, 1408, 1436, 1457, 1513, 1567, 1586, 1619, 2989, 3269, 3342, 3420 cm^{-1} ; ^1H NMR (CDCl_3) δ 2.63 (s, 3H), 3.75 (br s, 2H, NH_2), 6.63 (ddd, 1H, $J = 8.1$, 6.9 and 1.1 Hz), 6.69-6.72 (m, 2H), 6.95 (dd, 1H, $J = 8.6$ and 1.1 Hz), 7.03-7.06 (m, 2H), 7.24 (ddd, 1H, $J = 8.6$, 7.0 and 1.7 Hz), 7.77 (dd, 1H, $J = 8.1$ and 1.5 Hz), 10.29 (br s, 1H); ^{13}C NMR (CDCl_3) δ 28.2 (CH_3), 113.9 (CH), 115.4 (CH), 116.1 (2CH), 118.1 (C), 126.8 (2CH), 131.2 (C), 132.6 (CH), 134.7 (CH), 143.7 (C), 150.1 (C), 201.1 (C). Anal. Calcd for $\text{C}_{14}\text{H}_{14}\text{N}_2\text{O}$ (226.28): C, 74.31; H, 6.24; N, 12.38. Found: C, 74.19; H, 6.28; N, 12.29.

5.2.7. 2-(4-Nitrophenylamino)acetophenone (2f). The general procedure 1 using 1-iodo-4-nitrobenzene (2.2 g) gave **2f** after washing with water in 66% yield (1.0 g) as a beige powder: mp 140 °C; ^1H NMR (CDCl_3) δ 2.67 (s, 3H), 6.99 (ddd, 1H, $J = 8.2$, 6.9 and 1.4 Hz), 7.25-7.31 (m, 2H), 7.43-7.55 (m, 2H), 7.90 (dd, 1H, $J = 8.1$ and 1.5 Hz), 8.16-8.22 (m, 2H), 10.79 (br s, 1H); ^{13}C NMR (CDCl_3) δ 28.5 (CH_3), 116.7 (CH), 118.5 (2CH), 119.2 (C), 120.2 (CH), 122.2 (C), 125.9 (2CH), 132.7 (CH), 134.7 (CH), 144.1 (C), 147.6 (C), 202.0 (C). The spectral data are analogous to those described previously.⁴⁸

5.2.8. 2-(3-Nitrophenylamino)acetophenone (2g). The general procedure 1 using 1-iodo-3-nitrobenzene (2.2 g) gave **2g** after washing with water in 71% yield (1.1 g) as a beige powder: mp 160 °C (lit.⁵⁰ $94-95$ °C); ^1H NMR (CDCl_3) δ 2.67 (s, 3H), 6.89 (ddd, 1H, $J = 8.1$, 6.9 and 1.4 Hz), 7.35 (dd, 1H, $J = 8.5$ and 1.3 Hz), 7.38-7.51 (m, 3H), 7.86-7.90 (m, 2H), 8.13 (t, 1H, $J = 2.1$ Hz), 10.70 (br s,

1H); ^{13}C NMR (CDCl_3) δ 28.3 (CH_3), 114.6 (CH), 115.7 (CH), 117.7 (CH), 118.7 (CH), 120.5 (C), 127.4 (CH), 130.2 (CH), 132.8 (CH), 134.9 (CH), 142.3 (C), 145.8 (C), 149.2 (C), 201.8 (C).

5.2.9. 2-(4-Chlorophenylamino)acetophenone (2h). The general procedure 1 using 1-chloro-4-iodobenzene (2.1 g) gave **2h** (eluent: heptane-AcOEt 80:20) in 63% yield (0.93 g) as a beige powder: mp 70 °C; ^1H NMR (CDCl_3) δ 2.65 (s, 3H), 6.76 (ddd, 1H, $J = 8.2, 7.0$ and 1.2 Hz), 7.16-7.21 (m, 3H), 7.27-7.35 (m, 3H), 7.83 (dd, 1H, $J = 8.1$ and 1.6 Hz), 10.49 (br s, 1H); ^{13}C NMR (CDCl_3) δ 28.3 (CH_3), 114.3 (CH), 117.1 (CH), 119.5 (C), 124.4 (2CH), 129.0 (C), 129.6 (2CH), 132.7 (CH), 134.8 (CH), 139.2 (C), 147.7 (C), 201.5 (C). The spectral data are analogous to those described previously.⁴⁸

5.2.10. 2-(4-Bromophenylamino)acetophenone (2i).^{8b} The general procedure 1 using 1-bromo-4-iodobenzene (2.5 g) gave **2i** (eluent: heptane-AcOEt 80:20) in 94% yield (1.6 g) as a yellow oil: ^1H NMR (CDCl_3) δ 2.64 (s, 3H), 6.78 (ddd, 1H, $J = 8.2, 7.0$ and 1.3 Hz), 7.11-7.17 (m, 2H), 7.22 (dd, 1H, $J = 8.6$ and 1.2 Hz), 7.33 (ddd, 1H, $J = 8.6, 6.9$ and 1.5 Hz), 7.42-7.48 (m, 2H), 7.83 (dd, 1H, $J = 8.1$ and 1.6 Hz), 10.49 (br s, 1H); ^{13}C NMR (CDCl_3) δ 28.3 (CH_3), 114.3 (CH), 116.4 (C), 117.2 (CH), 119.6 (C), 124.5 (2CH), 132.5 (2CH), 132.7 (CH), 134.7 (CH), 139.7 (C), 147.4 (C), 201.5 (C).

5.2.11. 2-(4-(Trifluoromethyl)phenylamino)acetophenone (2j). The general procedure 1 using 1-iodo-4-(trifluoromethyl)benzene (1.3 mL) gave **2j** (eluent: heptane-AcOEt 80:20) in 90% yield (1.5 g) as a beige powder: mp 70 °C; ^1H NMR (CDCl_3) δ 2.68 (s, 3H), 6.88 (ddd, 1H, $J = 8.1, 5.8$ and 2.4 Hz), 7.34 (d, 2H, $J = 8.9$ Hz), 7.39-7.45 (m, 2H), 7.59 (d, 2H, $J = 8.8$ Hz), 7.88 (dd, 1H, $J = 8.1$ and 1.4 Hz), 10.69 (br s, 1H); ^{13}C NMR (CDCl_3) δ 28.3 (CH_3), 115.1 (CH), 118.3 (CH), 120.6 (C), 120.9 (2CH), 124.4 (q, C, $J = 270$ Hz), 124.7 (q, C, $J = 32.5$ Hz), 126.7 (q, 2CH, $J = 3.8$ Hz), 132.7 (CH), 134.7 (CH), 144.2 (q, C, $J = 1.5$ Hz), 146.0 (C), 201.7 (C). The spectral data are analogous to those described previously.⁴⁸

5.2.12. 2-(2-Thienylamino)acetophenone (2k). The general procedure 1 using 2-iodothiophene (0.99 mL) gave **2k** (eluent: heptane-AcOEt 80:20; Rf 0.56) in 69% yield (0.90 g) as a yellow oil: IR (ATR): 702, 751, 855, 954, 1158, 1241, 1311, 1358, 1451, 1490, 1499, 1538, 1571, 1607, 1633, 1738,

2924, 3244 cm^{-1} ; ^1H NMR (CDCl_3) δ 2.65 (s, 3H), 6.76 (ddd, 1H, $J = 8.1, 7.1$ and 1.2 Hz), 6.82 (dt, 1H, $J = 3.6$ and 1.2 Hz), 6.95 (dd, 1H, $J = 5.6$ and 3.6 Hz), 7.04-7.12 (m, 2H), 7.34 (dddd, 1H, $J = 8.6, 7.1, 1.6$ and 0.5 Hz), 7.81 (dd, 1H, $J = 8.1$ and 1.5 Hz), 10.43 (br s, 1H); ^{13}C NMR (CDCl_3) δ 28.1 (CH_3), 114.3 (CH), 117.0 (CH), 118.7 (C), 121.3 (CH), 121.9 (CH), 126.1 (CH), 132.2 (CH), 135.0 (CH), 143.3 (C), 149.8 (C), 201.5 (C). Anal. Calcd for $\text{C}_{12}\text{H}_{11}\text{NOS}$ (217.29): C, 66.33; H, 5.10; N, 6.45; S, 14.75. Found: C, 66.00; H, 5.15; N, 6.49; S, 14.66.

5.2.13. 2-(Ferrocenylamino)acetophenone (2l). The general procedure 1 using iodoferrocene (2.8 g) gave **2l** (eluent: heptane-AcOEt 80:20) in 87% yield (1.7 g) as an orange powder: mp 58°C (lit.⁵¹ 57-59 $^\circ\text{C}$), ^1H NMR (CDCl_3) δ 2.64 (s, 3H), 4.10 (t, 2H, $J = 1.9$ Hz), 4.25 (s, 5H), 4.33 (t, 2H, $J = 1.9$ Hz), 6.65 (ddd, 1H, $J = 8.1, 6.9$ and 1.2 Hz), 7.08 (dd, 1H, $J = 8.6$ and 1.2 Hz), 7.30 (ddd, 1H, $J = 8.6, 6.9$ and 1.6 Hz), 7.78 (dd, 1H, $J = 8.1$ and 1.6 Hz), 10.06 (br s, 1H); ^{13}C NMR (CDCl_3) δ 28.1 (CH_3), 65.2 (2CH), 65.6 (2CH), 69.5 (5CH), 96.0 (C), 114.3 (CH), 115.4 (CH), 118.0 (C), 132.4 (CH), 134.7 (CH), 150.5 (C), 201.2 (C). The spectral data are analogous to those described previously.⁵¹

5.2.14. 2-(3-Pyridylamino)acetophenone (2m).⁵² The general procedure 1 using 3-iodopyridine (1.8 g) gave **2m** (eluent: heptane-AcOEt 70:30) in 62% yield (0.79 g) as a yellow oil: IR (ATR): 706, 746, 794, 955, 1020, 1106, 1163, 1185, 1240, 1318, 1359, 1454, 1481, 1512, 1568, 1579, 1605, 1638, 1736, 3031, 3247 cm^{-1} ; ^1H NMR (CDCl_3) δ 2.66 (s, 3H), 6.81 (ddd, 1H, $J = 8.1, 7.1$ and 1.2 Hz), 7.20 (dd, 1H, $J = 8.6$ and 1.1 Hz), 7.28 (dd, 1H, $J = 8.2$ and 4.7 Hz), 7.35 (dddd, 1H, $J = 8.6, 7.0, 1.6$ and 0.5 Hz), 7.59 (ddd, 1H, $J = 8.3, 2.4$ and 1.5 Hz), 7.85 (dd, 1H, $J = 8.1$ and 1.5 Hz), 8.35 (d, 1H, $J = 4.7$ Hz), 8.57 (br s, 1H), 10.55 (br s, 1H); ^{13}C NMR (CDCl_3) δ 28.1 (CH_3), 113.9 (CH), 117.7 (CH), 119.7 (C), 123.8 (CH), 129.5 (CH), 132.6 (CH), 134.7 (CH), 137.2 (C), 144.7 (CH), 144.8 (CH), 147.0 (C), 201.5 (C).

