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From benzofuro-, benzothieno- and 10-methylindolo-[2,3-*b*]-fused benzothiopyrano[4,3,2-*de*]quinolines to the corresponding benzothiopyrano[4,3,2-*de*]1,8-naphthyridines: synthesis and properties of these hexacyclic heteroaromatic compounds†

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Polycyclic heterocycles such as 1- and 2-aminothioxanthones are important precursors to molecules endowed with different properties and original syntheses are always required. Here, 1-aminothioxanthone was obtained either in four steps from commercially available thioxanthone, or in five steps from 3-fluoroaniline. As for 2-aminothioxanthone, direct *N*-arylation using commercial 2-chlorothioxanthone gave its Boc-protected derivative. From 1-aminothioxanthone, original 10-methylbenzothiopyrano[4,3,2-*de*]indolo[2,3-*b*]quinoline was synthesized by tandem *N*-arylation-cyclization using 2-iodo-*N*-methylindole in the presence of copper. However, this approach being less efficient with 2-iodobenzothiophene, we also studied another strategy. Our efforts were next concentrated on the synthesis of benzofuro-, benzothieno- and indolo[2,3-*b*]benzothiopyrano[4,3,2-*de*]1,8-naphthyridines which are original hexacycles of helical nature. Different approaches were designed and we achieved our goal from 2-chloro-4-fluoropyridine, in five steps. The original polycyclic compounds obtained were evaluated as protein kinase inhibitors, and the results were rationalized by molecular modeling experiments. Finally, their photophysical properties were measured for the purpose of structure-property relationships.

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Introduction

Polyaromatic hydrocarbons (PAHs) are organic scaffolds that exhibit significant biological or/and physicochemical properties, especially when they incorporate heteroatoms such as nitrogen, oxygen and sulfur.[1,2] Moreover, compared to planar ones, heterocyclic PAHs that contain helical structures are more soluble, and therefore more suitable for applications.[3]

Thioxanthones are heterocycles that can be found in bioactive compounds such as lucanthone, hycanthone, and related compounds SR233377 and SR271425, which interact with DNA.[4,5] Additionally, as thioxanthone derivatives are P-glycoprotein modulators, they may impact drug bioavailability.[6] Due to their specific photophysical properties, thioxanthones have also caught the attention of chemists for applications in the field of photocatalysis (*e.g.* as photoinitiators in polymerization reactions and chemical transformations).[7] However, although synthetic routes exist,[8,9] they are limited to specific patterns,

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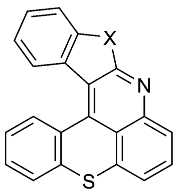
† Electronic supplementary information (ESI) available: NMR spectra of **3**, **4**, **5**, **6a**, **7**, **8**, **9**, **10**, **11**, **12-Boc**, **13**, **14**, **15a**, **15b**, **16**, **17**, 2-chloro-4-(methylthio)pyridine, **21**, **22a**, **22b**, **24a**, **24b**, **23**, **25**, **26**, **27**, *tert*-butyl *N*-(2-pyridyl)carbamate, **29**, 2-((*tert*-butoxycarbonyl)(methoxymethyl)amino)pyridine, 1,4-dihydro-4-phenylpyrido[2,3-*d*][1,3]2-oxazinone, **30**, **31**, **32**, **20**, its tautomeric form **20′**, **33**, **34**, **34′**, **36**, **37**, **28**, **39** and **35**. CCDC 2204831–2204837. For ESI and crystallographic data in CIF or other electronic format see DOI: **https://doi.org/10.1039/d2nj04567b**



Kinase inhibition:
X = S: IC_{50} (PIM1) = 370 nM;
IC_{50} (PIM2) = 460 nM
X = O: IC_{50} (PIM1) = 1.40 μM;
IC_{50} (PIM2) = 650 nM

Growth inhibition of melanoma cells:
X = S: 38.5% at 10 μM (72 h)

Absorption:
X = S: molar extinction coefficient ε_{max} = 6800 $M^{-1}\cdot cm^{-1}$
at λ_{abs} = 449 nm (blue-violet)
X = O: molar extinction coefficient ε_{max} = 8300 $M^{-1}\cdot cm^{-1}$
at λ_{abs} = 437 nm (blue-violet)

Fluorescence:
X = S: λ_{em} = 532 nm (green); quantum yield = 0.50
X = O: λ_{em} = 512 nm (green); quantum yield = 0.49

Fig. 1 Properties of benzothieno[2,3-*b*]benzothiopyrano[4,3,2-*de*]quinoline (**MN34-20**; X = S) and benzofuro[2,3-*b*]benzothiopyrano[4,3,2-*de*]quinoline (**MN42-62**; X = O).

and original approaches are still needed to access and functionalize thioxanthones.

During the development of lithium-zinc bases[10] for the functionalization of aromatic ketones,[11] we reported a one-pot synthesis of 1-iodothioxanthone (**1**) and its subsequent functionalization by copper-catalyzed C–N bond formation,[12] possibly followed by a cyclization.[13,14] The hexacycles **MN34-20** and **MN42-62**, obtained in this way, showed high fluorescence and were further established as promising inhibitors of the disease-related Provirus Integration site for Moloney leukemia virus (PIM) serine/threonine protein kinases (Fig. 1).[14]

These preliminary results convinced us to explore different accesses to 1-aminothioxanthone (**2**), the precursor of these hexacycles, and to consider the synthesis of analogs of **MN34-20** and **MN42-62** for property evaluation.

Results and discussion

Exploration of alternative routes to 1-aminothioxanthone

In our previous study,[14] 1-aminothioxanthone (**2**) was obtained in 50% yield from the corresponding iodide **1** by slightly modifying a literature procedure.[15] Thus, **1** was treated with excess aqueous ammonia, in the presence of catalytic copper(I) iodide and *N*,*N*′-dimethylethylenediamine, in dimethylsulfoxide (DMSO) at 130 °C. However, the use of a sealed tube limited the scaling up, leading us to investigate alternative approaches.

Inspired by a patent,[16] we first attempted to prepare **2** by stirring a tetrahydrofuran (THF) solution of thiosalicylic acid and aniline (1 equiv.) containing H_2SO_4 (0.08 equiv.) overnight at 65 °C, and then for 20 min at 90 °C in the presence of H_2O. However, we did not observe the formation of the expected product (not shown).

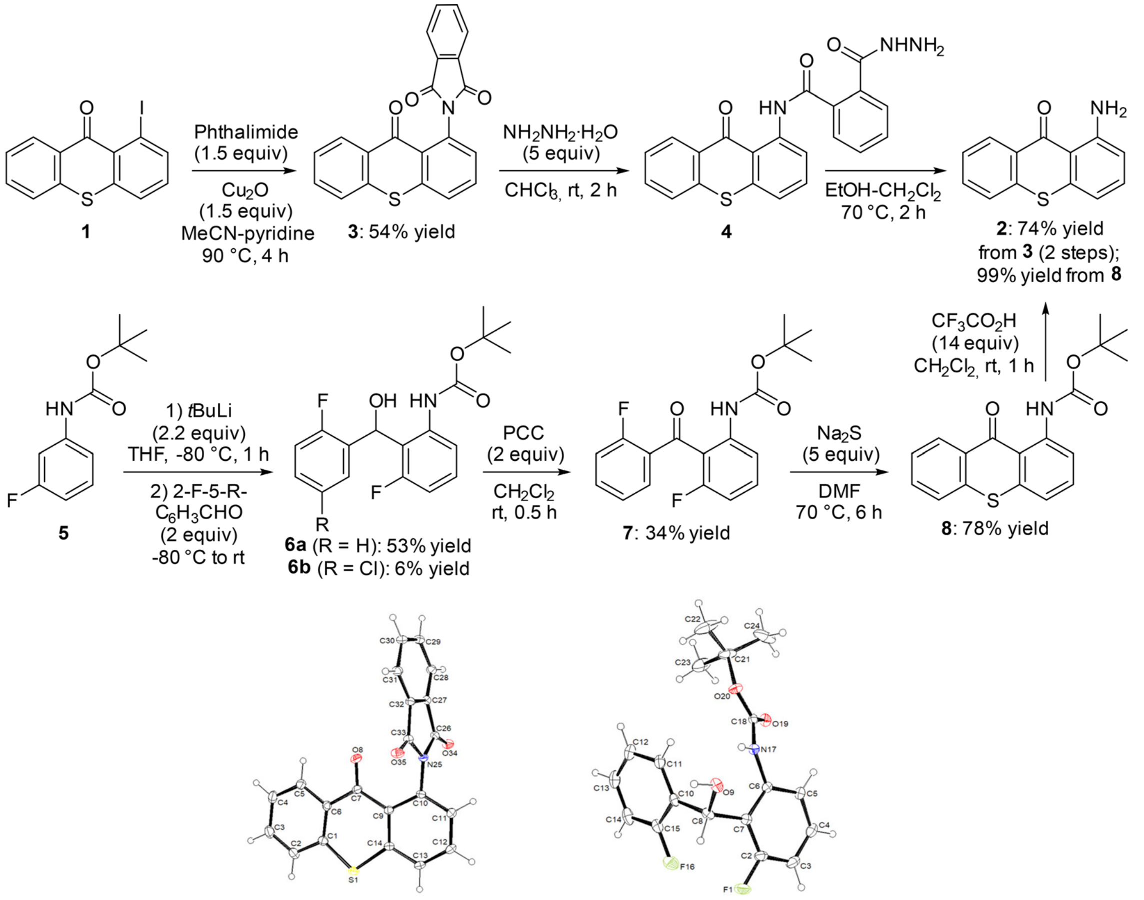
We therefore reverted to using 1-iodothioxanthone (**1**) as starting material, and chose to couple it with phthalimide in the presence of copper(I) oxide in 1 : 1 acetonitrile–pyridine at 90 °C, by adapting a procedure reported previously.[17] The phthalimide **3**, obtained in 54% yield, was identified unambiguously by X-ray diffraction (Scheme 1, top left and bottom left). It was conventionally[18] converted into **2** in 97% yield by treating it with hydrazine hydrate in 1 : 1 ethanol–dichloromethane (not shown). However, we faced reproducibility issues when scaling up (especially when we attempted to purify **2** by column chromatography over silica gel), and a two-step protocol was therefore preferred[19] (Scheme 1, top right). As the intermediate hydrazinamide **4** is insoluble in chloroform, it proved easy to isolate it and then heat it to 70 °C in 1 : 1 ethanol–dichloromethane. Thus, after filtration of phthalhydrazide, the pure 1-aminothioxanthone (**2**) was obtained with an overall yield of 74%.

An alternative way to access **2** involves building the thioxanthone ring from an appropriately substituted diarylketone. To explore this more general approach, we started with *tert*-butyl *N*-(3-fluorophenyl)carbamate (**5**), prepared quantitatively from 3-fluoroaniline by adapting a reported procedure.[20] Deprotolithiation of **5** was carried out by using *tert*-butyllithium in THF under conditions described by Warawa and co-workers,[21] and subsequent electrophilic trapping with 2-fluorobenzaldehyde afforded the alcohol **6a** in 53% yield (Scheme 1, middle left and bottom right). Replacing 2-fluorobenzaldehyde with 5-chloro-2-fluorobenzaldehyde (more acidic), to then access a substituted 1-aminothioxanthone, also led to **6b**, but in a low 6% yield. In order to progress to **2**, the alcohol **6a** was oxidized in the presence of pyridinium chlorochromate[22] (PCC; reaction not optimized) and the resulting ketone **7** was cyclized by using excess sodium sulfide under conditions documented by Peterson and co-workers.[23] The target compound **2** was finally obtained after quantitative aniline deprotection[24] (Scheme 1, right).

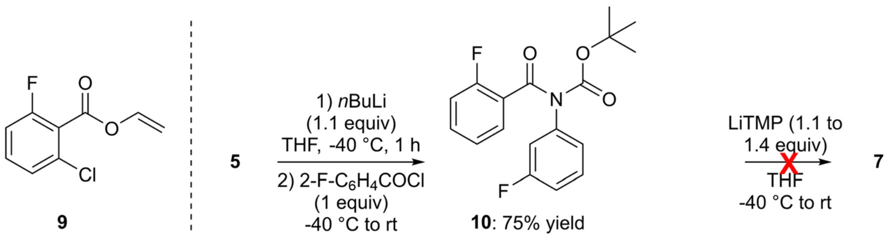
In order to directly obtain the ketone **7** from **5**, we also attempted to use 2-fluorobenzoyl chloride in place of 2-fluorobenzaldehyde after the deprotolithiation step. However, only traces of the expected ketone were detected and vinyl 2-chloro-6-fluorobenzoate (**9**) was the only isolatable product (Scheme 2, left). The latter probably results from the reaction of lithium enolate ($CH_2{=}CHOLi$), coming from the degradation of THF in the presence of strong bases,[25] with the acyl chloride used, as already reported during the butyllithium-mediated deprotolithiation of *N*-phenylpivalamide.[26]

Inspired by related work of Horne and Rodrigo,[27] we also prepared *tert*-butyl *N*-(2-fluorobenzoyl)-*N*-(3-fluorophenyl)carbamate (**10**) from **5**, and attempted a rearrangement to **7** by treatment with lithium 2,2,6,6-tetramethylpiperidide (LiTMP; 1.1 to 1.4 equiv.) at −40 °C before slowly warming (overnight) to room temperature. However, the expected reaction did not occur under these conditions (Scheme 2, right).

As some sulfur-containing rings can be formed by intramolecular electrophilic aromatic substitution with a remote



Scheme 1 Alternative routes to 1-aminothioxanthone (**2**) and ORTEP diagrams (30% probability) of the compounds **3** and **6a**.