5.2.15. General procedure 2: To the required iodide (2.0 g, 6.0 mmol) in Bu_2O (3 mL) were successively added activated Cu^{34} (0.15 g, 2.4 mmol), 2-aminoacetophenone (**1**, 1.5 mL, 12 mmol) and K_2CO_3 (2.5 g, 18 mmol). The mixture was degassed and refluxed under argon for 48 h. After cooling to

room temperature, the mixture was concentrated. Addition of H₂O (25 mL), filtration of the precipitate, washing with H₂O and heptane, and drying led to the expected compound.

5.2.16. *N,N'*-(1,3-Phenylene)-2,2'-bis(2-aminoacetophenone) (2n). The general procedure 2 using 1,3-diiodobenzene gave **2n** in 62% yield (1.3 g) as a beige powder: mp 126 °C (lit.³⁵ 129.5-132.5 °C); ¹H NMR (CDCl₃) δ 2.64 (s, 6H), 6.75 (ddd, 2H, *J* = 8.1, 5.8 and 2.3 Hz), 6.99 (dd, 2H, *J* = 8.0 and 2.1 Hz), 7.16 (t, 1H, *J* = 2.1 Hz), 7.28-7.36 (m, 5H), 7.81 (dd, 2H, *J* = 8.1 and 1.5 Hz), 10.53 (br s, 2H). The ¹H NMR data are analogous to those described previously.³⁵ ¹³C NMR (CDCl₃) δ 28.3 (2CH₃), 114.7 (2CH), 116.9 (2CH), 117.0 (CH), 118.4 (2CH), 119.4 (2C), 130.3 (CH), 132.6 (2CH), 134.7 (2CH), 141.7 (2C), 147.7 (2C), 201.4 (2C).

5.2.17. *N,N'*-(1,4-Phenylene)-2,2'-bis(2-aminoacetophenone) (2o). The general procedure 2 using 1,4-diiodobenzene gave **2o** in 100% yield (2.1 g) as a beige powder: mp 210 °C (lit.³⁵ 196-198 °C); ¹H NMR (CDCl₃) δ 2.65 (s, 6H), 6.72 (ddd, 2H, *J* = 8.1, 6.9 and 1.3 Hz), 7.20 (dd, 2H, *J* = 8.7 and 1.2 Hz), 7.24 (s, 4H), 7.32 (dddd, 2H, *J* = 8.6, 6.9, 1.6 and 0.5 Hz), 7.82 (dd, 2H, *J* = 8.1 and 1.5 Hz), 10.50 (br s, 2H). The ¹H NMR data are analogous to those described previously.³⁵ ¹³C NMR (CDCl₃) δ 27.2 (2CH₃), 113.2 (2CH), 115.5 (2CH), 118.0 (2C), 123.7 (4CH), 131.7 (2CH), 133.8 (2CH), 135.6 (2C), 147.5 (2C), 200.3 (2C).

5.3. Conversion of the *N*-arylated 2-aminoacetophenones to isatins

5.3.1. General procedure 3 (Method A): To the required *N*-arylated 2-aminoacetophenone (3.0 mmol) in dioxane (3 mL) was added SeO₂ (0.67 g, 6.0 mmol). The mixture was heated at 80 °C for 24 h. After cooling to room temperature, the mixture was concentrated and the compound was purified by chromatography on silica gel (the eluent is given in the product description).

5.3.2. 1-Phenylisatin (3a). The general procedure 3 using 2-(phenylamino)acetophenone (**2a**, 0.63 g) gave **3a** (eluent: heptane-AcOEt 80:20) in 90% yield (0.60 g) as an orange powder: mp 137 °C (lit.⁵³ 136-139 °C); ¹H NMR (CDCl₃) δ 6.90 (d, 1H, *J* = 8.0 Hz), 7.17 (td, 1H, *J* = 7.6 and 0.9 Hz), 7.40-7.59 (m, 6H), 7.70 (dd, 1H, *J* = 7.4 and 1.4 Hz); ¹³C NMR (CDCl₃) δ 111.4 (CH), 117.7 (C), 124.4 (CH),

125.8 (CH), 126.2 (2CH), 129.0 (CH), 130.1 (2CH), 133.1 (C), 138.4 (CH), 151.8 (C), 157.5 (C), 183.0 (C). The spectral data are analogous to those described previously.⁵³

5.3.3. 1-(4-Phenylphenyl)isatin (3b). The general procedure 3 using 2-((4-phenyl)phenylamino)acetophenone (**2b**, 0.86 g) gave **3b** (eluent: heptane-AcOEt 80:20) in 67% yield (0.60 g) as an orange powder: mp 178 °C; ¹H NMR (CDCl₃) δ 6.98 (dt, 1H, *J* = 8.0 and 0.75 Hz), 7.19 (td, 1H, *J* = 7.5 and 0.8 Hz), 7.37-7.52 (m, 5H), 7.57 (td, 1H, *J* = 7.8 and 1.4 Hz), 7.59-7.64 (m, 2H), 7.72 (ddd, 1H, *J* = 7.5, 1.4 and 0.6 Hz), 7.74-7.79 (m, 2H); ¹³C NMR (CDCl₃) δ 111.4 (CH), 117.7 (C), 124.5 (CH), 125.8 (CH), 126.4 (2CH), 127.3 (2CH), 128.0 (CH), 128.8 (2CH), 129.1 (2CH), 132.1 (C), 138.5 (CH), 140.1 (C), 142.0 (C), 151.8 (C), 157.6 (C), 183.0 (C). The spectral data are analogous to those described previously.^{8b}

5.3.4. 1-(3-Tolyl)isatin (3c). The general procedure 3 using 2-(3-tolylamino)acetophenone (**2c**, 0.68 g) gave **3c** (eluent: heptane-AcOEt 80:20) in 68% yield (0.48 g) as an orange powder: mp 150 °C; ¹H NMR (CDCl₃) δ 2.43 (s, 3H), 6.87 (dd, 1H, *J* = 8.0 and 0.75 Hz), 7.16 (td, 1H, *J* = 7.5 and 0.8 Hz), 7.18-7.28 (m, 3H), 7.43 (td, 1H, *J* = 7.6 and 0.8 Hz), 7.53 (td, 1H, *J* = 7.8 and 1.4 Hz), 7.68 (ddd, 1H, *J* = 7.4, 1.4 and 0.6 Hz); ¹³C NMR (CDCl₃) δ 21.5 (CH₃), 111.5 (CH), 117.6 (C), 123.1 (CH), 124.3 (CH), 125.7 (CH), 126.8 (CH), 129.8 (CH), 129.9 (CH), 132.9 (C), 138.4 (CH), 140.3 (C), 152.0 (C), 157.5 (C), 183.1 (C). The spectral data are analogous to those described previously.^{8b}

5.3.5. 1-(4-Methoxyphenyl)isatin (3d). The general procedure 3 using 2-(4-methoxyphenylamino)acetophenone (**2d**, 0.72 g) gave **3d** (eluent: heptane-AcOEt 80:20) in 71% yield (0.54 g) as an orange powder: mp 168 °C; ¹H NMR (CDCl₃) δ 3.86 (s, 3H), 6.82 (d, 1H, *J* = 8.0 Hz), 7.02-7.08 (m, 2H), 7.15 (td, 1H, *J* = 7.5 and 0.8 Hz), 7.28-7.34 (m, 2H), 7.52 (td, 1H, *J* = 7.8 and 1.4 Hz), 7.67 (ddd, 1H, *J* = 7.5, 1.3 and 0.5 Hz); ¹³C NMR (CDCl₃) δ 55.7 (CH₃), 111.3 (CH), 115.4 (2CH), 117.6 (C), 124.3 (CH), 125.5 (C), 125.6 (CH), 127.6 (2CH), 138.4 (CH), 152.2 (C), 157.8 (C), 159.9 (C), 183.2 (C). The spectral data are analogous to those described previously.^{8b}

5.3.6. 1-(4-Nitrophenyl)isatin (3f).^{8e} The general procedure 3 using 2-(4-nitrophenylamino)acetophenone (**2f**, 0.77 g) gave **3f** (eluent: heptane-AcOEt 80:20) in 20% yield (0.16 g) as an orange powder: mp 232 °C; ¹H NMR (CDCl₃) δ 7.04 (d, 1H, *J* = 8.1 Hz), 7.27 (td, 1H, *J* = 7.5 and 0.7 Hz), 7.63 (td, 1H, *J* = 7.8 and 1.4 Hz), 7.66-7.72 (m, 2H), 7.77 (ddd, 1H, *J* = 7.5, 1.4 and 0.6 Hz), 8.41-8.47 (m, 2H); ¹³C NMR (CDCl₃) δ 111.3 (CH), 118.0 (C), 125.4 (CH), 125.5 (2CH), 126.2 (2CH), 126.4 (CH), 138.7 (CH), 138.7 (C), 147.1 (C), 150.2 (C), 157.0 (C), 181.6 (C).

5.3.7. 1-(3-Nitrophenyl)isatin (3g).⁵⁴ The general procedure 3 using 2-(3-nitrophenylamino)acetophenone (**2g**, 0.77 g) gave **3g** (eluent: heptane-AcOEt 80:20) in 13% yield (0.10 g) as an orange powder: mp 160 °C; ¹H NMR (CDCl₃) δ 6.97 (d, 1H, *J* = 8.0 Hz), 7.26 (td, 1H, *J* = 7.6 and 0.7 Hz), 7.62 (td, 1H, *J* = 7.8 and 1.4 Hz), 7.75-7.86 (m, 3H), 8.31-8.37 (m, 2H); ¹³C NMR (CDCl₃) δ 111.1 (CH), 117.8 (C), 121.0 (CH), 123.5 (CH), 125.2 (CH), 126.3 (CH), 131.1 (CH), 132.1 (CH), 134.3 (C), 138.7 (CH), 150.4 (C), 157.1 (C), 181.7 (C), 1C not seen.

5.3.8. 1-(4-Chlorophenyl)isatin (3h). The general procedure 3 using 2-(4-chlorophenylamino)acetophenone (**2h**, 0.74 g) gave **3h** (eluent: heptane-AcOEt 80:20) in 45% yield (0.35 g) as an orange powder: mp 198 °C (lit.⁵³ 194-197 °C); ¹H NMR (CDCl₃) δ 6.89 (dt, 1H, *J* = 8.0 and 0.7 Hz), 7.19 (td, 1H, *J* = 7.6 and 0.9 Hz), 7.35-7.40 (m, 2H), 7.50-7.57 (m, 2H), 7.57 (dd, 1H, *J* = 7.8 and 1.4 Hz), 7.70 (ddd, 1H, *J* = 7.5, 1.4 and 0.6 Hz); ¹³C NMR (CDCl₃) δ 111.2 (CH), 117.7 (C), 124.7 (CH), 125.9 (CH), 127.4 (2CH), 130.3 (2CH), 131.5 (C), 134.7 (C), 138.5 (CH), 151.3 (C), 157.3 (C), 182.5 (C). The spectral data are analogous to those described previously.⁵³

5.3.9. 1-(4-Bromophenyl)isatin (3i). The general procedure 3 using 2-(4-bromophenylamino)acetophenone (**2i**, 0.87 g) gave **3i** (eluent: heptane-AcOEt 80:20) in 80% yield (0.73 g) as an orange powder: mp 182 °C (lit.⁵³ 178-180 °C); ¹H NMR (CDCl₃) δ 6.89 (d, 1H, *J* = 8.1 Hz), 7.19 (td, 1H, *J* = 7.5 and 0.8 Hz), 7.29-7.34 (m, 2H), 7.56 (td, 1H, *J* = 7.8 and 1.4 Hz), 7.66-7.72 (m, 3H); ¹³C NMR (CDCl₃) δ 111.2 (CH), 117.7 (C), 122.6 (C), 124.7 (CH), 125.9 (CH), 127.7 (2CH),

132.1 (C), 133.3 (2CH), 138.5 (CH), 151.2 (C), 157.3 (C), 182.5 (C). The spectral data are analogous to those described previously.⁵³

5.3.10. 1-(4-(Trifluoromethyl)phenyl)isatin (3j). The general procedure 3 using 2-(4-(trifluoromethyl)phenylamino)acetophenone (**2j**, 0.84 g) gave **3j** (eluent: heptane-AcOEt 80:20) in 62% yield (0.54 g) as an orange powder: mp 184 °C (lit.⁵³ 177-181 °C); ¹H NMR (CDCl₃) δ 6.97 (d, 1H, *J* = 8.0 Hz), 7.23 (td, 1H, *J* = 7.6 and 0.7 Hz), 7.56-7.62 (m, 3H), 7.73 (dd, 1H, *J* = 7.5 and 0.9 Hz), 7.83 (d, 2H, *J* = 8.4 Hz); ¹³C NMR (CDCl₃) δ 111.3 (CH), 117.8 (C), 123.7 (q, C, *J* = 271 Hz), 124.9 (CH), 126.1 (CH), 126.3 (2CH), 127.2 (q, 2CH, *J* = 15 Hz), 130.8 (q, C, *J* = 40 Hz), 136.3 (C), 138.6 (CH), 150.8 (C), 157.2 (C), 182.1 (C). The spectral data are analogous to those described previously.⁵³

5.3.11. 1-Ferrocenylisatin (3l). To isatin (0.29 g, 2.0 mmol) in Bu₂O (3 mL) was added iodoferrocene (0.31 g, 1.0 mmol) and activated Cu³⁴ (63 mg, 1.0 mmol). The mixture was degassed and heated at 150 °C under argon for 24 h. After cooling to room temperature, the mixture was concentrated and the residue was purified by chromatography on silica gel (eluent: heptane-AcOEt 80:20; R_f 0.30) gave **3l** in 16% yield (53 mg) as a black powder: mp 170 °C; IR (ATR): 753, 812, 945, 1093, 1105, 1155, 1173, 1301, 1341, 1354, 1458, 1473, 1495, 1599, 1721, 1735, 2925, 3114 cm⁻¹; ¹H NMR (CDCl₃) δ 4.30-4.31 (m, 7H), 4.66 (t, 2H, *J* = 2.0 Hz), 7.18 (td, 1H, *J* = 7.5 and 0.9 Hz), 7.56-7.67 (m, 3H); ¹³C NMR (CDCl₃) δ 63.3 (2CH), 66.1 (2CH), 69.8 (5CH), 89.8 (C), 112.5 (CH), 118.0 (C), 124.1 (CH), 125.2 (CH), 138.2 (CH), 151.3 (C), 157.5 (C), 182.9 (C). Anal. Calcd for C₁₈H₁₃FeNO₂ (331.14): C, 65.29; H, 3.96; N, 4.23. Found: C, 65.33; H, 4.14; N, 4.27. **Crystal data for 3l.** C₁₈H₁₃FeNO₂, *M* = 331.14, *T* = 150 K, triclinic, *P* -1, *a* = 7.6255(4), *b* = 13.3306(6), *c* = 14.5450(7) Å, α = 73.602(2), β = 84.944(2), γ = 77.362(2) °, *V* = 1383.48(12) Å³, *Z* = 4, *d* = 1.590 g cm⁻³, μ = 1.096 mm⁻¹. A final refinement on *F*² with 6295 unique intensities and 373 parameters converged at ω*R*(*F*²) = 0.0981 (*R*(*F*) = 0.0392) for 5336 observed reflections with *I* > 2σ(*I*). CCDC 1811743.

5.3.12. 1-(3-Pyridyl)isatin (3m, Method B). To 2-(3-pyridylamino)acetophenone (**2m**, 0.11 g, 0.50 mmol) in pyridine (1 mL) was added SeO₂ (115 mg, 1.0 mmol). The mixture was heated at 120 °C for

2 h. After cooling to room temperature, an aqueous 1 M solution of HCl (2 mL) was added before filtration and washing with H₂O (2 x 5 mL). Drying under vacuum afforded **3m** in 89% yield (0.10 g) as an orange powder: mp 204 °C; IR (ATR): 695, 704, 719, 759, 802, 927, 1028, 1098, 1150, 1170, 1180, 1200, 1300, 1365, 1426, 1461, 1490, 1578, 1608, 1733, 3049, 3106, 3456 cm⁻¹; ¹H NMR (CDCl₃) δ 6.92 (dd, 1H, *J* = 8.0 and 0.8 Hz), 7.23 (td, 1H, *J* = 7.6 and 0.9 Hz), 7.53 (dd, 1H, *J* = 8.2 and 4.8 Hz), 7.59 (td, 1H, *J* = 7.8 and 1.4 Hz), 7.74 (ddd, 1H, *J* = 7.5, 1.2 and 0.5 Hz), 7.82 (ddd, 1H, *J* = 8.1, 2.5 and 1.5 Hz), 8.70-8.78 (m, 2H); ¹³C NMR (CDCl₃) δ 111.1 (CH), 117.8 (C), 124.6 (CH), 125.0 (CH), 126.2 (CH), 130.1 (C), 133.9 (CH), 138.7 (CH), 147.2 (CH), 149.9 (CH), 150.9 (C), 157.4 (C), 182.0 (C). Anal. Calcd for C₁₃H₈N₂O₂ (224.22): C, 69.64; H, 3.60; N, 12.49. Found: C, 69.71; H, 3.83; N, 12.55. **Crystal data for 3m.** C₁₃H₈N₂O₂, *M* = 224.21, *T* = 150 K, orthorhombic, *F* *d d* 2, *a* = 31.035(3), *b* = 34.022(3), *c* = 3.7555(4) Å, *V* = 3965.3(7) Å³, *Z* = 16, *d* = 1.502 g cm⁻³, *μ* = 0.104 mm⁻¹. A final refinement on *F*² with 2262 unique intensities and 154 parameters converged at ω*R*(*F*²) = 0.1168 (*R*(*F*) = 0.0463) for 2126 observed reflections with *I* > 2σ(*I*). CCDC 1811744.

5.3.13. 1,1'-(1,4-Phenylene)bis(isatin) (3o). The procedure was adapted from a reported protocol.^{8j} To *N,N'*-(1,4-phenylene)-2,2'-bis(2-aminoacetophenone) (**2o**, 1.0 g, 3.0 mmol) in DMSO (6 mL) was added I₂ (2.0 g, 7.8 mmol). The mixture was heated at 130 °C for 7 h. After cooling to room temperature, an aqueous saturated solution of Na₂S₂O₃ (10 mL) was added before filtration and washing using AcOEt (20 mL). Drying afforded **3o** in 56% yield (0.62 g) as a beige powder: mp > 260 °C; IR (ATR): 701, 754, 815, 823, 928, 1029, 1094, 1151, 1182, 1302, 1358, 1426, 1461, 1515, 1608, 1737, 3059, 3458 cm⁻¹; ¹H NMR ((CD₃)₂SO) δ 6.98 (d, 2H, *J* = 7.9 Hz), 7.23 (t, 2H, *J* = 7.5 Hz), 7.62-7.71 (m, 8H); ¹³C NMR ((CD₃)₂SO) δ 110.9 (2CH), 117.8 (2C), 123.8 (2CH), 124.7 (2CH), 127.7 (4CH), 133.0 (2C), 138.0 (2CH), 150.9 (2C), 157.5 (2C), 182.5 (2C). Anal. Calcd for C₂₂H₁₂N₂O₄ (368.35): C, 71.74; H, 3.28; N, 7.61. Found: C, 71.92; H, 3.41; N, 7.67.