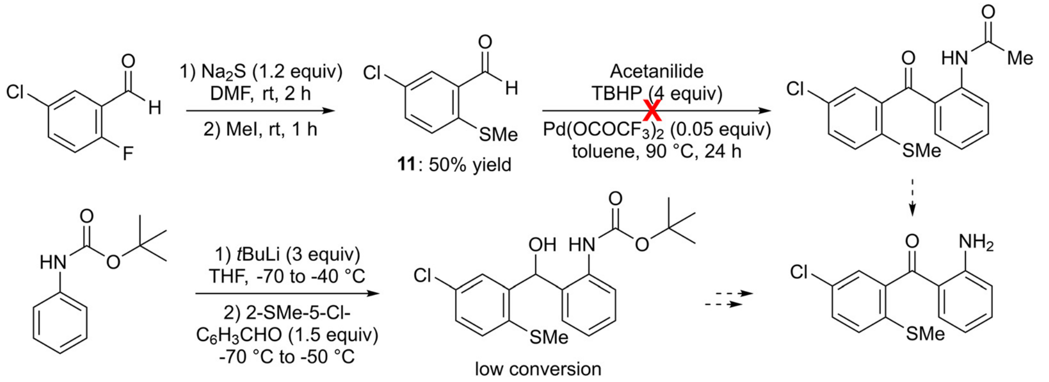


Scheme 2 Left: Example of a vinyl ester obtained as a side product using an acyl chloride to intercept an aryllithium prepared in THF. Right: Attempted rearrangement of *tert*-butyl *N*-(2-fluorobenzoyl)-*N*-(3-fluorophenyl)carbamate (**10**) and ORTEP diagram (30% probability) of **10**.

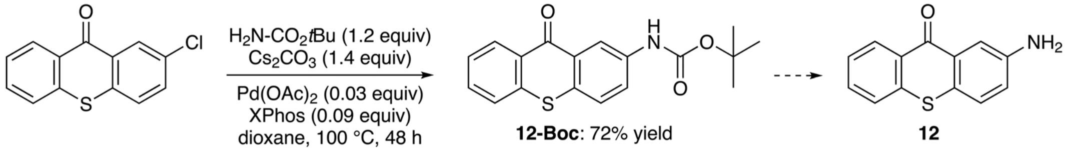
methylsulfinyl group,[28–30] we successfully prepared 5-chloro-2-(methylthio)benzaldehyde (**11**) from 5-chloro-2-fluorobenzaldehyde by substitution of the fluorine using sodium sulfide,[31] then carried out its *S*-methylation. However, an attempt coupling of **11** (2 equiv.) with acetanilide in the presence of excess *tert*-butyl hydroperoxide (TBHP) and catalytic palladium(II) trifluoroacetate, in toluene at 90 °C,[32] did not provide the expected *N*-(2-(5-chloro-2-methylthio)benzoyl)phenylacetamide (Scheme 3, top). Additionally, our attempts to intercept the lithiated derivative of *tert*-butyl *N*-phenylcarbamate (prepared by using *tert*-butyllithium in THF between −70 and −40 °C)[33] with **11** yielded only small amounts of the expected alcohol (Scheme 3, bottom).

Exploration of alternative routes to 2-aminothioxanthone

Despite the interest of 2-aminothioxanthone (**12**) for further functionalization,[34] very few well-described preparations are reported.[35,36] Therefore, we considered straightforward accesses from the available 2-chlorothioxanthone. First, it was treated with aqueous ammonia (10 equiv.) and copper(I) oxide (0.05 equiv.) in *N*-methyl-2-pyrrolidinone (NMP) at 80 °C overnight.[37] However, these conditions did not lead to the expected amine (not shown). The starting material was also recovered by treating 2-chlorothioxanthone with copper(II) sulfate or copper(I) oxide or copper(I) iodide (1.2 equiv.), in the presence of potassium carbonate (2.5 equiv.) in formamide at



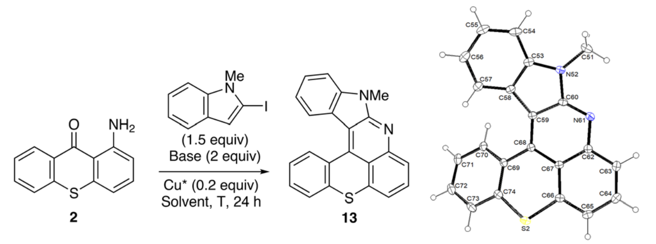
Scheme 3 Unsuccessful routes to 2-(5-chloro-2-methylthiobenzoyl)aniline, a potential precursor of 7-substituted 1-aminothioxanthone.



Scheme 4 Alternative route to (Boc-protected) 2-aminothioxanthone (**12**).

160 °C for 2.5 h[38] (not shown). Similarly, the use of copper(I) iodide (0.20 equiv.), *N*,*N*′-dimethylethylenediamine (0.30 equiv.), potassium hydroxide (1.5 equiv.) and cesium carbonate (0.50 equiv.) in acetonitrile–water at 100 °C for 15 h[39] did not yield the acetamide (not shown). To our satisfaction, the reaction with *tert*-butyl carbamate (1.2 equiv.) in the presence of cesium carbonate (1.4 equiv.), palladium(II) acetate (0.03 equiv.) and 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl (XPhos; 0.09 equiv.), in dioxane at 100 °C for 48 h,[40] in turn, gave the expected protected amine **12-Boc** in 72% yield (Scheme 4).

Table 1 Short optimization of the reaction conditions giving 10-methylbenzothiopyrano[4,3,2-*de*]indolo[2,3-*b*]quinoline (**13**)[a] and ORTEP diagram (30% probability) of the compound **13**



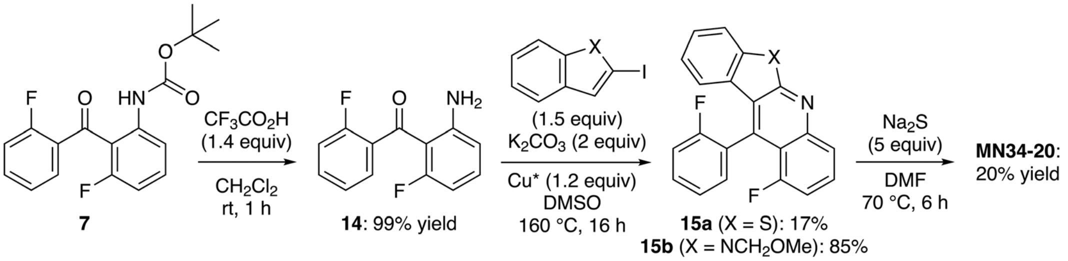
Entry	Solvent, *T*	Base	Yield of **13**[b]
1	Bu_2O, 160 °C	K_2CO_3	42%, 73%[c]
2	Bu_2O, 160 °C	K_3PO_4	—[d]
3	DMF, 170 °C	K_2CO_3	35%
4	DMSO, 170 °C	K_2CO_3	94%

[a] All the reactions (0.5 mmol) were run in a sealed tube in 2 mL of solvent. [b] Yield after purification (see experimental part). [c] In the presence of 4 Å molecular sieves (0.25 g). [d] Not purified since deiodination of 2-iodo-*N*-methylindole was observed by NMR.

On the conversion of 1-aminothioxanthone to 10-methylbenzothiopyrano[4,3,2-*de*]indolo[2,3-*b*]quinoline, benzothieno[2,3-*b*]benzothiopyrano[4,3,2-*de*]quinoline and benzofuro[2,3-*b*]benzothiopyrano[4,3,2-*de*]quinoline

In 2020, benzothieno[2,3-*b*]benzothiopyrano[4,3,2-*de*]quinoline and benzofuro[2,3-*b*]benzothiopyrano[4,3,2-*de*]quinoline (**MN34-20** and **MN42-62**) were obtained as side products upon *N*-arylation of **2** with 2-iodothiophene and 2-iodofuran, respectively.[14] These coupling reactions were carried out in the presence of potassium carbonate (2 equiv.) and activated copper[41] (Cu*; 0.2 equiv.) in dibutyl ether at 140 °C. Here we selected 2-iodo-*N*-methylindole[42] to optimize the reaction using three different solvents (dibutyl ether, dimethylformamide (DMF) and DMSO) and two bases (potassium carbonate and tripotassium phosphate) (Table 1). While tripotassium phosphate mainly led to deiodination, replacing dibutyl ether with DMSO resulted in marked improvement.

However, these conditions did not allow benzothieno[2,3-*b*]benzothiopyrano[4,3,2-*de*]quinoline (**MN34-20**) to be obtained efficiently (<20% yield). Without the sulfur bridge, 11-phenylbenzothieno[2,3-*b*]quinoline (**NM-049**) formed similarly in a modest 30% yield, suggesting that 2-iodobenzothiophene[43,44] is not a good coupling partner in these tandem *N*-arylation-cyclizations. Based on findings by Hartwig and co-workers of related palladium-catalyzed couplings in these series,[45,46] copper-catalyzed *N*-arylation reactions might be favored in the case of less electron-rich aryl groups as follows:[47] 2-benzofuryl (C2 Mulliken charge[48] = +0.07) > 2-indolyl (+0.02) > 2-benzothienyl (−0.38). On the contrary, the ability to cyclize must be favored in the case of more electron-rich aryl groups as follows: 3-indolyl (C3 Mulliken charge[48] = −0.24) ≥ 3-benzofuryl (−0.235) > 3-benzothienyl (−0.14). This might help explain why 2-iodo-*N*-methylindole is a more suitable substrate than 2-iodobenzothiophene for these *N*-arylation-cyclization reactions.



Scheme 5 Alternative route to benzothieno[2,3-*b*]benzothiopyrano[4,3,2-*de*]quinoline (**MN34-20**).

The fact that not all iodides react in the same way in these *N*-arylation-cyclizations prompted us to develop an alternative approach to **MN34-20** from *tert*-butyl *N*-(3-fluoro-2-(2-fluorobenzoyl)phenyl)carbamate (7) with the formation of the sulfur bridge as the final step. Once deprotected,[24] the aniline **14** (prone to cyclization to 1-fluoroacridone) was directly subjected to the tandem coupling-cyclization with 2-iodobenzothiophene. Despite the use of a stoichiometric amount of copper(I) iodide in order to obtain more reproducible results,[47] the benzothienoquinoline **15a** was isolated in a low 17% yield. This confirms the low reactivity of this particular halide since the use of 2-iodo-*N*-(methoxymethyl)indole[49] under the same conditions afforded the expected product **15b** in 85% yield (Scheme 5).

Cyclization to **MN34-20** was finally attempted by treating **15a** with excess sodium sulfide in dimethylformamide (DMF) at 70 °C for 6 h; however, the expected product was isolated in a low yield. From the substrate **15b**, the corresponding hexacycle was only detected in the crude by NMR (~10% estimated yield) after 5 h at 120 °C.

In search of aza analogs of 10-methylbenzothiopyrano[4,3,2-*de*]indolo[2,3-*b*]quinoline, benzothieno[2,3-*b*]benzothiopyrano[4,3,2-*de*]quinoline and benzofuro[2,3-*b*]benzothiopyrano[4,3,2-*de*]quinoline

For comparison, **NM-049** was tested[50] against the proto-oncogene protein kinases PIM1 and PIM2. However, while **MN34-20** has promising activity, the IC_{50} of **NM-049** were found to be surprisingly low (Fig. 2), highlighting the importance of the tetrahydrothiopyran ring to achieve good affinity. In addition, the inhibitory properties of benzothieno[2,3-*b*]1,8-naphthyridine (**MN65-45**) which is an aza analog of **NM-049** were also evaluated, leading to IC_{50} values close to those of **MN34-20**. Given this preliminary structure–activity analysis, we thought it would be interesting to synthesize compounds with both a sulfur ring and this extra nitrogen in order to evaluate them.

Our first approach started from 2-chloropyridine, from which deprotolithiation using LiTMP in THF at low temperature[51] followed by trapping with 2-bromobenzaldehyde furnished the alcohol **16** in high yield (Scheme 6, top left). While its oxidation using Dess–Martin periodinane[52] (1.4 equiv.) in THF at room temperature for 3 h afforded the ketone **17** in 62% yield (not shown), better results were obtained by using 2-iodoxybenzoic acid (IBX) in ethyl acetate at 60 °C for 6 h.[53] However, our preferred method of accessing the ketone **17** remained the Swern oxidation[54] which worked similarly (98% yield; Scheme 6, top middle). A direct synthesis of **17** from 2-chloropyridine was also investigated by using a lithium cuprate base derived from LiTMP,[55] but it gave the product in lower yields.

As coupling reactions have been reported between aryl sulfoxides and aryl bromides,[56] our next step was to introduce a *tert*-butylsulfinyl group at the 4-position of the pyridine ring in order to attempt cyclization. We thus studied the deprotolithiation of the ketone **17** in the presence of an *in situ* trap.[11,13] Different electrophiles (*tert*-butylsulfinyl chloride, *S*-*tert*-butyl-*tert*-butanethiosulfinate and di-*tert*-butyl disulfide) were tested

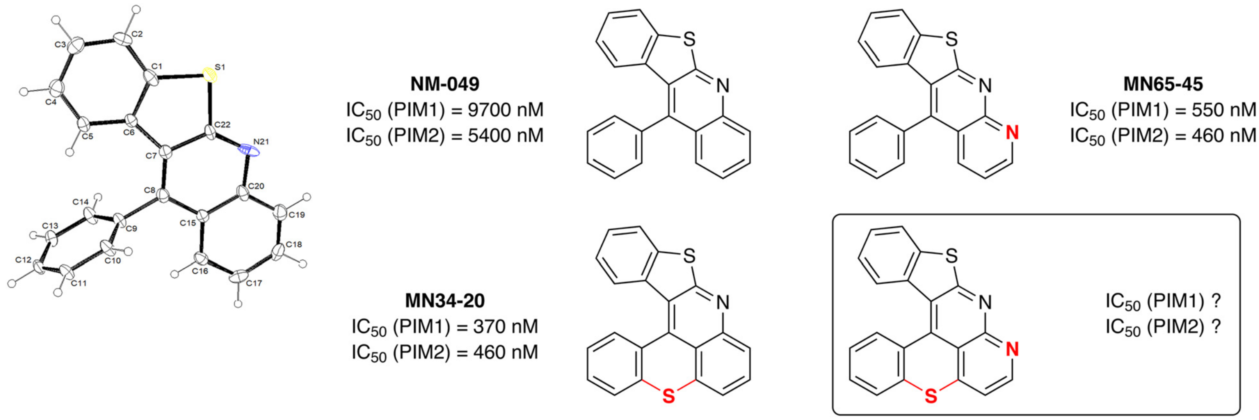
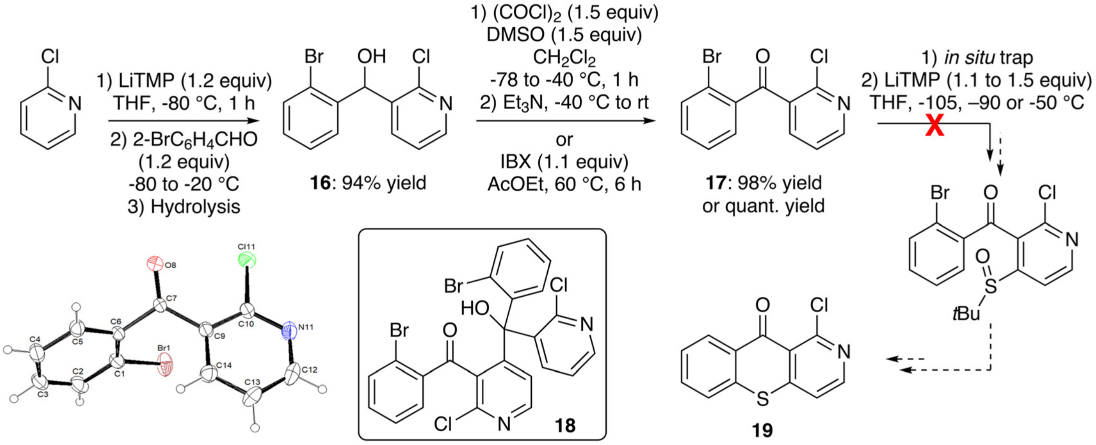