5.4. *N*-arylation of 2-aminobenzophenone (**5**) or 2-amino-3-benzoylpyridine (**7**)

5.4.1. 2-Amino-3-benzoylpyridine (7) was synthesized from 2-fluoro-3-benzoylpyridine as described previously.⁵⁵ Yield: 88%. White powder: mp 145 °C (lit.⁵⁵ 147 °C); ¹H NMR (CDCl₃) δ 6.61 (dd, 1H, *J* = 7.8 and 4.8 Hz), 6.80 (br s, 2H), 7.45-7.63 (m, 5H), 7.78 (dd, 1H, *J* = 7.8 and 1.9 Hz), 8.25 (dd, 1H, *J* = 4.8 and 1.9 Hz); ¹³C NMR (CDCl₃) δ 112.2 (CH), 113.2 (C), 128.5 (2CH), 129.2 (2CH), 131.7 (CH), 139.2 (C), 143.3 (CH), 153.5 (CH), 159.7 (C), 197.8 (C).

5.4.2. General procedure 4: The *N*-arylated substrates were prepared by slightly modifying a literature procedure.^{8b} To the required iodide (9.0 mmol) in Bu₂O (3 mL) were successively added activated Cu³⁴ (76 mg, 1.2 mmol), the aminoketone (6.0 mmol) and K₂CO₃ (1.7 g, 12 mmol). The mixture was degassed and refluxed under argon (the reaction time is given in the product description). After cooling to room temperature, the mixture was concentrated. Addition of H₂O (25 mL), extraction with AcOEt (3x10 mL), drying over Na₂SO₄, removal of the solvent and purification by chromatography on silica gel (the eluent is given in the product description) led to the expected compound.

5.4.3. 2-(4-Aminophenylamino)benzophenone (9e). The general procedure 4 (reaction time: 24 h) using 4-iodoaniline (2.0 g) and 2-aminobenzophenone (**5**, 1.1 g) gave **9e** (eluent: heptane-AcOEt 80:20) in 42% yield (0.73 g) as an orange oil: IR (ATR): 700, 730, 748, 819, 845, 925, 939, 1109, 1154, 1252, 1325, 1410, 1446, 1514, 1567, 1616, 2923, 3031, 3356 cm⁻¹; ¹H NMR (CDCl₃) δ 3.4-4.4 (br s, 2H), 6.59 (t, 1H, *J* = 7.5 Hz), 6.75 (d, 2H, *J* = 8.6 Hz), 7.06 (d, 1H, *J* = 8.6 Hz), 7.11 (d, 2H, *J* = 8.5 Hz), 7.26-7.29 (m, 1H), 7.45-7.55 (m, 4H), 7.66-7.68 (m, 2H), 10.02 (br s, 1H); ¹³C NMR (CDCl₃) δ 114.0 (CH), 115.3 (CH), 116.5 (2CH), 118.3 (C), 126.1 (2CH), 128.2 (2CH), 129.3 (2CH), 131.1 (CH), 131.8 (C), 134.6 (CH), 135.3 (CH), 140.4 (C), 142.9 (C), 150.5 (C), 199.3 (C). Anal. Calcd for C₁₉H₁₆N₂O (288.35): C, 79.14; H, 5.59; N, 9.72. Found: C, 79.25; H, 5.70; N, 9.89.

5.4.4. 2-(4-Bromophenylamino)benzophenone (9i). The general procedure 4 (reaction time: 24 h) using 1-bromo-4-iodobenzene (2.5 g) and 2-aminobenzophenone (**5**, 1.1 g) gave **9i** (eluent: heptane-AcOEt 80:20) in 74% yield (1.6 g) as a yellow oil: ¹H NMR (CDCl₃) δ 6.85 (ddd, 1H, *J* = 8.1, 7.1 and

1.2 Hz), 7.33 (d, 2H, $J = 8.5$ Hz), 7.42 (ddd, 1H, $J = 8.5$, 7.1 and 1.6 Hz), 7.44-7.59 (m, 7H), 7.72-7.75 (m, 2H); ^{13}C NMR (CDCl_3) δ 114.9 (CH), 115.8 (C), 117.3 (CH), 120.4 (C), 123.5 (2CH), 128.3 (2CH), 129.6 (2CH), 131.7 (CH), 132.5 (2CH), 134.4 (CH), 135.1 (CH), 139.7 (C), 140.0 (C), 147.4 (C), 199.3 (C). The spectral data are similar to those reported previously.⁵⁶

5.4.5. 2-(4-(Trifluoromethyl)phenylamino)benzophenone (9j).⁵⁷ The general procedure 4 (reaction time: 24 h) using 1-iodo-4-(trifluoromethyl)benzene (2.4 g) and 2-aminobenzophenone (**5**, 1.1 g) gave **9j** (eluent: heptane-AcOEt 90:10) in 81% yield (1.7 g) as a yellow powder: mp 74 °C; IR (ATR): 699, 745, 760, 827, 840, 926, 939, 1011, 1065, 1106, 1157, 1256, 1316, 1449, 1525, 1572, 1591, 1617, 3067, 3302 cm^{-1} ; ^1H NMR (CDCl_3) δ 6.88 (ddd, 1H, $J = 8.1$, 7.1 and 1.1 Hz), 7.36 (d, 2H, $J = 8.5$ Hz), 7.45 (ddd, 1H, $J = 8.5$, 7.2 and 1.5 Hz), 7.50-7.55 (m, 3H), 7.58-7.62 (m, 4H), 7.75-7.77 (m, 2H), 10.09 (br s, 1H); ^{13}C NMR (CDCl_3) δ 116.1 (CH), 118.6 (CH), 119.7 (2CH), 121.9 (C), 124.2 (q, C, $J = 32.8$ Hz), 124.5 (q, C, $J = 272$ Hz), 126.8 (q, 2CH, $J = 3.8$ Hz), 128.4 (2CH), 129.8 (2CH), 132.1 (CH), 134.2 (CH), 134.9 (CH), 139.3 (C), 144.4 (C), 145.8 (C), 199.2 (C).

5.4.6. 2-(2-Thienylamino)benzophenone (9k). The general procedure 4 (reaction time: 24 h) using 2-iodothiophene (0.99 mL) and 2-aminobenzophenone (**5**, 1.1 g) gave **9k** (eluent: heptane) in 50% yield (0.84 g) as a brown oil: R_f (heptane-AcOEt 80:20) 0.31; IR (ATR): 682, 697, 748, 923, 937, 1154, 1179, 1224, 1251, 1310, 1324, 1442, 1495, 1542, 1574, 1599, 1616, 1738, 3061, 3252 cm^{-1} ; ^1H NMR (CDCl_3) δ 6.71 (ddd, 1H, $J = 8.1$, 7.1 and 1.1 Hz), 6.87 (dt, 1H, $J = 3.6$ and 1.2 Hz), 6.96 (dd, 1H, $J = 5.6$ and 3.6 Hz), 7.07 (dd, 1H, $J = 5.6$ and 1.3 Hz), 7.17 (dd, 1H, $J = 8.6$ and 1.1 Hz), 7.33-7.40 (m, 1H), 7.45-7.59 (m, 4H), 7.66-7.70 (m, 2H), 10.1 (br s, 1H); ^{13}C NMR (CDCl_3) δ 114.4 (CH), 116.7 (CH), 118.7 (C), 121.2 (CH), 121.6 (CH), 126.1 (CH), 128.3 (2CH), 129.4 (2CH), 131.4 (CH), 134.9 (CH), 135.0 (CH), 140.0 (C), 143.5 (C), 150.3 (C), 199.6 (C). Anal. Calcd for $\text{C}_{17}\text{H}_{13}\text{NOS}$ (279.36): C, 73.09; H, 4.69; N, 5.01; S, 11.48. Found: C, 73.23; H, 4.81; N, 4.77; S, 11.34.

5.4.7. 2-(Ferrocenylamino)benzophenone (9l). The general procedure 4 (reaction time: 24 h) using iodoferrocene (2.8 g) and 2-aminobenzophenone (**5**, 1.1 g) gave **9l** (eluent: heptane- CH_2Cl_2 80:20) in

85% yield (1.9 g) as a sticky red oil; Rf (heptane-AcOEt 80:20) 0.71; IR (ATR): 698, 731, 748, 804, 821, 919, 932, 1000, 1105, 1152, 1249, 1322, 1452, 1509, 1570, 1599, 1615, 1738, 3083, 3275 cm^{-1} ; ^1H NMR (CDCl_3) δ 4.14-4.57 (m, 9H), 6.55 (t, 1H, $J = 7.0$ Hz), 7.07 (br s, 1H), 7.34 (t, 1H, $J = 6.7$ Hz), 7.45-7.57 (m, 4H), 7.62-7.70 (m, 2H), 9.64 (br s, 1H); ^{13}C NMR (CDCl_3) δ 65.1 (2CH), 65.6 (2CH), 69.5 (5CH), 96.1 (C), 114.2 (CH), 115.2 (CH), 117.8 (C), 128.2 (2CH), 129.2 (2CH), 131.1 (CH), 134.6 (CH), 135.2 (CH), 140.4 (C), 151.2 (C), 199.6 (C). Anal. Calcd for $\text{C}_{23}\text{H}_{19}\text{FeNO}$ (381.26): C, 72.46; H, 5.02; N, 3.67. Found: C, 72.52; H, 5.30; N, 3.59.