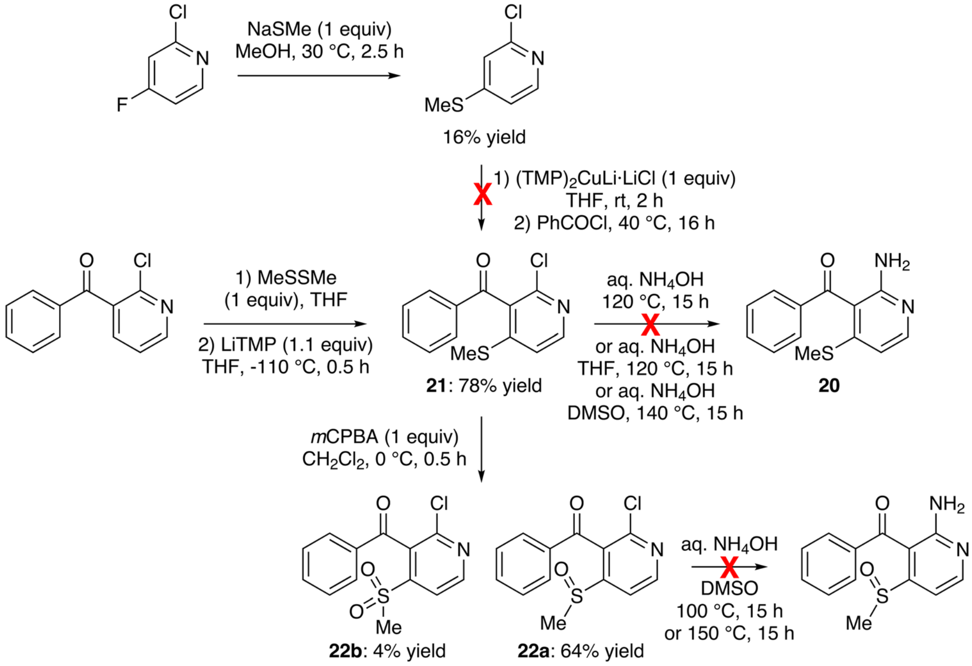
Fig. 2 Structure-activity relationships leading to benzothieno[2,3-*b*]benzothiopyrano[4,3,2-*de*]1,8-naphthyridine, and ORTEP diagram (30% probability) of the compound **NM-049**.



Scheme 6 Unsuccessful attempt toward 1-chlorobenzothiopyrano[3,2-c]pyridin-10-one (**19**) and ORTEP diagram (30% probability) of the compound **17**.

for their ability to intercept the aryllithiums generated by LiTMP-mediated deprotolithiation in THF. While the first electrophile led to the recovery of starting material at temperatures between −105 and −50 °C, the second gave only traces of the expected sulfoxide at −90 °C. With the third, we only obtained the tertiary alcohol **18** resulting from an attack of the aryllithium formed on the ketone **17**. This last result tends to indicate that the di-*tert*-butyl disulfide does not trap the lithiated intermediate quickly enough, probably due to high steric hindrance (Scheme 6, right and bottom).

Another potential precursor of our targets is 2-amino-3-benzoyl-4-(methylthio)pyridine (**20**) which could be prepared from 2-chloro-4-(methylthio)pyridine. The synthesis of the latter was attempted from 2-chloro-4-fluoropyridine at room temperature, treating it successively with sodium hydrosulfide (1.5 equiv.) in methanol for 0.5 h and iodomethane (2 equiv.) for 1 h.[57] However, under these conditions, we only recovered the starting material. Furthermore, when the more reactive sodium thiomethoxide (1 equiv.) was employed in methanol at 30 °C for 2.5 h, the expected sulfide was only isolated in a low 16% yield (Scheme 7, top) due to the recovery of starting material but also the competitive formation of a product that could result from the substitution of chlorine. Using CH$_2$Cl$_2$, acetone and THF as the solvent, extending the reaction time or using 2,4-difluoropyridine as the substrate did not give better results. Note that replacing sodium thiomethoxide with sodium thio-*tert*-butoxide, either in THF at 40 °C or in MeOH at room temperature, also did not furnish the expected 4-(*tert*-butylthio)pyridine.



Scheme 7 Unsuccessful attempts toward 2-amino-3-benzoyl-4-(methylthio)pyridine (**20**) and 2-amino-3-benzoyl-4-(methylsulfinyl)pyridine.

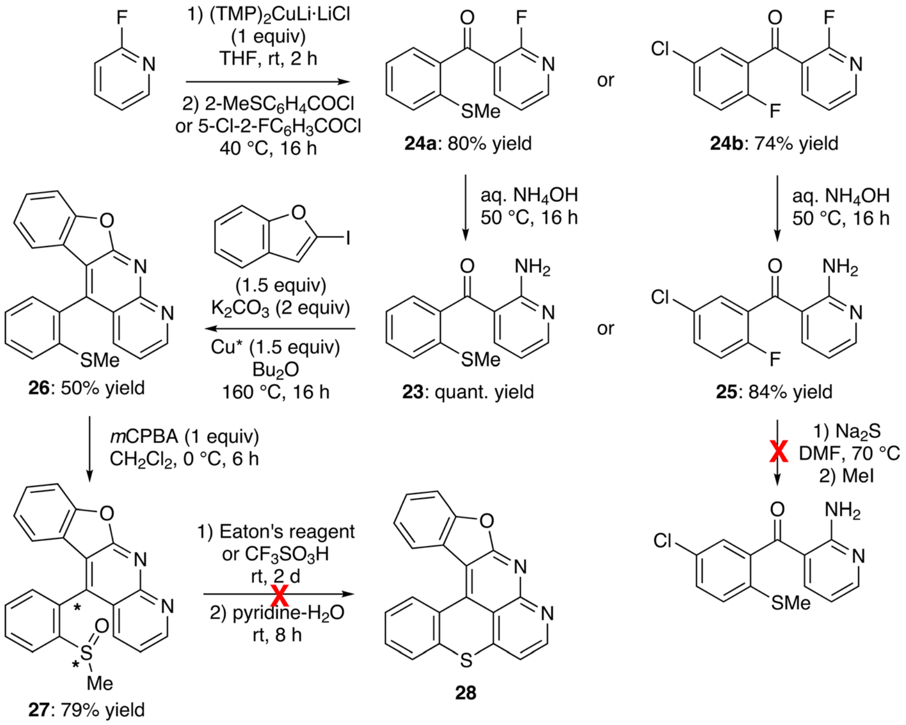
Furthermore, our attempts to convert this methyl sulfide into the expected ketone **21**, by using successively the lithium cuprate base $(TMP)_2CuLi{\cdot}LiCl$[58] and the benzoyl chloride, failed. Faced with these disappointing results, we turned to another path to obtain **20**.

Thus, we explored the use of dimethyl disulfide as an *in situ* trap for the LiTMP-mediated deprotometallation of 3-benzoyl-2-chloropyridine.[59] Pleasingly, the reaction performed at −110 °C furnished the expected sulfide **21** in 78% yield. However, all attempts to replace its chloro group with an amino,[60] whether using aqueous ammonia on overnight heating,[61] with THF[61] at 120 °C,[62] or with DMSO at 140 °C, did not provide **20** (starting material recovered; Scheme 7, middle).

Since we had succeeded in converting 2-chlorothioxanthone into the corresponding Boc-protected amine (Scheme 4), we also attempted the coupling between the chloride **21** and *tert*-butyl carbamate (5.0 equiv.) in the presence of palladium(0) bis(dibenzylideneacetone) ($Pd_2(dba)_3$; 0.02 equiv.), XPhos (0.05 equiv.) and cesium carbonate (7.6 equiv.) in THF at 70 °C for 24 h.[63] However, we only recovered the starting material (not shown).

As a substitution from an analog of **21** lacking the methylthio group is known,[60] we suspected that this substituent disfavors the reaction, probably for electronic reasons. Therefore, we decided to oxidize[64] **21** into the corresponding sulfoxide. The use of *meta*-chloroperbenzoic acid (*m*CPBA; 1 equiv.) led to the expected product **22a**, isolated in 64% yield, but also to the sulfone **22b** (4% yield; Scheme 7, bottom). By using cerium ammonium nitrate (CAN; 4 equiv.) in acetonitrile at room temperature,[65] the sulfoxide **22a** was formed selectively, but the conversion proved incomplete after 24 h (not shown). Disappointingly, all attempts to replace the chloro group in aqueous ammonia upon heating overnight with DMSO at 100 °C or 150 °C led to degradation (Scheme 7, bottom).

Since substitution of the chloro group with an amino turned out to be an issue for the methylthio- and methylsulfinyl-containing 2-chloropyridines **21** and **22a**, we attempted the LiTMP-mediated deprotometallation of 3-benzoyl-2-fluoropyridine[59] in the presence of dimethyl disulfide, aiming to achieve a more easily substitutable fluorinated analog of **21**. Unfortunately, the reaction only gave a complex mixture (not shown). This led us to consider the synthesis of 2-amino-3-(2-methylthio)benzoylpyridine (**23**), an isomer of 2-amino-3-benzoyl-4-(methylthio)pyridine (**20**), as another precursor of our targets. To this purpose, 2-fluoropyridine was easily deprotocuprated at its 3-position by using $(TMP)_2CuLi{\cdot}LiCl$, *in situ* prepared from LiTMP and CuCl, in THF at room temperature for 2 h;[55] subsequent trapping with 2-(methylthio)benzoyl chloride[66] afforded the ketone **24a** in 80% yield (Scheme 8, top left). As expected, the replacement of the fluoro group using aqueous ammonia at 50 °C for 16 h[67] provided the 2-aminopyridine **23** in a quantitative yield. It is interesting to note that the methylthio group cannot be introduced from a 2-amino-3-(2-fluorobenzoyl)pyridine (*e.g.* **25**; Scheme 8, right). The amine **23** was then involved in the tandem *N*-arylation-cyclization with 2-iodobenzofuran as before,[47] to furnish 11-(2-(methylthio)-phenyl)benzofuro[2,3-*b*]1,8-naphthyridine (**26**) in 50% yield (Scheme 8, middle). It was oxidized[64] to the sulfoxide **27** in 79% yield by using *m*CPBA. NMR analysis seemed to show that **27** exists as a mixture of diastereomers, even at 100 °C



Scheme 8 Unsuccessful attempt toward benzofuro[2,3-*b*]benzothiopyrano[4,3,2-*de*]1,8-naphthyridine (**28**).

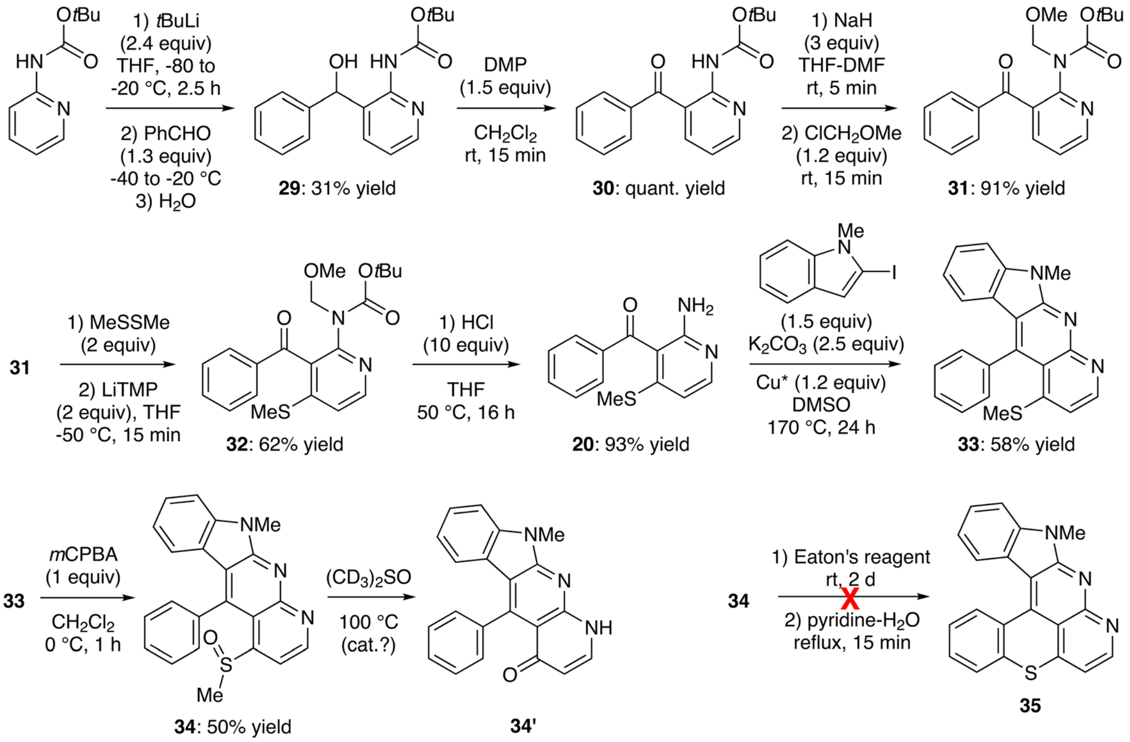
(see experimental part), possibly due to impeded rotation around the biaryl bond.

Unfortunately, all attempts to convert **27** into the hexacycle **28** have failed, whether in the presence of Eaton's reagent and then pyridine,[28] or using trifluoromethanesulfonic (triflic) acid before demethylation,[29] due to degradation (Scheme 8, bottom). Softer conditions using triflic acid in dichloromethane[30] or pyridinium chloride at 220 °C for 15 min[68] have also been tested, but without greater success (not shown).

Even though intramolecular reactions of pyridines with remote (methylsulfinyl)aryl moieties have been claimed,[69] electrophilic aromatic substitutions are generally less favored from π-deficient heteroaromatic compounds. Therefore, we decided to undertake the synthesis of a substrate in which the methylsulfinyl group would be at the 4-position of the pyridine ring, and designed another synthesis of 2-amino-3-benzoyl-4-(methylthio)pyridine (**20**). To discard issues related to nucleophilic aromatic substitution, we started from Boc-protected 2-aminopyridine, prepared from 2-aminopyridine by modifying a reported procedure.[20] This substrate can also be obtained, albeit in a lower 32% yield, by coupling 2-chloropyridine with *tert*-butyl carbamate in the presence of cesium carbonate, catalytic palladium(II) acetate and 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (Xantphos) in dioxane at 80 °C.[70] However, no product was formed by replacing Xantphos by XPhos.[40]

Deprotolithiation of Boc-protected 2-aminopyridine was carried out as reported, using *tert*-butyllithium (2.4 equiv.) in THF at −20 °C for 2.5 h.[71] Subsequent trapping with benzaldehyde led to the expected alcohol **29** in a moderate 31% yield (Scheme 9, top left). Alternatively, we attempted to deprotolithiate 2-aminopyridine doubly protected by Boc and CH_2OMe (MOM) groups, this by using *tert*-butyllithium in THF at −80 °C. However, the expected alcohol was not formed at all and only 10% of the substrate was recovered (not shown).

While the Swern oxidation failed to deliver the ketone **30** due to a competitive intramolecular reaction of the alcohol function with the carbamate, the use of Dess–Martin periodinane in dichloromethane[52] led to **30** in quantitative yield (Scheme 9, top middle). In order to introduce the methylthio group at the 4-position of the pyridine ring, **30** was treated with LiTMP (2 or 3 equiv.) at different temperatures between −90 and −50 °C in the presence of dimethyl disulfide as an *in situ* trap.[59] Unfortunately, regardless of the conditions used, only an unidentified side product formed in addition to the recovered starting material (not shown). However, after MOM-protection, functionalization of the ketone **31** was found to be much easier, affording the 4-methylthio derivative **32** in 62% yield (Scheme 9, middle left). The amine was finally deprotected to deliver 2-amino-3-benzoyl-4-(methylthio)pyridine (**20**). A few attempts were necessary to optimize the reaction and revealed the superiority of hydrochloric acid (10 equiv.) in THF at 50 °C over trifluoroacetic acid (5 equiv.) in dichloromethane under the same conditions (93% *vs.* 65% yield). Tandem *N*-arylation-cyclization on the amine **20** was performed with 2-iodo-*N*-methylindole as usual,[47] to give 11-phenyl-10-(methylthio)indolo[2,3-*b*]1,8-naphthyridine (**33**) in 58% yield. However, while the latter was easily oxidized[64] to the sulfoxide **34** (50% yield), an attempt to cyclize to the hexacycle **35** using Eaton's reagent



Scheme 9 Unsuccessful attempt toward 10-methylbenzothiopyrano[4,3,2-*de*]indolo[2,3-*b*]1,8-naphthyridine (**35**).

gave only a complex mixture from which the product has not been identified (Scheme 9, bottom).

During the NMR experiment (several hours in deuterated DMSO at 375 K), the sulfoxide **34** was quantitatively converted into what could the pyridone **34′**,[72] on the basis of its NMR and high-resolution mass spectra. However, when these NMR experiments were repeated on a repurified sample, no reaction occurred, suggesting it was catalyzed by traces of an impurity.

With evidence that electrophilic aromatic substitution with a remote sulfoxide will hardly deliver the target hexacycles, we reasoned that the presence of the pyridine ring would favor the nucleophilic aromatic substitution and reverted to using a difluorinated diarylketone as in Schemes 1 and 5. Thus, 2-chloro-4-fluoropyridine was deprotolithiated by using LiTMP (1.2 equiv.) in THF at low temperature, before trapping with 2-fluorobenzaldehyde. The expected alcohol **36**, isolated in 76% yield, was then engaged in a Swern oxidation[54] to deliver the ketone **37** in high yield (Scheme 10, top). Successive treatment of 2-chloro-4-fluoropyridine with $(TMP)_2CuLi{\cdot}LiCl$ in THF at room temperature for 2 h and 2-fluorobenzoyl chloride also afforded **37**, but with lower yields (not shown).

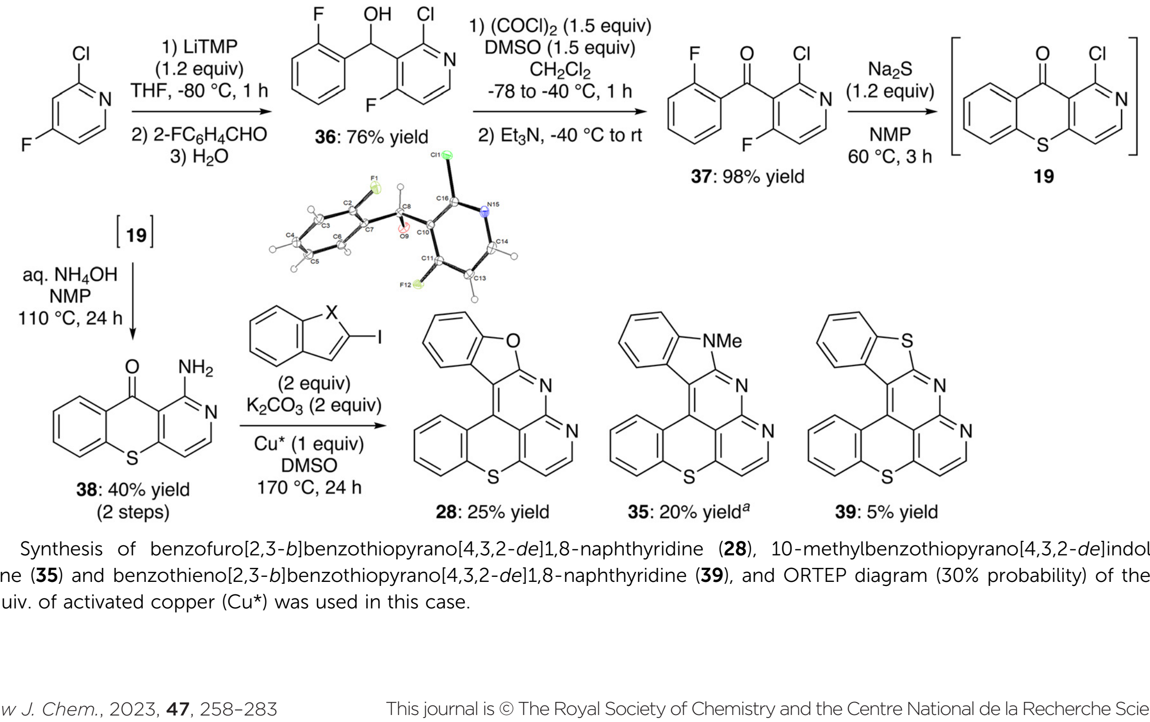
The difluoroketone **37** was then reacted with sodium sulfide in NMP,[73] and the resulting 1-chlorobenzothiopyrano[3,2-*c*]pyridin-10-one (**19**) was directly involved in the substitution reaction with aqueous ammonia at 110 °C to give **38** with an overall yield of 40% for two steps. Our targets **28**, **35** and **39** were finally reached from **38** through the *N*-arylation-cyclization tandem reaction using 2-iodobenzofuran, 2-iodo-*N*-methylindole and 2-iodobenzothiophene as coupling partners. Competitive deiodination is responsible for the moderate yields recorded.

Evaluation on kinases and molecular modeling experiments

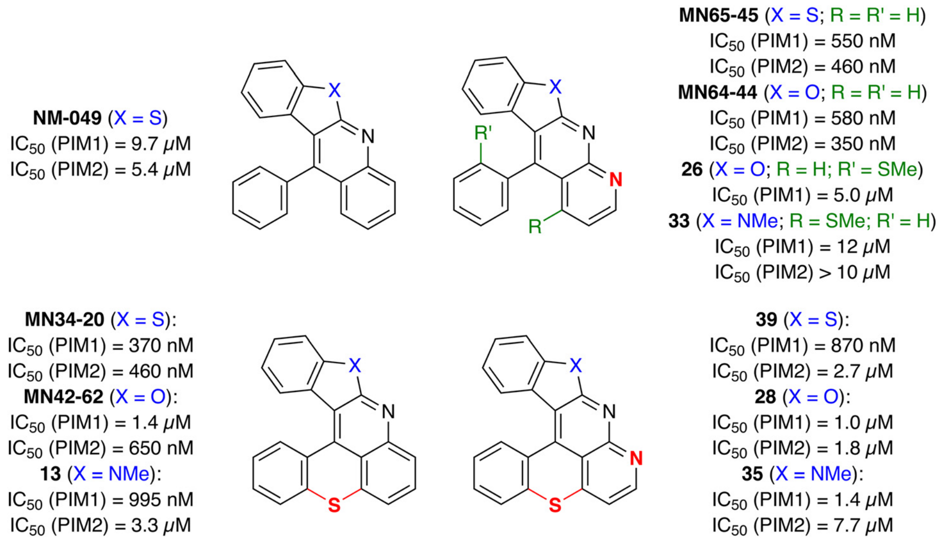
Our target compounds finally in hand, their ability to act as inhibitors of PIM kinases was evaluated and compared to those of benzothieno[2,3-*b*]benzothiopyrano[4,3,2-*de*]quinoline (**MN34-20**) and benzofuro[2,3-*b*]benzothiopyrano[4,3,2-*de*]-quinoline (**MN42-62**) previously studied[14] (Fig. 1). The results collected in Fig. 3 show that, if there is a certain interest in introducing an additional nitrogen on structures devoid of a sulfur bridge (top), its presence in the hexacycles has a deleterious effect on the affinity for the PIM kinases (bottom).

To better understand these results and highlight the structural features essential to the inhibition of PIM1/2 kinases in these series, molecular modeling studies on the hexacycle **39** and the compounds **NM-049** and **MN65-45** were undertaken. After geometry optimization, docking experiments were performed with PIM1 model generated from 3JPV structure[74] using AutoDock Vina.[75,76] The putative binding mode of **MN34-20** with the hexacyclic scaffold highly stabilized in the ATP-binding pocket *via* several hydrophobic interactions involving ILE104, LEU120, VAL126, LEU174 and ILE185 residues as well as LEU44, PHE49 and VAL52 residues from the P-loop flexible domain was previously described (see compound **6b** in ref. 14 and Fig. 4A). The presence of an additional nitrogen group in the analogous structure **39** leads to a sliding of the molecule into the binding pocket which has the consequence of selecting the P helix. The interaction with PHE49 then becomes impossible leading to a much lower binding score. Indeed, the region delimited by residues LYS67, LEU93, ASP186 and GLU89 seems unable to accept the presence of a nitrogen group (Fig. 4B).

As described in Fig. 4, similar binding modes were observed for the compounds **NM-049** and **MN65-45** with the planar tetracyclic moiety inserted into the ATP-binding pocket, and also stabilized *via* hydrophobic interactions with VAL52, ILE104, LEU174 and LEU44 residues (Fig. 4C and D). Compared to **MN34-20**, these two compounds did not fit into the pocket



Scheme 10 Synthesis of benzofuro[2,3-*b*]benzothiopyrano[4,3,2-*de*]1,8-naphthyridine (**28**), 10-methylbenzothiopyrano[4,3,2-*de*]indolo[2,3-*b*]1,8-naphthyridine (**35**) and benzothieno[2,3-*b*]benzothiopyrano[4,3,2-*de*]1,8-naphthyridine (**39**), and ORTEP diagram (30% probability) of the compound **36**. [a] 0.2 equiv. of activated copper (Cu*) was used in this case.



NM-049 (X = S)
IC_{50} (PIM1) = 9.7 μM
IC_{50} (PIM2) = 5.4 μM

MN65-45 (X = S; R = R' = H)
IC_{50} (PIM1) = 550 nM
IC_{50} (PIM2) = 460 nM
MN64-44 (X = O; R = R' = H)
IC_{50} (PIM1) = 580 nM
IC_{50} (PIM2) = 350 nM
26 (X = O; R = H; R' = SMe)
IC_{50} (PIM1) = 5.0 μM
33 (X = NMe; R = SMe; R' = H)
IC_{50} (PIM1) = 12 μM
IC_{50} (PIM2) > 10 μM

MN34-20 (X = S):
IC_{50} (PIM1) = 370 nM
IC_{50} (PIM2) = 460 nM
MN42-62 (X = O):
IC_{50} (PIM1) = 1.4 μM
IC_{50} (PIM2) = 650 nM
13 (X = NMe):
IC_{50} (PIM1) = 995 nM
IC_{50} (PIM2) = 3.3 μM

39 (X = S):
IC_{50} (PIM1) = 870 nM
IC_{50} (PIM2) = 2.7 μM
28 (X = O):
IC_{50} (PIM1) = 1.0 μM
IC_{50} (PIM2) = 1.8 μM
35 (X = NMe):
IC_{50} (PIM1) = 1.4 μM
IC_{50} (PIM2) = 7.7 μM

Fig. 3 IC_{50} values for some of the synthesized products and related compounds. ATP concentration used in the kinase assays was 10 μM.