5.4.8. *N*-Ferrocenyl-2-amino-3-benzoylpyridine (10l). The general procedure 4 (reaction time: 5 h) using 2-amino-3-benzoylpyridine (**7**, 1.2 g) and iodoferrocene (2.8 g) gave **10l** (eluent: heptane-AcOEt 70:30) in 82% yield (1.9 g) as an orange powder: mp 170 $^\circ\text{C}$; Rf (heptane-AcOEt 80:20) 0.50; IR (ATR): 697, 713, 764, 802, 821, 924, 1005, 1076, 1104, 1245, 1300, 1396, 1516, 1586, 1617, 3095, 3269 cm^{-1} ; ^1H NMR (CDCl_3) δ 4.12 (s, 2H), 4.21 (s, 5H), 4.76 (s, 2H), 6.59 (dd, 1H, $J = 7.8$ and 4.6 Hz), 7.47-7.65 (m, 5H), 7.80 (dd, 1H, $J = 7.8$ and 1.9 Hz), 8.39 (dd, 1H, $J = 4.7$ and 1.9 Hz), 10.13 (br s, 1H); ^{13}C NMR (CDCl_3) δ 64.0 (2CH), 65.1 (2CH), 69.4 (5CH), 95.4 (C), 111.6 (CH), 112.9 (C), 128.5 (2CH), 129.2 (2CH), 131.6 (CH), 139.4 (C), 143.4 (CH), 154.4 (CH), 157.9 (C), 198.4 (C). Anal. Calcd for $\text{C}_{22}\text{H}_{18}\text{FeN}_2\text{O}$ (382.24): C, 69.13; H, 4.75; N, 7.33. Found: C, 69.24; H, 4.96; N, 7.51.

Crystal data for 10l. $\text{C}_{22}\text{H}_{18}\text{FeN}_2\text{O}$, $M = 382.23$, $T = 150$ K, triclinic, $P -1$, $a = 7.9601(9)$, $b = 8.0753(9)$, $c = 14.2210(16)$ \AA , $\alpha = 75.571(4)$, $\beta = 87.859(4)$, $\gamma = 72.932(4)$ $^\circ$, $V = 845.67(17)$ \AA^3 , $Z = 2$, $d = 1.501$ g cm^{-3} , $\mu = 0.905$ mm^{-1} . A final refinement on F^2 with 3892 unique intensities and 238 parameters converged at $\omega R(F^2) = 0.0894$ ($R(F) = 0.0332$) for 3657 observed reflections with $I > 2\sigma(I)$. CCDC 1811746.

5.4.9. 2-(3-Pyridylamino)benzophenone (9m). The general procedure 4 (reaction time: 24 h) using 3-iodopyridine (1.8 g) and 2-aminobenzophenone (**5**, 1.1 g) gave **9m** (eluent: heptane-AcOEt 70:30) in 88% yield (1.4 g) as a yellow oil: Rf (heptane-AcOEt 80:20) 0.08; IR (ATR): 698, 748, 926, 938, 1156, 1249, 1315, 1448, 1509, 1576, 1625, 3029, 3056, 3264 cm^{-1} ; ^1H NMR (CDCl_3) δ 6.79 (ddd, 1H, $J =$

8.1, 6.9 and 1.2 Hz), 7.31 (br s, 1H), 7.33 (d, 1H, $J = 7.7$ Hz), 7.38 (td, 1H, $J = 7.7, 7.0$ and 1.5 Hz), 7.46-7.50 (m, 2H), 7.54-7.58 (m, 2H), 7.61 (d, 1H, $J = 8.1$ Hz), 7.70-7.73 (m, 2H), 8.39 (br s, 1H), 8.68 (br s, 1H), 10.1 (br s, 1H); ^{13}C NMR (CDCl_3) δ 114.6 (CH), 117.9 (CH), 120.8 (C), 124.2 (CH), 128.3 (2CH), 128.5 (C), 129.6 (2CH), 131.8 (CH), 134.4 (CH), 135.1 (CH), 137.7 (CH), 139.5 (C), 144.0 (CH), 144.4 (CH), 147.1 (C), 199.4 (C). Anal. Calcd for $\text{C}_{18}\text{H}_{14}\text{N}_2\text{O}$ (274.32): C, 78.81; H, 5.14; N, 10.21. Found: C, 79.05; H, 5.33; N, 10.28.

5.5. *N*-arylation-cyclization of 2-ketoanilines

5.5.1. General procedure 5: To the required aniline (1.5 mmol) and iodide (the amount is given in the product description) in Bu_2O (2 mL) were successively added activated Cu^{34} (19 mg, 0.30 mmol) and K_2CO_3 (0.43 g, 3.0 mmol). The mixture was degassed and refluxed under argon (the reaction time is given in the product description). After cooling to room temperature, the expected compound was isolated as described in the product description.

5.5.2. 11-Methyl[1]benzothieno[2,3-*b*]quinoline (4p). The general procedure 5 (reaction time: 24 h) using 2-iodobenzothiophene (2.2 mmol, 0.57 g) and 2-aminoacetophenone (0.18 g) gave **4p** after filtration of the precipitate, washing with water (10 mL) and heptane (10 mL), dissolution in CH_2Cl_2 (20 mL), filtration to remove copper and evaporation of the solvent. The product was isolated in 46% yield (0.17 g) as a beige powder: mp 172 °C; Rf (heptane-AcOEt 80:20) 0.45; IR (ATR): 702, 728, 751, 823, 855, 928, 1071, 1110, 1165, 1183, 1302, 1359, 1425, 1461, 1515, 1575, 1608, 1737, 3060 cm^{-1} ; ^1H NMR (CDCl_3) δ 3.19 (s, 3H), 7.46-7.53 (m, 2H), 7.57 (ddd, 1H, $J = 8.3, 7.7$ and 1.3 Hz), 7.74 (ddd, 1H, $J = 8.3, 7.6$ and 1.3 Hz), 7.83-7.88 (m, 1H), 8.12 (dd, 1H, $J = 8.5$ and 0.7 Hz), 8.27 (dd, 1H, $J = 8.6$ and 0.8 Hz), 8.34-8.39 (m, 1H); ^{13}C NMR (CDCl_3) δ 16.0 (CH_3), 123.3 (CH), 124.2 (CH), 125.0 (CH), 125.4 (CH), 125.6 (C), 126.1 (CH), 126.8 (C), 127.5 (CH), 128.8 (CH), 129.5 (CH), 134.1 (C), 138.6 (C), 140.4 (C), 147.0 (C), 163.0 (C). Anal. Calcd for $\text{C}_{16}\text{H}_{11}\text{NS}$ (249.32): C, 77.08; H, 4.45; N, 5.62; S, 12.86. Found: C, 77.13; H, 4.56; N, 5.64; S, 12.75. **Crystal data for 4p.** $\text{C}_{16}\text{H}_{11}\text{NS}$, $M = 249.32$, $T = 150$ K, monoclinic, $P 2_1/n$, $a = 15.5283(13)$, $b = 9.1423(6)$, $c = 17.4157(15)$ Å, $\beta = 106.444(2)$ °, $V =$

2371.3(3) Å³, $Z = 8$, $d = 1.397 \text{ g cm}^{-3}$, $\mu = 0.250 \text{ mm}^{-1}$. A final refinement on F^2 with 5353 unique intensities and 357 parameters converged at $\omega R(F^2) = 0.1896$ ($R(F) = 0.0806$) for 3124 observed reflections with $I > 2\sigma(I)$. CCDC 1811748.

5.5.3. 11-Phenyl[1]benzothieno[2,3-*b*]quinoline (6p). The general procedure 5 (reaction time: 24 h) using 2-iodobenzothiophene (2.2 mmol, 0.57 g) and 2-aminobenzophenone (**5**, 0.27 g) gave **6p** after filtration over celite[®] using AcOEt (20 mL), removal of the solvent and purification by chromatography on silica gel (eluent: heptane). The product was isolated in 64% yield (0.30 g) as a yellow powder: mp 179 °C (lit.^{36a} 175-177 °C); ¹H NMR (CDCl₃) δ 6.79 (dd, 1H, $J = 8.2$ and 0.5 Hz), 7.09 (ddd, 1H, $J = 8.3$, 7.3 and 1.2 Hz), 7.37-7.48 (m, 4H), 7.62 (ddd, 1H, $J = 8.5$, 1.4 and 0.5 Hz), 7.64-7.71 (m, 3H), 7.77 (ddd, 1H, $J = 8.4$, 6.7 and 1.5 Hz), 7.81 (ddd, 1H, $J = 8.0$, 1.0 and 0.6 Hz), 8.19 (ddd, 1H, $J = 8.5$, 1.1 and 0.6 Hz); ¹³C NMR (CDCl₃) δ 123.0 (CH), 124.7 (CH), 125.5 (CH), 125.6 (CH), 125.7 (C), 126.0 (C), 126.7 (CH), 127.9 (CH), 128.2 (CH), 129.0 (CH), 129.1 (2CH), 129.6 (2CH), 129.7 (CH), 133.2 (C), 136.5 (C), 138.7 (C), 143.9 (C), 147.3 (C), 163.3 (C). The spectral data are analogous to those described previously.^{36a}

5.5.4. 5-Phenylbenzothieno[2,3-*b*][1,8]naphthyridine (8p). The general procedure 5 (reaction time: 24 h) using 2-iodobenzothiophene (1.2 mmol, 0.31 g) and 2-amino-3-benzoylpyridine (**7**, 0.30 g) gave, after removal of the solvent and purification by chromatography on silica gel (eluent: heptane-AcOEt 70:30), **8p** in 63% yield (0.24 g) as a beige powder: mp 252 °C; R_f (AcOEt) 0.53; IR (ATR): 702, 723, 742, 761, 781, 820, 882, 1018, 1054, 1100, 1147, 1183, 1312, 1367, 1381, 1454, 1581, 1592, 3049 cm⁻¹; ¹H NMR (CDCl₃) δ 6.85 (d, 1H, $J = 7.9$ Hz), 7.12 (ddd, 1H, $J = 8.3$, 7.3 and 1.2 Hz), 7.41-7.47 (m, 3H), 7.66-7.71 (m, 3H), 7.84 (d, 1H, $J = 8.1$ Hz), 8.04 (d, 1H, $J = 7.4$ Hz); ¹³C NMR (CDCl₃) δ 123.1 (CH), 124.9 (CH), 125.5 (CH), 126.9 (C), 128.4 (CH), 129.1 (2CH), 129.4 (CH), 129.7 (2CH), 132.4 (C), 135.3 (C), 135.9 (CH), 139.0 (C), 144.5 (C), 153.4 (C), 154.2 (C), 166.5 (C), 2CH not seen. Anal. Calcd for C₂₀H₁₂N₂S (312.39): C, 76.90; H, 3.87; N, 8.97; S, 10.26. Found: C, 77.06; H, 4.01; N, 9.05; S, 10.29.