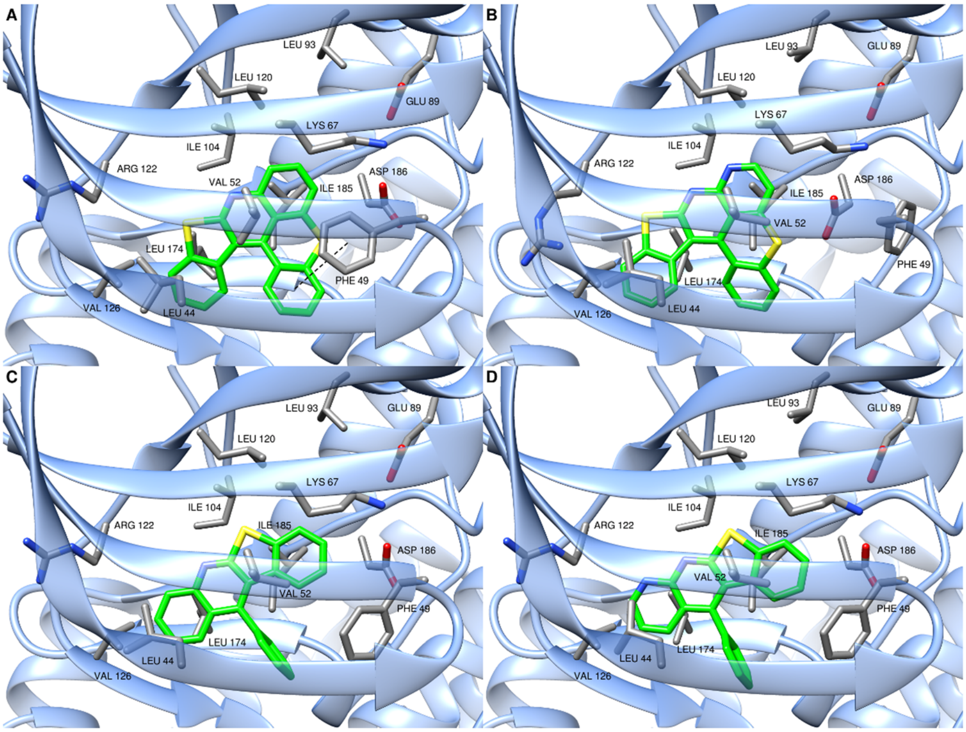


Fig. 4 Plausible binding mode of **MN34-20** (A), **39** (B), **NM-049** (C) and **MN65-45** (D) within PIM1 ATP-binding site. The images were produced using UCSF Chimera.[77]

with the same orientation but with a 180° flip due to the presence of the phenyl group. Thus, **NM-049** and **MN65-45** were not able to interact anymore with the PHE49 residue while this interaction seems crucial in this series. Altogether, the results obtained only explain partially the differences in PIM1 inhibitory potency observed between these compounds. This may result from different solubilities in testing media or solvation networks for the studied compounds.

Biological evaluation on melanoma cells

For six compounds produced, **3**, **13**, **28**, **35**, **39** and **NM-049**, the properties were evaluated against A2058 human melanoma cells. Moderate growth inhibitions of 33.2% ± 3.2%, 32.8% ± 9.7%, 18.7% ± 1.5%, 25.9% ± 2.0%, 32.5% ± 2.6% and 16.9% ± 9.7%, respectively, were observed at 10^{-5} M after 72 h (Fig. 5). Thus, the introduction of an additional nitrogen to **13** (32.8% ± 9.7%) and **MN34-20** (38.5% ± 4.2%)[14] led to compounds

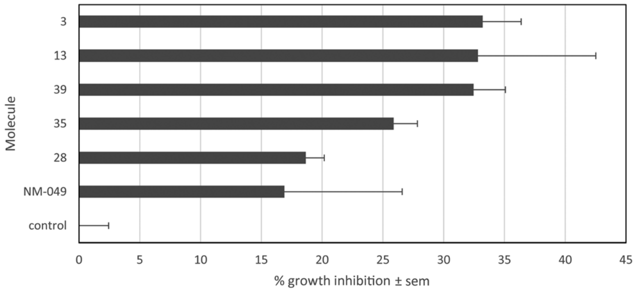


Fig. 5 Antiproliferative activity (% growth inhibition) of the compounds **3**, **13**, **28**, **35**, **39** and **NM-049**. 2000 A2058 human melanoma cells were treated for 72 h with 10^{-5} M of compound. Control cells were treated with an equivalent dose of DMSO (solvent of the tested compounds).

possessing reduced antiproliferative activity (25.9% ± 2.0% for **35** and 32.5% ± 2.6% for **39**, respectively).

Photophysical properties

As the hexacycles **MN34-20** and **MN42-62** are strongly fluorescent (Fig. 1), it was of interest to examine the photophysical properties of their analog **13** (X = NMe), as well as those of the corresponding hexacycles with an additional nitrogen **39**, **28** and **35**, respectively (Fig. 3).

The UV-visible absorption and fluorescence emission properties of these six hexacycles are collected in Table 2. All compounds exhibit a lower energy band in the violet-blue part of the visible region (Fig. 6), with maximum wavelengths ranging between 426 and 470 nm. This value increases depending on X (Fig. 3) in the order O < S < NMe, and introduction of an extra nitrogen atom leads to a hypsochromic shift of about 10 nm. The three compounds bearing this extra nitrogen (**39**, **28** and **35**) emit in the blue region, whereas the three other ones (**MN34-20**, **MN42-62** and **13**) emit at higher wavelengths in the green (Fig. 7), the introduction of the heteroatom leading to a marked hypsochromic shift of more than 40 nm, and therefore to a decrease of the Stokes shifts of more than 1000 cm^{-1}.

All compounds are highly fluorescent, with quantum yields ranging between 49% and 86%. The lifetimes vary between 8 and 16 ns, in agreement with a fluorescence emission. It should be noticed that the most fluorescent compounds are **28** and **39** with the extra nitrogen, which is consistent with their much higher radiative decay rate, but also with their slightly lower nonradiative decay rate, in comparison with their analogs **MN42-62** and **MN34-20** lacking this nitrogen, respectively.

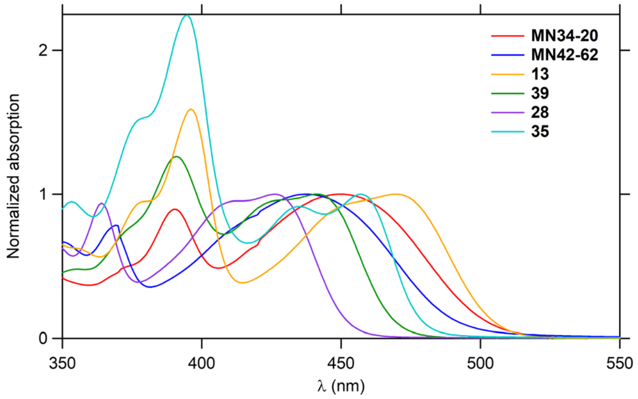


Fig. 6 Absorption spectra of the hexacycles in toluene.

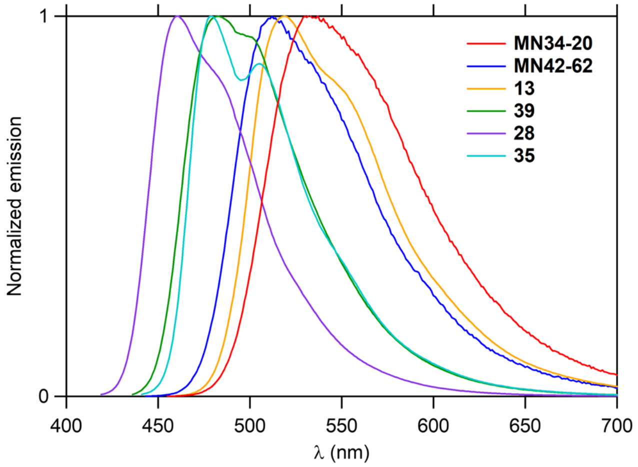


Fig. 7 Emission spectra of the hexacycles in toluene.

Conclusions

Our objective was to develop syntheses of analogs of **MN34-20** and **MN42-62** and to evaluate their biological and photophysical properties. Through this study, we were confronted with the difficulty of reaching sulfur aromatic compounds and functionalizing them in a controlled way toward helical structures.

Table 2 Absorption and emission properties of the hexacycles in toluene at 25 °C

Compound	$\lambda_{\text{abs}}{}^{a}$ (nm)	$\varepsilon_{\max}{}^{b}$ ($\text{M}^{-1}\ \text{cm}^{-1}$)	$\lambda_{\text{em}}{}^{c}$ (nm)	Stokes shift^{d} (cm^{-1})	$\Phi_{\text{F}}{}^{e}$	τ^{f} (ns)	$k_{\text{r}}{}^{g}$ (s^{-1})	$k_{\text{nr}}{}^{g}$ (s^{-1})
MN34-20	449	6800	532	3470	0.50	16.5	3.0×10^7	3.0×10^7
MN42-62	437	8300	512	3350	0.49	13.6	3.6×10^7	3.8×10^7
13	470	6800	519	2010	0.61	14.1	4.3×10^7	2.8×10^7
39	441	3100	483	1970	0.76	9.7	7.8×10^7	2.5×10^7
28	426	11 100	460	1740	0.86	7.8	11.0×10^7	1.8×10^7
35	457	3900	479	1010	0.50	10.7	4.7×10^7	4.7×10^7

[a] Absorption maximum. [b] Molar extinction coefficient at λ_{abs}. [c] Emission maximum. [d] Stokes shift = $(1/\lambda_{\text{abs}} - 1/\lambda_{\text{em}})$. [e] Fluorescence quantum yield using quinine bisulfate in 0.5 M H_2SO_4 as a standard. [f] Fluorescence lifetime. [g] Radiative (k_{r}) and nonradiative (k_{nr}) decay rates derived from fluorescence quantum yield and lifetime values: $k_{\text{r}} = \Phi_{\text{F}}/\tau$ and $k_{\text{nr}} = (1 - \Phi_{\text{F}})/\tau$.

Different approaches have thus been successively designed and carefully evaluated, taking advantage of successes and failures. Not only did this work ultimately lead to original hexacycles as the first fluorescent helical PIM kinase inhibitors, but we also established dimethyl disulfide as an original *in situ* trap to functionalize aromatic ketones using LiTMP. Given the usefulness of sulfides in chemistry, the ability to perform such a simple transformation will greatly enhance the interest of *in situ* traps in organic synthesis.

Experimental

General details

THF and dioxane were freshly distilled from sodium-benzophenone. Acetonitrile, dichloromethane, dibutyl ether and pyridine were distilled over CaH_2 under argon. Dimethylformamide and dimethylsulfoxide were distilled over CaH_2 under vacuum. All alkyllithiums were titrated before use.[78] 2,2,6,6-Tetramethylpiperidine (TMPH) was distilled over CaH_2 and stored under argon. The other commercially available starting materials were used without further purification. 1-Iodo-9-thioxanthone,[14] *tert*-butyl *N*-(4-fluorophenyl)carbamate,[20] 2-iodo-*N*-methylindole,[42] 2-iodobenzothiophene,[43,44] 2-iodo-*N*-(methoxymethyl)indole,[49] 3-benzoyl-2-chloropyridine[59] and 2-(methylthio)benzoyl chloride[66] were prepared as described. 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 PerkinElmer Spectrum 100 spectrometer. The ^{1}H, $^{13}C\{^{1}H\}$ and $^{19}F\{^{1}H\}$ Nuclear Magnetic Resonance (NMR) spectra were recorded on Bruker Avance III spectrometers equipped with a BBFO probe (the solvent, temperature and frequency are specified below, in the product description). ^{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.[79] High resolution mass spectra measurements were performed at the CRMPO in Rennes (Centre Régional de Mesures Physiques de l'Ouest).

Safety considerations. Due to its high pyrophoric character, *t*BuLi should only be used by well-trained people under anhydrous conditions and nitrogen or argon atmosphere.

General crystallographic details

The X-ray diffraction data were collected at T = 150(2) K either on an APEXII Kappa-CCD (Bruker-AXS) diffractometer equipped with a CDD plate detector (graphite monochromator; **3**, **6a**, **9**, **13** and **NM-049**), or on a D8 Venture (Bruker-AXS) diffractometer equipped with a CMOS-PHOTON70 detector (multilayer monochromator; **17** and **36**), using Mo-Kα radiation (λ = 0.71073 Å). The crystal structure was solved by dual-space algorithm using the SHELXT program,[80] and then refined with full-matrix least-squares methods based on F2 (SHELXL program).[81] All non-hydrogen atoms were refined with anisotropic atomic displacement parameters. Except those linked to nitrogen and oxygen that were introduced in the structural model through Fourier difference maps analysis in the case of **6a** and **36**, 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).[82]

Synthesis of 1-aminothioxanthone (2) from 1-iodothioxanthone (1)

1-(*N*-Phthalimido)thioxanthone (3). In a dried Schlenk tube filled with argon, 1-iodothioxanthone (**1**; 1.4 g, 4.0 mmol), phthalimide (0.89 g, 6.0 mmol) and Cu_2O (0.89 g, 6.0 mmol) were dissolved in acetonitrile (8 mL) and pyridine (8 mL). The reaction mixture was stirred for 4 h in a preheated oil bath at 90 °C and then cooled down to rt, diluted with AcOEt (2 × 50 mL) and filtered over a pad of silica gel to remove copper. The solvents were removed under reduced pressure. The dark green slurry was diluted with AcOEt (10 mL) and washed with a 5% H_2SO_4 aqueous solution (40 mL) and brine (20 mL). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure to afford 1-(*N*-phthalimido)-thioxanthone (**3**) in 54% yield (0.77 g) as a white solid: R_f (CH_2Cl_2) = 0.40; mp 250 °C (dec.); IR (ATR) ν 785, 882, 896, 936, 1034, 1084, 1114, 1151, 1225, 1302, 1318, 1385, 1449, 1466, 1591, 1628, 1709, 1774, 3009 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 K, 300 MHz) δ 7.35–7.42 (m, 2H), 7.52–7.61 (m, 2H), 7.71–7.73 (m, 2H), 7.82 (dd, 2H, J = 5.5 and 3.1 Hz, phthalimide), 8.00 (dd, 2H, J = 5.5 and 3.0 Hz, phthalimide), 8.32 (dd, 1H, J = 8.3 and 1.5 Hz, H8) ppm; $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 300 K, 75 MHz) δ 124.0 (2CH), 125.5 (CH), 125.9 (C), 126.6 (CH), 128.0 (CH), 129.7 (CH), 130.1 (CH), 130.5 (C), 132.1 (CH), 132.4 (CH), 132.8 (2C), 133.3 (C), 134.3 (2CH), 135.8 (C), 140.0 (C), 167.8 (2C, N–C=O), 180.0 (C, C=O) ppm; HRMS (ASAP; Maxis 4G), m/z = 357.0453 (0 ppm) found (calcd for $C_{21}H_{11}NO_3S$, $M^{+\bullet}$, requires 357.04542). *Crystal data for* **3**: $2(C_{21}H_{11}NO_3S)\cdot CH_2Cl_2$, M = 799.66, triclinic, $P\bar{1}$, a = 8.2771(3), b = 13.4367(6), c = 15.9360(6) Å, α = 95.3390(10), β = 93.9650(10), γ = 99.893(2) °, V = 1731.86(12) $Å^3$, Z = 2, d = 1.533 g cm^{-3}, μ = 0.365 mm^{-1}. A final refinement on F^2 with 7818 unique intensities and 500 parameters converged at $\omega R(F^2)$ = 0.1502 ($R(F)$ = 0.0591) for 5578 observed reflections with $I > 2\sigma(I)$. CCDC 2204834.†

1-Aminothioxanthone (2).

Without isolation of the hydrazinocarboxamide. To 1-(*N*-phthalimido)thioxanthone (**3**; 0.12 g, 0.30 mmol) were added EtOH (2 mL), CH_2Cl_2 (2 mL) and hydrazine hydrate (51% in H_2O; 0.10 mL, 1.6 mmol). The reaction mixture was stirred at reflux for 3 h and then cooled down to rt. The white precipitate of phthalhydrazide was discarded by filtration, and the solvent was removed under reduced pressure to afford 1-aminothioxanthone (**1**) in 97% yield (66 mg) as a yellow solid. Further purification by column chromatography over silica gel (eluent: petroleum ether–CH_2Cl_2–AcOEt 75 : 15 : 10) afforded the title product, but with non-reproducible yields.

With isolation of the hydrazinocarboxamide. 1-(*N*-phthalimido)thioxanthone (**3**; 1.4 g, 4.0 mmol) was dissolved in $CHCl_3$ (30 mL) before slow addition of hydrazine hydrate (51% in H_2O; 2.0 mL, 31 mmol). The stirring was continued for 2 h at rt.

The yellow precipitate was then filtered, washed with $CHCl_3$ (30 mL) and identified by NMR: ^1H NMR ($(CD_3)_2SO$, 300 K, 300 MHz) δ 4.35 (br s, 2H, NH_2), 7.55–7.70 (m, 5H), 7.76–7.89 (m, 4H), 8.45 (d, 1H, J = 8.3 Hz), 8.81 (d, 1H, J = 8.2 Hz), 9.70 (br s, 1H, NH), 13.42 (s, 1H, NH) ppm. The solid was next dissolved in CH_2Cl_2 (15 mL) and EtOH (15 mL), and the mixture was stirred for 2 h at reflux and cooled to rt. After filtration of the phthalhydrazide, the solvent was removed under reduced pressure to afford pure 1-aminothioxanthone (**1**) in 74% overall yield (0.67 g) as a yellow solid. Its ^1H NMR spectrum was found similar to that reported previously:[14] ^1H NMR ($CDCl_3$, 300 K, 300 MHz) δ 6.55 (dd, 1H, J = 8.2 and 1.1 Hz), 6.76 (dd, 1H, J = 7.7 and 1.1 Hz), 7.00 (br s, 2H, NH_2), 7.25 (t, 1H, J = 8.0 Hz), 7.37–7.46 (m, 2H), 7.50–7.55 (m, 1H), 8.50 (dd, 1H, J = 8.1 and 1.5 Hz).

Synthesis of 1-aminothioxanthone (2) from 3-fluoroaniline

***tert*-Butyl *N*-(3-fluorophenyl)carbamate (5).** It was first prepared as described.[33] However, adapting another procedure[20] led to the product as white needles (after recrystallization from CH_2Cl_2–petroleum ether) in a quantitative yield: IR (ATR) ν 726, 763, 774, 792, 857, 974, 1002, 1028, 1050, 1087, 1143, 1236, 1281, 1313, 1368, 1393, 1440, 1527, 1604, 1613, 1689 cm^{-1}; ^1H NMR ($CDCl_3$, 300 K, 300 MHz) δ 1.52 (s, 9H, *t*Bu), 6.49 (br s, 1H, NH), 6.72 (td, 1H, J = 8.4 and 2.3 Hz), 6.98 (d, 1H, J = 8.2 Hz), 7.20 (dd, 1H, J = 8.3 and 6.3 Hz), 7.31 (d, 1H, J = 11.2 Hz) ppm; ^{19}F NMR ($CDCl_3$, 300 K, 282 MHz) δ −111.8 ppm.

***tert*-Butyl *N*-(3-fluoro-2-((1-(2-fluorophenyl)hydroxymethyl)-phenyl)carbamate (6a).** To a solution of *tert*-butyl *N*-(3-fluorophenyl)carbamate (**5**; 0.42 g, 2.0 mmol) in THF (25 mL) at −80 °C under argon, was added dropwise a 1.6 M pentane solution of *t*BuLi (2.8 mL, 4.5 mmol). The mixture was stirred at this temperature for 1 h before slow addition of 2-fluorobenzaldehyde (0.42 mL, 4.0 mmol). The resulting mixture was stirred for 1 h at −80 °C, and then warmed up to rt for 3 h before quenching by a saturated aqueous solution of NH_4Cl (10 mL). After extraction with AcOEt (3 × 15 mL), the organic layer was washed with brine (10 mL) and dried over $MgSO_4$. CH_2Cl_2 (5 mL) was added to the solid residue obtained after removal of the solvents under reduced pressure. The precipitate formed after 1 h in the freezer was isolated by filtration, and the residual solvent removed under reduced pressure to give the title product in 53% yield as a white solid: mp 148–150 °C; IR (ATR) ν 750, 777, 787, 811, 822, 860, 896, 967, 1036, 1089, 1151, 1170, 1237, 1249, 1270, 1367, 1391, 1441, 1476, 1530, 1593, 1693, 2932, 2982, 3326 cm^{-1}; ^1H NMR ($CDCl_3$, 300 K, 300 MHz) δ 1.43 (s, 9H, *t*Bu), 3.11 (t, 1H, J = 3.0 Hz), 6.65 (d, 1H, J = 3.1 Hz), 6.77 (ddd, 1H, J = 9.8, 8.3 and 1.2 Hz), 7.03 (ddd, 1H, J = 10.8, 8.1 and 1.2 Hz), 7.09 (td, 1H, J = 7.6 and 1.3 Hz), 7.23–7.29 (m, 2H), 7.32 (td, 1H, J = 7.7 and 2.1 Hz), 7.73 (d, 1H, J = 8.3 Hz), 8.20 (br s, 1H) ppm; $^{13}C\{^1H\}$ NMR ($CDCl_3$, 300 K, 75 MHz) δ 28.4 ($3CH_3$, C*Me*$_3$), 64.2 (dd, CH, J = 8.3 and 3.4 Hz, CH(OH)), 80.5 (C, *C*Me$_3$), 110.1 (d, CH, J = 22.9 Hz, C4 or C3′), 115.7 (d, CH, J = 21.2 Hz, C4 or C3′), 117.0 (d, C, J = 14.3 Hz, C2 or C1′), 117.7 (d, CH, J = 3.5 Hz), 124.1 (d, CH, J = 3.5 Hz), 127.8 (d, CH, J = 3.6 Hz), 128.0 (d, C, J = 12.8 Hz, C2 or C1′), 129.8 (d, CH, J = 5.6 Hz), 129.9 (d, CH, J = 7.6 Hz), 139.7 (d, C, J = 4.8 Hz, C1), 153.2 (C, C=O), 160.1 (d, C, J = 246 Hz, C3 or C2′, C–F), 160.6 (d, C, J = 247 Hz, C3 or C2′, C–F) ppm; $^{19}F\{^1H\}$ NMR ($CDCl_3$, 300 K, 471 MHz) δ −117.3 (d, J = 9.3 Hz), −117.1 (d, J = 9.2 Hz) ppm. *Crystal data for* **6a**: $C_{18}H_{19}F_2NO_3$, M = 335.34, monoclinic, $P2_1/n$, a = 11.5846(9), b = 7.0406(5), c = 21.0857(13) Å, β = 101.424(2) °, V = 1685.7(2) Å^3, Z = 4, d = 1.321 g cm^{-3}, μ = 0.104 mm^{-1}. A final refinement on F^2 with 3823 unique intensities and 226 parameters converged at $\omega R(F^2)$ = 0.1244 (R_F = 0.0430) for 2812 observed reflections with ($I > 2\sigma$). CCDC 2204836.†

Replacing 2-fluorobenzaldehyde with 5-chloro-2-fluorobenzaldehyde in the present procedure only furnished the expected alcohol **6b** in 6% yield (oxidation of **6b** worked in ∼60% conversion using Dess–Martin periodinane while using pyridinium chlorochromate (PCC) proved much less efficient).

***tert*-Butyl *N*-(3-fluoro-2-(2-fluorobenzoyl)phenyl)carbamate (7).** To a stirred solution of *tert*-butyl *N*-(3-fluoro-2-((1-(2-fluorophenyl)hydroxymethyl)phenyl)carbamate (**6a**; 0.33 g, 1.0 mmol) in CH_2Cl_2 (10 mL) containing Celite® (1 g) at rt, was added PCC (0.41 g, 2.0 mmol) in several portions. After 0.5 h, the reaction mixture was filtered and the solvent was removed under reduced pressure. Purification of the residue by column chromatography on silica gel (eluent: petroleum ether–Et_2O 90 : 10) led to the title product in 34% yield (0.11 g) as a white solid: mp 81 °C; IR (ATR) ν 667, 682, 729, 757, 780, 802, 829, 887, 929, 966, 1035, 1086, 1103, 1150, 1222, 1248, 1277, 1311, 1368, 1393, 1419, 1454, 1467, 1517, 1579, 1611, 1639, 1732, 2980, 3354 cm^{-1}; ^1H NMR ($CDCl_3$, 300 K, 300 MHz) δ 1.51 (s, 9H, *t*Bu), 6.71 (ddd, 1H, J = 10.7, 8.3 and 1.0 Hz), 7.10 (ddd, 1H, J = 10.7, 8.3 and 1.1 Hz), 7.24 (td, 1H, J = 7.5 and 1.0 Hz), 7.46 (td, 1H, J = 8.3 and 6.2 Hz), 7.49–7.56 (m, 1H), 7.64 (td, 1H, J = 7.5 and 1.8 Hz), 8.18 (d, 1H, J = 8.6 Hz), 9.37 (br s, 1H, NH) ppm; $^{13}C\{^1H\}$ NMR ($CDCl_3$, 300 K, 75 MHz) δ 28.4 ($3CH_3$, C*Me*$_3$), 81.2 (C, *C*Me$_3$), 109.1 (d, CH, J = 22.8 Hz, C4 or C3′), 114.9 (d, C, J = 14.3 Hz, C2 or C1′), 115.8 (d, CH, J = 3.1 Hz), 116.4 (d, CH, J = 22.0 Hz, C4 or C3′), 124.4 (d, CH, J = 3.7 Hz), 129.0 (d, C, J = 2.4 Hz), 129.1 (d, C, J = 2.5 Hz), 130.5 (C), 134.3 (d, CH, J = 8.9 Hz), 134.8 (d, CH, J = 11.1 Hz), 141.2 (d, CH, J = 4.1 Hz), 152.8 (C), 160.7 (d, C, J = 253 Hz, C3 or C2′, C–F), 162.4 (d, C, J = 251 Hz, C3 or C2′, C–F), 191.9 (d, C, J = 1.7 Hz, C=O) ppm; $^{19}F\{^1H\}$ NMR ($CDCl_3$, 300 K, 282 MHz) δ −113.3, −106.6 ppm.

1-(*tert*-Butoxycarbonylamino)thioxanthone (8). *tert*-Butyl *N*-(3-fluoro-2-(2-fluorobenzoyl)phenyl)carbamate (**7**; 0.11 g, 0.30 mmol) in dry dimethylformamide (DMF; 2.5 mL) was treated under argon with Na_2S (0.13 g, 1.5 mmol). The orange–brown mixture was stirred at 70 °C for 6 h and poured onto ice-water (50 mL). The precipitate was collected by filtration. It was then dissolved in Et_2O (15 mL), and washed with brine (10 mL). The organic layer was dried over $MgSO_4$ before removal of the solvents under reduced pressure. 1-(*tert*-Butoxycarbonylamino)thioxanthone (**8**) was obtained in 78% yield (77 mg) and identified by NMR: ^1H NMR ($CDCl_3$, 300 K, 400 MHz) δ 1.57 (s, 9H, *t*Bu), 7.17 (d, 1H, J = 7.9 Hz), 7.46 (t, 1H, J = 7.6 Hz), 7.51–7.54 (m, 2H), 7.60 (t, 1H, J = 7.8 Hz), 8.51 (d, 1H, J = 8.5 Hz), 8.57 (d, 1H, J = 8.1 Hz), 12.36 (br s, 1H, NH) ppm.