5.5.5. 11-Methyl[1]benzofuro[2,3-*b*]quinoline (4q). The general procedure 5 (reaction time: 24 h) using 2-iodobenzofuran (2.2 mmol, 0.54 g) and 2-aminoacetophenone (0.18 g) gave **4q** after filtration of the precipitate, washing with water (10 mL) and heptane (10 mL), dissolution in CH₂Cl₂ (20 mL), filtration to remove copper and evaporation of the solvent. The product was isolated in 57% yield (0.20 g) as a beige powder: mp 187 °C (lit.^{37a} 189-190.5 °C); IR (ATR): 719, 744, 757, 853, 1021, 1102, 1191, 1208, 1310, 1386, 1456, 1463, 1513, 1592, 1607, 1738, 3060 cm⁻¹; ¹H NMR (CDCl₃) 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); ¹³C NMR (CDCl₃) δ 15.3 (CH₃), 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).

5.5.6. 11-Phenyl[1]benzofuro[2,3-*b*]quinoline (6q). The general procedure 5 (reaction time: 24 h) using 2-iodobenzofuran (2.2 mmol, 0.54 g) and 2-aminobenzophenone (**5**, 0.27 g) gave **6q** after filtration over celite[®] using AcOEt (20 mL), removal of the solvent and purification by chromatography on silica gel (eluent: heptane-CH₂Cl₂-AcOEt 80:15:5). The product was isolated in 85% yield (0.38 g) as a pale pink powder: mp 208 °C (lit.^{37d} 204-206 °C); ¹H NMR (CDCl₃) δ 7.06-7.11 (m, 1H), 7.12 (td, 1H, *J* = 7.8 and 1.0 Hz), 7.44-7.51 (m, 2H), 7.54-7.57 (m, 2H), 7.61 (d, 1H, *J* = 8.2 Hz), 7.63-7.71 (m, 3H), 7.74-7.82 (m, 2H), 8.21 (dd, 1H, *J* = 8.4 and 0.5 Hz); ¹³C NMR (CDCl₃) 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).

Crystal data for 6q. C₂₁H₁₃NO, *M* = 295.32, *T* = 150 K, triclinic, *P* -1, *a* = 6.9518(5), *b* = 10.5357(8), *c* = 10.7838(9) Å, α = 113.375(3), β = 95.636(3), γ = 94.534(3)°, *V* = 715.45(10) Å³, *Z* = 2, *d* = 1.371 g cm⁻³, μ = 0.084 mm⁻¹. A final refinement on *F*² with 3245 unique intensities and 218 parameters converged at ω*R*(*F*²) = 0.1585 (*R*(*F*) = 0.0681) for 2802 observed reflections with *I* > 2σ(*I*). CCDC 1811745.

5.5.7. 5-Phenylbenzofuro[2,3-*b*][1,8]naphthyridine (8q). The general procedure 5 (reaction time: 6 h) using 2-iodobenzofuran (1.2 mmol, 0.29 g) and 2-amino-3-benzoylpyridine (**7**, 0.30 g) gave, after removal of the solvent and purification by chromatography on silica gel (eluent: heptane-AcOEt 70:30), **8q** in 70% yield (0.25 g) as a beige powder: mp 261 °C; Rf (AcOEt) 0.53; IR (ATR): 702, 723, 742, 761, 781, 820, 1054, 1100, 1147, 1183, 1215, 1312, 1367, 1381, 1454, 1581, 1592, 3049 cm⁻¹; ¹H NMR (CD₃OD) δ 7.12-7.22 (m, 2H), 7.52-7.66 (m, 5H), 7.66-7.78 (m, 3H), 8.29 (d, 1H, *J* = 8.3 Hz), 9.05 (br s, 1H); ¹³C NMR ((CD₃)₂CO/CDCl₃) δ 112.7 (CH), 116.9 (C), 121.8 (CH), 122.7 (C), 123.7 (CH), 124.5 (CH), 129.2 (C), 130.2 (2CH), 130.2 (2CH), 130.3 (CH), 130.7 (CH), 135.3 (C), 136.1 (CH), 145.7 (C), 153.9 (CH), 155.1 (C), 156.9 (C), 164.7 (C). Anal. Calcd for C₂₀H₁₂N₂O (296.33): C, 81.07; H, 4.08; N, 9.45. Found: C, 81.13; H, 4.35; N, 9.32.

5.5.8. 4-Phenylfuro[2,3-*b*]quinoline (6r).⁵⁸ The general procedure 5 (reaction time: 24 h) using 2-iodofuran (2.2 mmol, 0.43 g) and 2-aminobenzophenone (**5**, 0.27 g) gave **6r** after filtration over celite[®] using AcOEt (20 mL), removal of the solvent and purification by chromatography on silica gel (eluent: heptane-AcOEt 50:50). The product was isolated in 61% yield (0.22 g) as a beige powder: mp 118 °C; ¹H NMR (CDCl₃) δ 6.74 (dd, 1H, *J* = 2.7 and 0.4 Hz), 7.43-7.65 (m, 6H), 7.73 (ddd, 1H, *J* = 8.4, 6.8 and 1.5 Hz), 7.78 (d, 1H, *J* = 2.7 Hz), 7.97 (ddd, 1H, *J* = 8.5, 1.4 and 0.6 Hz), 8.19 (ddd, 1H, *J* = 8.5, 1.3 and 0.6 Hz); ¹³C NMR (CDCl₃) δ 121.4 (CH), 124.1 (C), 125.5 (CH), 126.6 (CH), 128.1 (CH), 128.7 (CH), 128.7 (2CH), 128.8 (CH), 129.2 (CH), 130.2 (2CH), 130.5 (C), 136.3 (C), 143.0 (C), 147.1 (C), 163.1 (C).

5.6. Cyclization of the *N*-arylated 2-ketoanilines

5.6.1. General procedure 6: The cyclized products were prepared by adapting a literature procedure.³⁸ To the required *N*-arylated 2-ketoaniline (1.0 mmol) in CH₃CO₂H (3 mL) was added 96% H₂SO₄ (2.8 mmol, 0.15 mL). The mixture was stirred at 110 °C. The reaction time is given in the product description. After cooling to room temperature, water (5 mL) was added and the mixture was basified using 25% NH₄OH. Extraction using AcOEt (3x20 mL), removal of the solvent and

purification by chromatography on silica gel (the eluent is given in the product description) led to the expected compound.

5.6.2. 2-Amino-9-phenylacridine (6e).⁵⁹ The general procedure 6 (reaction time: 15 min) using 2-(4-aminophenylamino)benzophenone (**7e**, 0.29 g) gave **6e** (eluent: heptane-AcOEt 50:50) in 59% yield (0.16 g) as an orange powder: mp 84 °C; Rf (AcOEt) 0.62; IR (ATR): 700, 729, 752, 826, 907, 1029, 1072, 1140, 1171, 1242, 1294, 1363, 1418, 1448, 1483, 1559, 1608, 1636, 3191, 3327 cm⁻¹; ¹H NMR (CDCl₃) δ 3.93 (br s, 2H), 6.67 (d, 1H, *J* = 2.5 Hz), 7.29 (dd, 1H, *J* = 9.2 and 2.5 Hz), 7.35 (ddd, 1H, *J* = 8.7, 6.5 and 1.2 Hz), 7.42 (d, 2H, *J* = 6.8 Hz), 7.55-7.61 (m, 4H), 7.64 (ddd, 1H, *J* = 8.7, 6.5 and 1.4 Hz), 8.12 (d, 1H, *J* = 9.2 Hz), 8.19 (d, 1H, *J* = 8.7 Hz); ¹³C NMR (CDCl₃) δ 104.2 (CH), 124.6 (CH), 125.7 (CH), 125.8 (C), 126.3 (CH), 126.8 (C), 128.2 (CH), 128.4 (CH), 128.6 (2CH), 129.7 (CH), 130.6 (2CH), 131.1 (CH), 136.8 (C), 143.1 (C), 143.6 (C), 145.4 (C), 146.7 (C).

5.6.3. 2-Amino-9-methylacridine (4e). The general procedure 6 (reaction time: 10 min) using 2-(4-aminophenylamino)acetophenone (**2e**, 0.23 g) gave **4e** (eluent: heptane-AcOEt 50:50) in 94% yield (0.20 g) as an orange powder: mp 218 °C (lit.⁶⁰ 210-211 °C); Rf (AcOEt) 0.45; ¹H NMR (CDCl₃) δ 2.98 (s, 3H), 4.07 (br s, 2H), 7.23-7.31 (m, 2H), 7.50 (t, 1H, *J* = 7.7 Hz), 7.65 (t, 1H, *J* = 7.6 Hz), 8.08 (d, 1H, *J* = 9.1 Hz), 8.16 (dd, 2H, *J* = 8.7 and 4.2 Hz); ¹³C NMR (CDCl₃) δ 13.7 (CH₃), 102.6 (CH), 124.2 (CH), 124.4 (CH), 125.5 (CH), 126.1 (C), 127.1 (C), 128.3 (CH), 130.2 (CH), 131.6 (CH), 138.1 (C), 143.5 (C), 144.8 (C), 146.4 (C).

5.6.4. 2-Chloro-9-methylacridine (4h). The general procedure 6 (reaction time: 10 min) using 2-(4-chlorophenylamino)acetophenone (**2h**, 0.25 g) gave **4h** (eluent: heptane-AcOEt 80:20; Rf 0.32) in 92% yield (0.21 g) as a pale yellow powder: mp 126 °C (lit.⁶¹ 124-125 °C); ¹H NMR (CDCl₃) δ 3.08 (s, 3H), 7.58 (ddd, 1H, *J* = 8.8, 6.6 and 1.3 Hz), 7.68 (dd, 1H, *J* = 9.2 and 2.3 Hz), 7.78 (ddd, 1H, *J* = 8.8, 6.6 and 1.4 Hz), 8.16 (dd, 1H, *J* = 9.3 and 0.5 Hz), 8.18-8.25 (s, 3H); ¹³C NMR (CDCl₃) δ 13.9 (CH₃), 123.3 (CH), 124.6 (CH), 125.9 (C), 126.0 (C), 126.2 (CH), 130.2 (CH), 130.4 (CH), 131.1 (CH), 131.5 (C), 132.1 (CH), 141.6 (C), 146.8 (C), 148.6 (C).

5.6.5. 9-Phenyl-2-bromoacridine (6i). The general procedure 6 (reaction time: 15 min) using 2-(4-bromophenylamino)benzophenone (**7i**, 0.35 g) gave **6i** (eluent: heptane-AcOEt 90:10) in 46% yield (0.15 g) as a yellow powder: mp 129 °C; Rf (heptane-AcOEt 80:20) 0.41; IR (ATR): 670, 701, 749, 788, 818, 860, 934, 950, 1000, 1012, 1056, 1143, 1269, 1331, 1411, 1428, 1453, 1469, 1494, 1537, 3060 cm⁻¹; ¹H NMR (CDCl₃) δ 7.42-7.46 (m, 3H), 7.61-7.65 (m, 3H), 7.69 (d, 1H, *J* = 8.7 Hz), 7.78-7.82 (m, 2H), 7.85 (d, 1H, *J* = 1.1 Hz), 8.15 (d, 1H, *J* = 9.3 Hz), 8.26 (d, 1H, *J* = 8.6 Hz); ¹³C NMR (CDCl₃) δ 120.0 (C), 125.6 (C), 126.2 (CH), 126.4 (CH), 127.0 (CH), 128.7 (CH), 128.8 (2CH), 129.9 (CH), 130.5 (CH), 130.5 (2CH), 131.6 (CH), 133.7 (CH), 135.4 (C), 146.5 (C), 147.3 (C), 149.1 (C), 1C not seen. Anal. Calcd for C₁₉H₁₂BrN (334.22): C, 68.28; H, 3.62; N, 4.19. Found: C, 68.44; H, 3.70; N, 4.11.

5.6.6. 2-Bromo-9-methylacridine (4i). The general procedure 6 (reaction time: 10 min) using 2-(4-bromophenylamino)acetophenone (**2i**, 0.29 g) gave **4i** (eluent: heptane-AcOEt 80:20; Rf 0.36) in 95% yield (0.26 g) as a yellow powder: mp 121 °C; IR (ATR): 663, 710, 746, 822, 850, 911, 1048, 1150, 1324, 1373, 1413, 1516, 1554, 1602, 1623, 3050 cm⁻¹; ¹H NMR (CDCl₃) δ 3.05 (s, 3H), 7.57 (ddd, 1H, *J* = 8.9, 6.5 and 1.3 Hz), 7.76-7.80 (m, 2H), 8.07 (d, 1H, *J* = 9.2 Hz), 8.18 (dt, 1H, *J* = 8.8 and 0.9 Hz), 8.22 (dt, 1H, *J* = 8.8 and 1.0 Hz), 8.39 (d, 1H, *J* = 2.1 Hz); ¹³C NMR (CDCl₃) δ 13.9 (CH₃), 119.8 (C), 124.6 (CH), 125.8 (C), 126.2 (CH), 126.6 (C), 126.8 (CH), 130.3 (CH), 130.5 (CH), 132.1 (CH), 133.4 (CH), 141.5 (C), 146.9 (C), 148.7 (C). The spectral data are analogous to those reported previously.⁶²

5.6.7. 9-Phenyl-2-(trifluoromethyl)acridine (6j). The general procedure 6 (reaction time: 10 min) using 2-(4-(trifluoromethyl)phenylamino)benzophenone (**7j**, 0.34 g) gave **6j** (eluent: heptane-AcOEt 90:10) in 96% yield (0.31 g) as a pale yellow powder: mp 158 °C; Rf (heptane-AcOEt 80:20) 0.38; IR (ATR): 668, 706, 753, 829, 963, 1059, 1115, 1140, 1168, 1179, 1260, 1285, 1308, 1421, 1616, 1641, 3048 cm⁻¹; ¹H NMR (CDCl₃) δ 7.43-7.52 (m, 3H), 7.62-7.67 (m, 3H), 7.74 (ddd, 1H, *J* = 8.8, 1.5 and 0.8 Hz), 7.85 (ddd, 1H, *J* = 8.8, 6.5 and 1.4 Hz), 7.90 (dd, 1H, *J* = 9.1 and 2.0 Hz), 8.03 (pent, 1H, *J* = 1.1 Hz), 8.31 (dt, 1H, *J* = 8.8 and 1.0 Hz), 8.39 (dt, 1H, *J* = 9.2 and 0.9 Hz); ¹³C NMR (CDCl₃) δ 123.8

(C), 124.2 (q, C, $J = 271$ Hz), 125.2 (q, CH, $J = 2.8$ Hz), 125.4 (q, CH, $J = 4.9$ Hz), 125.7 (C), 126.6 (CH), 127.2 (CH), 127.4 (q, C, $J = 32.2$ Hz), 128.8 (2CH), 129.1 (CH), 129.9 (CH), 130.5 (2CH), 131.3 (CH), 131.3 (CH), 135.0 (C), 149.1 (C), 149.2 (C), 150.2 (C). Anal. Calcd for $C_{20}H_{12}F_3N$ (323.32): C, 74.30; H, 3.74; N, 4.33. Found: C, 74.38; H, 3.87; N, 4.40.

5.6.8. 9-Methyl-2-(trifluoromethyl)acridine (4j).⁶² The general procedure 6 (reaction time: 30 min) using 2-(4-(trifluoromethyl)phenylamino)acetophenone (**2j**, 0.28 g) gave **4j** (eluent: heptane-AcOEt 80:20; Rf 0.36) in 98% yield (0.26 g) as an orange powder: mp 152 °C; 1H NMR ($CDCl_3$) δ 3.19 (s, 3H), 7.63 (ddd, 1H, $J = 8.9, 6.6$ and 1.3 Hz), 7.85 (ddd, 1H, $J = 8.0, 6.6$ and 1.4 Hz), 7.90 (dd, 1H, $J = 9.4$ and 2.2 Hz), 8.23-8.32 (m, 2H), 8.34 (d, 1H, $J = 9.1$ Hz), 8.59 (ddd, 1H, $J = 2.0, 1.3$ and 0.7 Hz); ^{13}C NMR ($CDCl_3$) δ 14.0 (CH_3), 123.2 (q, CH, $J = 4.9$ Hz), 124.1 (C), 124.4 (q, C, $J = 271$ Hz), 124.8 (CH), 125.0 (q, CH, $J = 3.0$ Hz), 126.0 (C), 126.4 (CH), 127.2 (q, C, $J = 32.1$ Hz), 130.4 (CH), 131.2 (CH), 131.7 (CH), 144.6 (C), 148.6 (C), 149.6 (C). **Crystal data for 4j.** $C_{15}H_{10}F_3N$, $M = 261.24$, $T = 150$ K, monoclinic, $P 2_1/n$, $a = 12.813(3)$, $b = 6.7599(15)$, $c = 14.414(3)$ Å, $\beta = 109.355(7)$ °, $V = 1177.9(4)$ Å³, $Z = 4$, $d = 1.473$ g cm⁻³, $\mu = 0.120$ mm⁻¹. A final refinement on F^2 with 2699 unique intensities and 173 parameters converged at $\omega R(F^2) = 0.1675$ ($R(F) = 0.0655$) for 1457 observed reflections with $I > 2\sigma(I)$. CCDC 1811747.

5.6.9. 4-Phenylthieno[2,3-*b*]quinoline (6k). The general procedure 6 (reaction time: 30 min) using 2-(2-thienylamino)benzophenone (**7k**, 0.28 g) gave **6k** (eluent: AcOEt) in 80% yield (0.21 g) as a beige powder: mp 118 °C (lit.⁶³ 119-120 °C); 1H NMR ($CDCl_3$) δ 7.11 (d, 1H, $J = 6.3$ Hz), 7.44-7.62 (m, 7H), 7.74 (ddd, 1H, $J = 7.7, 6.7$ and 1.4 Hz), 7.86 (ddd, 1H, $J = 8.6, 1.5$ and 0.7 Hz), 8.21 (ddd, 1H, $J = 8.6, 1.5$ and 0.7 Hz); ^{13}C NMR ($CDCl_3$) δ 121.4 (CH), 124.1 (C), 125.5 (CH), 126.5 (CH), 128.1 (CH), 128.6 (CH), 128.7 (2CH), 128.8 (CH), 129.2 (CH), 130.2 (2CH), 130.4 (C), 136.3 (C), 143.0 (C), 147.0 (C), 163.1 (C).

5.6.10. 4-Methylthieno[2,3-*b*]quinoline (4k). The general procedure 6 (reaction time: 10 min) using 2-(2-thienylamino)acetophenone (**2k**, 0.22 g) gave **4k** (eluent: CH_2Cl_2) in 61% yield (0.12 g) as an

orange powder: mp 89 °C (lit.⁶³ 91-92 °C); ¹H NMR (CDCl₃) δ 3.00 (s, 3H), 7.47 (d, 1H, *J* = 6.3 Hz), 7.55 (d, 1H, *J* = 6.3 Hz), 7.58 (ddd, 1H, *J* = 8.6, 6.7 and 1.2 Hz), 7.55 (d, 1H, *J* = 6.3 Hz), 8.13-8.19 (m, 2H); ¹³C NMR (CDCl₃) δ 15.5 (CH₃), 120.2 (CH), 124.3 (CH), 124.9 (C), 125.3 (CH), 127.5 (CH), 129.1 (CH), 129.2 (CH), 131.0 (C), 138.7 (C), 146.6 (C), 163.1 (C).