1-Aminothioxanthone (2). To a solution of **8** (22 mg, 70 μmol) in dry CH_2Cl_2 (1.5 mL), trifluoroacetic acid (TFA; 0.10 mL, 1.0 mmol) was added dropwise at 0 °C. The reaction mixture was stirred for 1 h at rt before removal of the solvent and TFA under reduced pressure. The residue was dissolved in dry CH_2Cl_2 (10 mL) and washed with a saturated aqueous solution of $NaHCO_3$ until pH 7–8. The organic layer was dried over $MgSO_4$ and the solvent was removed under reduced pressure to afford 1-aminothioxanthone (**2**) in an almost quantitative yield (15 mg) as a yellow solid. Its ^{1}H NMR spectrum was found similar to that reported previously.[14]

Vinyl 2-chloro-6-fluorobenzoate (9). It was obtained as a brown oil: R_f (petroleum ether–AcOEt 80 : 20) = 0.40; IR (ATR) ν 692, 762, 785, 852, 901, 943, 1057, 1099, 1123, 1151, 1185, 1251, 1296, 1451, 1524, 1576, 1602, 1647, 1747, 2857, 2928, 2960, 3095 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 K, 500 MHz) δ 4.77 (dd, 1H, J = 6.2 and 2.0 Hz, OCH = C*H*H), 5.07 (dd, 1H, J = 13.9 and 2.0 Hz, OCH = CH*H*), 7.07 (td, 1H, J = 8.7 and 1.1 Hz, H5), 7.24 (d, 1H, J = 8.1 Hz, H3), 7.37 (td, 1H, J = 8.3 and 5.9 Hz, H4), 7.47 (dd, 1H, J = 13.9 and 6.2 Hz, OC*H*=CH_2) ppm; $^{13}C\{^1H\}$ NMR ($CDCl_3$, 300 K, 126 MHz) δ 99.8 (CH_2), 114.7 (d, CH, J = 21.5 Hz, C5), 121.2 (d, C, J = 19.3 Hz, C1), 125.8 (d, CH, J = 3.3 Hz, C3), 132.4 (d, CH, J = 9.1 Hz, C4), 133.1 (d, C, J = 4.4 Hz, C2), 141.1 (CH, O*C*H=CH_2), 160.2 (d, C, J = 255 Hz, C6, C–F), 160.3 (C, C=O) ppm; $^{19}F\{^1H\}$ NMR ($CDCl_3$, 300 K, 471 MHz) δ −111.0 ppm.

***tert*-Butyl *N*-(2-fluorobenzoyl)-*N*-(3-fluorophenyl)carbamate (10).** To a solution of *tert*-butyl *N*-(3-fluorophenyl)carbamate (**5**; 0.42 g, 2.0 mmol) in THF (10 mL) at −40 °C under argon, was added dropwise a 1.4 M hexane solution of *n*BuLi (1.6 mL, 2.2 mmol). The mixture was stirred at −40 °C for 1 h, and cannulated onto a solution of 2-fluorobenzoyl chloride (0.265 mL, 2.2 mmol) in THF (5 mL) at the same temperature. The resulting mixture was slowly (2 h) warmed up to rt before addition of a saturated aqueous solution of NH_4Cl (10 mL). The product was extracted with Et_2O (3 × 15 mL). The organic layer was washed with brine (10 mL) and dried over $MgSO_4$. After removal of the solvents under reduced pressure, purification by column chromatography over silica gel (eluent: petroleum ether–Et_2O 95 : 5 to 50 : 50), the title product was isolated in 75% yield (0.50 g) as white crystals: R_f ($CHCl_3$–petroleum ether 65 : 35) = 0.26; mp 102 °C; IR (ATR) ν 732, 752, 770, 802, 819, 841, 854, 913, 937, 1006, 1030, 1053, 1078, 1103, 1145, 1240, 1279, 1352, 1370, 1395, 1455, 1489, 1598, 1612, 1682, 1741, 2852, 2923 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 K, 500 MHz) δ 1.25 (s, 9H, *t*Bu), 7.03 (dt, 1H, J = 9.3 and 2.3 Hz), 7.07–7.13 (m, 3H), 7.25 (td, 1H, J = 7.6 and 1.1 Hz), 7.41 (td, 1H, J = 8.1 and 6.2 Hz), 7.46–7.52 (m, 1H), 7.63 (td, 1H, J = 7.2 and 1.8 Hz) ppm; $^{13}C\{^1H\}$ NMR ($CDCl_3$, 300 K, 126 MHz) δ 27.5 (3CH_3, C*Me*$_3$), 84.3 (C, *C*Me$_3$), 115.4 (d, CH, J = 10.4 Hz), 115.6 (d, CH, J = 11.0 Hz), 116.2 (d, CH, J = 22.9 Hz), 124.4 (d, CH, J = 3.2 Hz), 124.6 (d, CH, J = 3.5 Hz), 125.7 (d, C, J = 13.9 Hz), 130.2 (d, CH, J = 2.5 Hz), 130.3 (d, CH, J = 8.8 Hz), 132.9 (d, CH, J = 8.3 Hz), 139.9 (d, C, J = 10.0 Hz), 152.2 (C), 159.2 (d, C, J = 250 Hz), 162.9 (d, C, J = 247.1 Hz), 167.8 (C) ppm; $^{19}F\{^1H\}$ NMR ($CDCl_3$, 300 K, 282 MHz) δ −115.25, −112.0 ppm. *Crystal data for* **9**: $C_{18}H_{17}F_2NO_3$, M = 333.33, triclinic, $P\bar{1}$, a = 9.0170(11), b = 11.7369(15), c = 17.176(2) Å, α = 70.454(4), β = 81.368(4), γ = 75.963(4) °, V = 1657.2(4) Å^3, Z = 4, d = 1.336 g cm^{-3}, μ = 0.106 mm^{-1}. A final refinement on F^2 with 7335 unique intensities and 443 parameters converged at $\omega R(F^2)$ = 0.1316 (R_F = 0.0468) for 5203 observed reflections with ($I > 2\sigma$). CCDC 2204831.†

Unsuccessful attempt to prepare 2-(5-chloro-2-methylthiobenzoyl)aniline

5-Chloro-2-(methylthio)benzaldehyde (11). 5-Chloro-2-fluorobenzaldehyde (0.48 g, 3.0 mmol) and Na_2S (0.29 g, 3.7 mmol) were dissolved in dry DMF (5 mL) under argon. After 2 h stirring at rt, MeI (0.56 mL, 9.0 mmol) was added dropwise, and the reaction mixture was stirred for another hour before addition of aqueous 1 M NaOH (20 mL). After extraction with CH_2Cl_2, the organic layer was washed with aqueous HCl 1 M (10 mL) and dried over $MgSO_4$. Removal of the solvent under reduced pressure and purification by column chromatography over silica gel neutralized with Et_3N (eluent: petroleum ether–Et_2O 95 : 5 to 90 : 100) led to the title product which was isolated in 50% yield (0.28 g) as a white solid: R_f (petroleum ether–AcOEt 80 : 20) = 0.34; mp 70 °C; IR (ATR) ν 675, 698, 730, 818, 876, 973, 1060, 1077, 1105, 1155, 1187, 1252, 1293, 1372, 1425, 1437, 1457, 1541, 1582, 1682, 2734, 2839, 3047 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 K, 500 MHz) δ 2.50 (s, 3H, Me), 7.29 (d, 1H, J = 8.6 Hz, H3), 7.49 (dd, 1H, J = 8.6 and 2.4 Hz, H4), 7.78 (d, 1H, J = 2.4 Hz, H6), 10.24 (s, 1H, CHO) ppm; $^{13}C\{^1H\}$ NMR ($CDCl_3$, 300 K, 126 MHz) δ 16.0 (CH_3, SMe), 127.6 (CH, C3), 131.1 (C), 132.2 (CH, C6), 134.0 (CH, C4), 134.1 (C), 141.9 (C), 190.0 (CH, CHO) ppm.

Synthesis of Boc-protected 2-aminothioxanthone

2-(*tert*-Butoxycarbonylamino)thioxanthone (12-Boc). It was prepared under argon by treating 2-chlorothioxanthone (0.25 g, 1.0 mmol) with *tert*-butyl carbamate (0.14 g, 1.2 mmol) and Cs_2CO_3 (0.46 g, 1.4 mmol), in the presence of $Pd(OAc)_2$ (6.7 mg, 30 μmol) and XPhos (43 mg, 90 μmol) in dioxane (5 mL) at 100 °C for 48 h. The reaction mixture was next cooled to rt and water (10 mL) was added. The aqueous layer was extracted with AcOEt (3 × 20 mL). The organic layers were combined, dried over $MgSO_4$ and concentrated *in vacuo*. After purification by column chromatography over silica gel (eluent: $CHCl_3$–petroleum ether 60 : 40 to 100 : 0), the title product was isolated in 72% yield (0.24 g) as a yellow solid: R_f (CH_2Cl_2) = 0.29; mp 225 °C; IR (ATR) ν 732, 744, 778, 811, 908, 922, 1007, 1058, 1086, 1122, 1158, 1184, 1245, 1309, 1368, 1482, 1519, 1572, 1591, 1604, 1624, 1702, 2979, 3315 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 K, 300 MHz) δ 1.54 (d, 9H, J = 4.8 Hz, *t*Bu), 6.70 (br s, 1H), 7.48 (ddd, 1H, J = 8.2, 6.2 and 2.0 Hz), 7.55 (d, 1H, J = 8.9 Hz), 7.59–7.60 (m, 2H), 8.11 (br d, 1H, J = 9.1 Hz), 8.26 (d, 1H, J = 2.5 Hz), 8.61 (d, 1H, J = 8.1 Hz) ppm; ^{1}H NMR ($(CD_3)_2SO$, 300 K, 500 MHz) δ 1.51 (s, 9H, *t*Bu), 7.56 (ddd, 1H, J = 8.1, 7.5 and 1.3 Hz, H7), 7.73–7.76 (m, 2H, H5 and H6), 7.81 (d, 1H, J = 8.9 Hz, H4), 7.83 (dd, 1H, J = 8.9 and 2.3 Hz, H3), 8.46 (dd, 1H, J = 8.1 and 0.8 Hz, H8), 8.66 (d, 1H, J = 2.3 Hz, H1), 9.75 (br s, 1H, NH) ppm; $^{13}C\{^1H\}$ NMR ($CDCl_3$, 300 K, 75 MHz) δ 28.5

(3CH_3, C*Me*$_3$), 81.3 (C, *C*Me$_3$), 118.3 (CH), 124.1 (CH), 126.2 (CH), 126.3 (CH), 127.0 (CH), 128.9 (C), 129.8 (C), 130.1 (CH), 131.2 (C), 132.3 (CH), 137.5 (C), 137.7 (C), 152.8 (C), 179.8 (C, C═O) ppm; $^{13}C\{^1H\}$ NMR ($(CD_3)_2SO$, 300 K, 126 MHz) δ 28.1 (3CH_3, C*Me*$_3$), 79.6 (C, *C*Me$_3$), 116.9 (CH), 123.9 (CH), 126.5 (CH), 126.5 (CH), 127.0 (CH), 128.0 (C), 128.8 (C), 129.1 (CH), 129.3 (C), 132.7 (CH), 136.7 (C), 138.6 (C), 152.7 (C), 178.6 (C, C═O) ppm.

N-Arylation-cyclization from 1-aminothioxanthone using 2-iodo-*N*-methylindole

10-Methylbenzothiopyrano[4,3,2-*de*]indolo[2,3-*b*]quinoline (13). To 1-aminothioxanthone (**2**; 0.11 g, 0.50 mmol) in degassed DMSO (2 mL) under argon, were added 2-iodo-*N*-methylindole (0.19 g, 0.75 mmol), activated Cu (6 mg, 0.10 mmol) and K_2CO_3 (0.14 g, 1.0 mmol). The reaction mixture was stirred for 24 h in a preheated oil bath at 170 °C. After cooling to rt, it was diluted with AcOEt (10 mL) and filtered through a pad of silica gel to remove copper. Solvents were removed under reduced pressure. Purification was performed by column chromatography over silica gel (eluent: petroleum ether–CH_2Cl_2–NEt_3 60 : 39 : 1) to give the title product in 94% yield (0.16 g) as an orange solid: R_f ($CHCl_3$–petroleum ether 65 : 35) = 0.14; mp 190 °C; IR (ATR) ν 803, 811, 839, 870, 972, 1125, 1160, 1245, 1268, 1288, 1337, 1392, 1425, 1475, 1554, 1583, 1616, 2166, 2921 cm^{-1}; ^1H NMR ($CDCl_3$, 300 K, 300 MHz) δ 4.00 (s, 3H, Me), 7.17 (ddd, 1H, J = 8.2, 7.1 and 1.1 Hz), 7.31 (d, 1H, J = 7.3 Hz), 7.34 (dd, 1H, J = 7.3 and 1.6 Hz), 7.39 (dd, 1H, J = 7.8 and 1.7 Hz), 7.41 (d, 1H, J = 7.3 Hz), 7.49 (dd, 1H, J = 7.8 and 1.7 Hz), 7.50–7.57 (m, 2H), 7.83 (d, 1H, J = 8.4 Hz), 8.33 (d, 1H, J = 8.0 Hz), 8.48 (dd, 1H, J = 7.8 and 1.7 Hz) ppm; $^{13}C\{^1H\}$ NMR ($CDCl_3$, 300 K, 75 MHz) δ 28.0 (CH_3), 108.9 (CH), 112.8 (C), 117.8 (CH), 119.5 (CH), 120.8 (C), 122.0 (C), 123.8 (CH), 124.1 (CH), 126.1 (CH), 127.3 (CH), 128.0 (CH), 128.5 (CH), 129.6 (C), 129.9 (C), 130.0 (CH), 130.6 (CH), 135.7 (C), 136.4 (C), 143.2 (C), 147.7 (C), 154.6 (C) ppm; HRMS (ASAP; Maxis 4G), m/z = 338.0865 (2 ppm) found (calcd for $C_{22}H_{14}N_2S$, $M^{+\cdot}$, requires 338.0872). *Crystal data for* **13**: $C_{22}H_{14}N_2S$, M = 338.41, monoclinic, $P2_1/c$, a = 13.8094(10), b = 12.1986(9), c = 19.1371(15) Å, β = 99.043(3)°, V = 3183.7(4) Å^3, Z = 8, d = 1.412 g cm^{-3}, μ = 0.209 mm^{-1}. A final refinement on F^2 with 7274 unique intensities and 453 parameters converged at $\omega R(F^2)$ = 0.0990 ($R(F)$ = 0.0477) for 4807 observed reflections with $I > 2\sigma(I)$. CCDC 2204832.†