5.6.11. 10-Phenylbenzo[*b*]-1,5-naphthyridine (6m). The general procedure 6 (reaction time: 2 h) using 2-(3-pyridylamino)benzophenone (**7m**, 0.27 g) gave **6m** (eluent: heptane-AcOEt 70:30) in 54% yield (0.14 g) as a yellow powder: mp 121 °C; R_f (heptane-AcOEt 80:20) 0.08; IR (ATR): 700, 751, 762, 788, 937, 1023, 1073, 1107, 1128, 1156, 1254, 1317, 1422, 1452, 1468, 1509, 1578, 1626, 1731, 2851, 2922, 3061, 3288 cm⁻¹; ¹H NMR (CDCl₃) δ 7.50 (ddd, 1H, *J* = 8.8, 6.6 and 1.2 Hz), 7.52-7.64 (m, 5H), 7.67 (dd, 1H, *J* = 8.8 and 3.8 Hz), 7.83 (ddd, 1H, *J* = 8.8, 6.6 and 1.4 Hz), 7.89 (ddd, 1H, *J* = 8.8, 1.4 and 0.7 Hz), 8.30 (dt, 1H, *J* = 8.8 and 1.0 Hz), 8.57 (dd, 1H, *J* = 8.8 and 1.8 Hz), 9.04 (dd, 1H, *J* = 3.8 and 1.7 Hz); ¹³C NMR (CDCl₃) δ 124.6 (CH), 126.6 (CH), 127.4 (C), 127.5 (CH), 128.3 (2CH), 128.6 (CH), 129.8 (CH), 130.7 (CH), 131.1 (2CH), 135.3 (C), 137.5 (CH), 138.5 (C), 144.9 (C), 147.7 (C), 149.4 (C), 151.9 (CH). Anal. Calcd for C₁₈H₁₂N₂ (256.31): C, 84.35; H, 4.72; N, 10.93. Found: C, 84.49; H, 4.70; N, 11.07.

5.6.12. 10-Methylbenzo[*b*]-1,5-naphthyridine (4m). The general procedure 6 (reaction time: 30 min) using 2-(3-pyridylamino)acetophenone (**2m**, 0.21 g) gave **4m** (eluent: heptane-AcOEt 80:20; R_f 0.11) in 57% yield (0.11 g) as a yellow oil: IR (ATR): 710, 752, 785, 819, 858, 951, 1046, 1144, 1247, 1374, 1423, 1452, 1476, 1514, 1556, 1623, 1733, 2925, 3061 cm⁻¹; ¹H NMR (CDCl₃) δ 3.33 (s, 3H), 7.63 (ddd, 1H, *J* = 8.8, 6.6 and 1.3 Hz), 7.68 (dd, 1H, *J* = 8.8 and 3.8 Hz), 7.83 (ddd, 1H, *J* = 8.8, 6.6 and 1.4 Hz), 8.24 (dt, 1H, *J* = 8.8 and 1.0 Hz), 8.32 (ddd, 1H, *J* = 8.8, 1.5 and 0.7 Hz), 8.51 (dd, 1H, *J* = 8.8 and 1.7 Hz), 9.07 (dd, 1H, *J* = 3.8 and 1.7 Hz); ¹³C NMR (CDCl₃) δ 12.6 (CH₃), 124.8 (CH), 125.3 (CH), 126.3 (CH), 127.9 (C), 130.3 (CH), 130.6 (CH), 137.8 (CH), 139.5 (C), 144.3 (C), 145.1 (C), 148.8 (C), 150.6 (CH). Anal. Calcd for C₁₃H₁₀N₂ (194.24): C, 80.39; H, 5.19; N, 14.42. Found: C, 80.42; H, 5.47; N, 14.38.

5.6.13. 8,14-Dimethyldibenzo[*b,j*][1,7]phenanthroline (4n). The general procedure 6 (reaction time: 1.5 h) using *N,N'*-(1,3-phenylene)-2,2'-bis(2-aminoacetophenone) (**2n**, 0.34 g) gave **4n** (washing with water and, next, heptane) in 70% yield (0.22 g) as a beige powder: mp 180 °C; IR (ATR): 738, 753, 818, 855, 928, 1019, 1093, 1181, 1305, 1359, 1461, 1498, 1515, 1608, 1734, 2925, 3059 cm⁻¹; ¹H NMR (CDCl₃) δ 3.10 (s, 3H), 3.90 (s, 3H), 7.64-7.72 (m, 1H), 7.79-7.88 (m, 1H), 7.92 (d, 1H, *J* = 9.8 Hz), 8.24 (d, 1H, *J* = 9.8 Hz), 8.28 (br d, 3H, *J* = 8.6 Hz), 8.37 (ddd, 1H, *J* = 8.5, 1.4 and 0.6 Hz), 8.52 (ddd, 1H, *J* = 8.7, 1.4, 0.6 Hz). These ¹H NMR data are as described previously.³⁵ ¹³C NMR (CDCl₃) δ 14.0 (CH₃), 19.7 (CH₃), 124.0 (C), 124.0 (C), 124.2 (CH), 125.4 (CH), 125.7 (C), 126.1 (CH), 126.5 (CH), 127.3 (CH), 128.2 (C), 129.3 (CH), 129.7 (CH), 130.1 (CH), 130.1 (CH), 130.7 (CH), 140.3 (C), 145.8 (C), 147.7 (C), 147.8 (C), 150.2 (C), 151.5 (C).

5.6.14. 7,14-Dimethylquino[2,3-*b*]acridine (4o). The general procedure 6 (reaction time: 1 h) using *N,N'*-(1,4-phenylene)-2,2'-bis(2-aminoacetophenone) (**2o**, 0.34 g) gave **4o** (eluent: AcOEt) in 90% yield (0.28 g) as a beige powder: mp 211 °C (lit.³⁵ 211.5-213 °C); IR (ATR): 753, 830, 975, 1019, 1101, 1129, 1146, 1184, 1454, 1593, 1609, 1738, 2924, 3049 cm⁻¹; ¹H NMR (CDCl₃) δ 2.80 (s, 6H), 7.68 (ddd, 2H, *J* = 8.3, 6.8 and 1.3 Hz), 7.83 (ddd, 2H, *J* = 8.3, 6.8 and 1.4 Hz), 7.84 (s, 2H), 8.21 (dd, 2H, *J* = 8.5 and 0.8 Hz), 8.27 (dd, 2H, *J* = 8.5 and 0.7 Hz). These ¹H NMR data are as described previously.³⁵ ¹³C NMR (CDCl₃) δ 19.6 (2CH₃), 123.3 (2C), 124.6 (2CH), 126.6 (2C), 126.9 (2CH), 129.6 (2CH), 129.9 (2CH), 133.8 (2CH), 142.3 (2C), 146.8 (2C), 150.6 (2C). **Crystal data for 4o.** C₂₂H₁₆N₂, *M* = 308.37, *T* = 150 K, monoclinic, *P* 2₁/*c*, *a* = 12.4194(11), *b* = 13.3041(13), *c* = 9.3331(8) Å, β = 92.897(4) °, *V* = 1540.1(2) Å³, *Z* = 4, *d* = 1.330 g cm⁻³, μ = 0.078 mm⁻¹. A final refinement on *F*² with 3509 unique intensities and 219 parameters converged at ω*R*(*F*²) = 0.1209 (*R*(*F*) = 0.0480) for 2717 observed reflections with *I* > 2σ(*I*). CCDC 1811749.

5.7. Antiproliferative activity

The antiproliferative activity 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% CO₂ 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 dehydrogenase 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 $GI (\%) = 100 - ((A550 \text{ nm sample} - A550 \text{ nm BG}) / (A550 \text{ nm control} - A550 \text{ nm BG})) \times 100$ 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.

5.8. Kinase activities

The kinase activities were assayed using the ADP-Glo™ bioluminescent kinase assay kit (Promega, Madison, WI) according to the recommendations of the manufacturer. Reactions were carried out in a final volume of 5 µL for 30 min at 30 °C in ADP-Glo buffer (40 mM Tris pH 7.5, 20 mM MgCl₂ and 0.1 mg/mL of BSA). After that, 5 µL of ADP-Glo™ Kinase Reagent was added to stop the kinase reaction. After an incubation time of 50 min at room temperature, 10 µL of Kinase Detection Reagent was added for 1 h at room temperature. The transmitted signal was measured using the Envision (PerkinElmer, Waltham, MA) microplate luminometer and expressed in Relative Light Unit (RLU). Assays were performed in the absence or presence of 10 µM or 1 µM of tested compounds. Peptide substrates were obtained from Proteogenix (Oberhausbergen, France). The following kinases were analyzed during this study: CDK2/CyclinA (cyclin-dependent kinase-2, human, kindly provided by Dr. A. Echalié-Glazer, Leicester, UK); CDK5/p25 (human, recombinant, expressed in bacteria); CDK9/CyclinT (human, recombinant, expressed by baculovirus in Sf9 insect cells); PIM1 (human proto-oncogene, recombinant, expressed in bacteria); *SscGSK-3α/β* (glycogen synthase kinase-3, porcine brain, native, affinity purified); Haspin-kd (human, kinase domain, amino acids 470 to 798, recombinant, expressed in bacteria); Aurora B (human, recombinant, expressed by baculovirus in Sf9 insect cells, SignalChem, product #A31-10G); *MmCLK1* (from *Mus musculus*, recombinant, expressed in bacteria); *LmCK1* (from *Leishmania major*, recombinant, expressed in bacteria); *RnDYRK1A-kd* (*Rattus norvegicus*, amino acids 1 to 499 including the kinase domain, recombinant, expressed in bacteria, DNA vector kindly provided by Dr. W. Becker, Aachen, Germany); *SscCK1δ/ε* (casein kinase 1δ/ε, porcine brain, native, affinity purified). To validate the kinase assay, model inhibitors were used for each tested enzyme: Barasertib (AZD1152-HQPA, #S1147, purity 97.31%, Selleckchem) for Aurora B; Staurosporine from *Streptomyces* sp. (#S5921, purity ≥95%, Sigma-Aldrich) for *SscCK1δ/ε* and *LmCK1*; Indirubin-3'-oxime (#I0404, purity ≥98%, Sigma-Aldrich) for *SscGSK-3α/β*, PIM1, CDKs, *RnDYRK1A* and *MmCLK1*; CHR-6494 (#SML0648, purity ≥98%, Sigma-Aldrich) for Haspin.

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