11-Phenylbenzothieno[2,3-*b*]quinoline (**NM-049**) was similarly prepared in 30% yield. Its analyses proved similar to those reported.[50] *Crystal data for* **NM-049**: $C_{21}H_{13}NS$, M = 311.38, triclinic, $P\bar{1}$, a = 8.8473(9), b = 9.7021(9), c = 10.1837(10) Å, α = 66.774(3), β = 69.333(4), γ = 77.281(3)°, V = 748.26(13) Å^3, Z = 2, d = 1.382 g cm^{-3}, μ = 0.214 mm^{-1}. A final refinement on F^2 with 3338 unique intensities and 208 parameters converged at $\omega R(F^2)$ = 0.2687 ($R(F)$ = 0.0991) for 2620 observed reflections with $I > 2\sigma(I)$. CCDC 2204837.†

Synthesis of 2-amino-6,2′-difluorobenzophenone and its *N*-arylation-cyclization

2-Amino-6,2′-difluorobenzophenone (14). TFA (2.8 mL, 28 mmol) was added dropwise at 0 °C to a solution of **7** (0.47 g, 2.0 mmol) in dry CH_2Cl_2 (20 mL). The reaction mixture was stirred for 1 h at rt. After removal of the solvent and TFA under reduced pressure, the residue was dissolved in dry CH_2Cl_2 (50 mL) and washed with a saturated aqueous solution of $NaHCO_3$ until pH 7–8. The organic layer was dried over $MgSO_4$ and the solvent was removed under reduced pressure to afford 2-amino-6,2′-difluorobenzophenone (**14**) as a yellow solid in an almost quantitative yield: R_f (petroleum ether–AcOEt 80 : 20) = 0.24; mp 99 °C; ^1H NMR ($CDCl_3$, 300 K, 400 MHz) δ 6.03 (bs s, 2H, NH_2), 6.29 (ddd, 1H, J = 11.5, 8.0 and 0.64 Hz), 6.48 (d, 1H, J = 8.3 Hz), 7.08 (ddd, 1H, J = 10.5, 8.4 and 1.0 Hz), 7.18 (td, 1H, J = 8.2 and 5.9 Hz), 7.20 (td, 1H, J = 7.5 and 1.1 Hz), 7.44 (tdd, 1H, J = 7.2, 5.1 and 1.9 Hz), 7.55 (td, 1H, J = 7.4 and 1.7 Hz) ppm; $^{19}F\{^1H\}$ NMR ($CDCl_3$, 300 K, 282 MHz) δ −115.3 (d, J = 2.6 Hz), −106.5 (d, J = 3.5 Hz) ppm.

General procedure for the tandem coupling-cyclization from 14. To 2-amino-6,2′-difluorobenzophenone (**14**; 0.20 g, ∼0.50 mmol) in degassed DMSO (2 mL) under argon, were added the aromatic iodide (0.75 mmol), activated Cu (12 mg, 0.20 mmol) and K_2CO_3 (0.21 g, 1.0 mmol). The reaction mixture was stirred for 16 h in a preheated oil bath at 170 °C while activated Cu (6 mg, 0.10 mmol) was added after 2 h, 4 h, 6 h and 8 h. After cooling to rt and filtration through Celite® to remove copper, H_2O (10 mL) was added before extraction with AcOEt (2 × 20 mL). The solvents were removed under reduced pressure. Purification was performed by column chromatography over silica gel (eluent given in the product description).

10-Fluoro-11-(2-fluorophenyl)benzothieno[2,3-*b*]quinoline (15a) and benzothieno[2,3-*b*]benzothiopyrano[4,3,2-*de*]quinoline (MN34-20). The general procedure using 2-iodobenzothiophene (0.14 g) gave (eluent: $CHCl_3$–petroleum ether 65 : 35) 10-fluoro-11-(2-fluorophenyl)benzothieno[2,3-*b*]quinoline (**15a**) in 17% yield (29 mg). It was identified by NMR: ^1H NMR ($CDCl_3$, 300 K, 400 MHz) δ 6.65 (d, 1H, J = 8.3 Hz), 7.09–7.17 (m, 2H), 7.33–7.40 (m, 3H), 7.43 (td, 1H, J = 7.7 and 1.2 Hz), 7.60–7.66 (m, 1H), 7.70 (ddd, 1H, J = 8.6, 7.7 and 5.4 Hz), 7.82 (d, 1H, J = 7.8 Hz), 8.03 (d, 1H, J = 8.6 Hz) ppm; $^{19}F\{^1H\}$ NMR ($CDCl_3$, 300 K, 376 MHz) δ −114.3, −111.0 ppm. This compound was directly involved in the cyclization step to the hexacycle as follows. To **15a** (29 mg, 0.80 mmol) in dry DMF (5 mL) under argon, was added Na_2S (0.34 g, 4.3 mmol). The mixture was stirred at 70 °C for 6 h and poured onto ice-water (20 mL). The precipitate was collected by filtration. It was then dissolved in Et_2O (40 mL), and washed with brine (20 mL). The organic layer was dried over $MgSO_4$ before removal of the solvents under reduced pressure. Benzothieno[2,3-*b*]benzothiopyrano[4,3,2-*de*]quinoline (**MN34-20**) was obtained in 20% yield (6 mg) and identified by comparison of its ^1H NMR spectrum with the one reported:[14] ^1H NMR ($CDCl_3$, 300 K, 400 MHz) δ 7.22–7.27 (m, 2H), 7.38–7.44 (m, 2H), 7.46 (dd, 1H, J = 7.3, 1.0 Hz), 7.54 (dd, 1H, J = 7.8 and 1.2 Hz), 7.60 (dd, 1H, J = 8.4 and 7.2 Hz), 7.82 (d, 1H, J = 7.9 Hz), 7.85 (dd, 1H, J = 8.4 and 1.1 Hz), 8.20 (dd, 1H, J = 8.1 and 1.0 Hz), 8.24 (d, 1H, J = 8.2 Hz) ppm.

10-Fluoro-11-(2-fluorophenyl)-5-(methoxymethyl)indolo[2,3-*b*]quinoline (15b) and 10-(methoxymethyl)benzothiopyrano[4,3,2-*de*]indolo[2,3-b]quinoline. The general procedure (but at a 0.20 mmol scale) using 2-iodo-*N*-(methoxymethyl)indole (69 mg, 0.20 mmol) gave (eluent: petroleum ether–Et_2O 85 : 15; R_f = 0.14) 10-fluoro-11-(2-fluorophenyl)-*N*-(methoxymethyl)-indolo[2,3-*b*]quinoline (**15b**) in 85% yield (62 mg) as a brown solid: mp 168 °C; IR (ATR) ν 695, 752, 830, 882, 918, 995, 1076, 1177, 1233, 1268, 1284, 1315, 1396, 1487, 1595, 1716, 2149, 2863, 2943 cm^{-1}; ^1H NMR ($CDCl_3$, 300 K, 500 MHz) δ 3.45 (s, 3H, Me), 5.97 (d, 1H, *J* = 11.0 Hz, C*H*H), 6.00 (d, 1H, *J* = 11.0 Hz, CH*H*), 6.84 (d, 1H, *J* = 7.8 Hz), 7.04 (ddd, 1H, *J* = 7.6, 2.7 and 1.1 Hz), 7.05 (t, 1H, *J* = 7.6 Hz), 7.34 (t, 1H, *J* = 8.9 Hz), 7.38 (td, 1H, *J* = 7.5 and 1.1 Hz), 7.48 (td, 1H, *J* = 7.4 and 1.8 Hz), 7.50 (t, 1H, *J* = 7.1 Hz), 7.58–7.60 (m, 2H), 7.63 (ddd, 1H, *J* = 8.7, 7.6 and 5.5 Hz), 7.99 (d, 1H, *J* = 8.5 Hz) ppm; $^{13}C\{^1H\}$ NMR ($CDCl_3$, 300 K, 126 MHz) δ 56.8 (CH_3), 72.7 (CH_2), 108.7 (d, CH, *J* = 21.7 Hz), 110.1 (CH), 114.8 (d, C, *J* = 9.6 Hz), 116.0 (d, CH, *J* = 21.5 Hz), 117.9 (C), 120.9 (C), 121.3 (CH), 123.2 (CH), 124.5 (CH), 124.5 (d, CH, *J* = 7.9 Hz), 126.6 (dd, C, *J* = 17.4 and 3.3 Hz), 128.4 (d, CH, *J* = 10.1 Hz), 128.7 (CH), 130.4 (t, CH, *J* = 2.9 Hz), 130.5 (d, CH, *J* = 7.7 Hz), 133.3 (C), 142.3 (C), 148.3 (C), 152.8 (C), 159.5 (d, C, *J* = 243 Hz, C–F), 159.8 (d, C, *J* = 256 Hz, C–F) ppm; $^{19}F\{^1H\}$ NMR ($CDCl_3$, 300 K, 471 MHz) δ −114.5, −112.4 ppm. This compound was directly involved in the cyclization step to the hexacycle as follows. To **15b** (40 mg, 0.11 mmol) in dry DMF (1 mL) under argon, was added Na_2S (52 mg, 0.60 mmol). The mixture was stirred at 120 °C for 5 h and poured onto ice-water (5 mL). The product was extracted with AcOEt (3 × 10 mL), and the organic layer washed with brine (10 mL). The organic layer was dried over $MgSO_4$ before removal of the solvents under reduced pressure. The expected product was only detected in the crude by NMR (~10% yield).

Attempts to prepare 1-chlorobenzothiopyrano[3,2-*c*]pyridin-10-one (19) from 2-chloropyridine

3-(1-(2-Bromophenyl)hydroxymethyl)-2-chloropyridine (16). To a solution of TMPH (0.22 mL, 1.3 mmol) in THF (4 mL) at −80 °C under argon, was added dropwise a 1.4 M solution of *n*BuLi in hexane (0.90 mL, 1.2 mmol). The mixture was stirred for 15 min at this temperature before slow addition of 2-chloropyridine (95 μL, 1.0 mmol). After 1 h at −80 °C, 2-bromobenzaldehyde (0.14 mL, 1.2 mmol) was slowly added to the formed pyridyllithium. After warming to −10 °C, H_2O (10 mL) was added to the reaction mixture. The product was extracted with AcOEt (3 × 15 mL). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure to afford, after purification by column chromatography over silica gel (eluent: petroleum ether–AcOEt 80 : 20; R_f = 0.11), the title product in 94% yield (0.28 g) as a white solid: mp 114 °C; IR (ATR) ν 738, 750, 816, 854, 949, 1018, 1072, 1132, 1196, 1228, 1313, 1414, 1440, 1467, 1569, 3265 cm^{-1}; ^1H NMR ($CDCl_3$, 300 K, 500 MHz) δ 2.77 (d, 1H, *J* = 4.1 Hz, OH), 6.43 (d, 1H, *J* = 4.1 Hz, C*H*(OH)), 7.21 (ddd, 1H, *J* = 9.1, 7.4 and 2.1 Hz, H4′ or H5′), 7.27 (dd, 1H, *J* = 7.6 and 4.7 Hz, H5), 7.30 (dd, 1H, *J* = 7.8 and 2.1 Hz, H3′ or H6′), 7.33 (td, 1H, *J* = 7.4 and 0.95 Hz, H4′ or H5′), 7.60 (dd, 1H, *J* = 8.0 and 0.9 Hz, H3′ or H6′), 7.73 (dd, 1H, *J* = 7.6 and 1.7 Hz, H4), 8.35 (dd, 1H, *J* = 4.7 and 1.9 Hz, H6) ppm; JMOD$\{^1H\}$ NMR ($CDCl_3$, 300 K, 126 MHz) δ 71.7 (CH, CH(OH)), 122.8 (CH, C5), 123.8 (C), 127.9 (CH, C4′ or C5′), 128.6 (CH, C3′ or C6′), 129.9 (CH, C4′ or C5′), 133.3 (CH, C3′ or C6′), 136.3 (C), 137.4 (CH, C4), 140.1 (C), 148.9 (CH, C6), 150.7 (C) ppm.

3-(2-Bromobenzoyl)-2-chloropyridine (17).[83]

With Dess–Martin periodinane. To the alcohol **16** (0.88 g, 2.9 mmol) in THF (30 mL) under argon, was added Dess–Martin periodinane (DMP; 1.8 g, 4.2 mmol). The reaction mixture was stirred at rt for 3 h before being quenched with a saturated aqueous solution of $Na_2S_2O_3$ (9 mL). The product was extracted with AcOEt (3 × 20 mL). The organic layer was washed with a saturated aqueous solution of Na_2CO_3 (10 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure, and the residue was purified by column chromatography over silica gel (eluent: petroleum ether–AcOEt 75 : 25) to give the title product in 62% yield (0.53 g). It was identified by NMR: ^1H NMR ($CDCl_3$, 300 K, 300 MHz) δ 7.37 (dd, 1H, *J* = 7.6 and 4.8 Hz, H5), 7.39 (td, 1H, *J* = 7.5 and 2.1 Hz, H4′ or H5′), 7.43 (td, 1H, *J* = 7.4 and 1.9 Hz, H4′ or H5′), 7.51–7.54 (m, 1H, H3′ or H6′), 7.64–7.67 (m, 1H, H3′ or H6′), 7.90 (dd, 1H, *J* = 7.6 and 2.0 Hz, H4), 8.54 (dd, 1H, *J* = 4.8 and 2.0 Hz, H6) ppm; JMOD$\{^1H\}$ NMR ($CDCl_3$, 300 K, 126 MHz) δ 119.7 (C), 121.5 (CH), 123.8 (CH), 127.7 (CH), 129.6 (CH), 132.5 (CH), 133.7 (CH), 138.5 (C), 145.4 (C), 150.9 (CH), 152.8 (C), 193.7 (C, C=O) ppm. These data are close to those already reported.[55] *Crystal data for* **17**: $C_{12}H_7BrClNO$, *M* = 296.55, orthorhombic, *Pna*2_1, *a* = 13.664(2), *b* = 8.7402(15), *c* = 18.815(4) Å, *V* = 2247.0(7) Å^3, *Z* = 8, *d* = 1.753 g cm^{-3}, μ = 3.871 mm^{-1}. A final refinement on F^2 with 4810 unique intensities and 293 parameters converged at $\omega R(F^2)$ = 0.1482 (R_F = 0.0564) for 3506 observed reflections with ($I > 2\sigma$). CCDC 2204833.†

With 2-iodoxybenzoic acid. 2-Iodoxybenzoic acid (IBX; 0.84 g, 3.0 mmol) was added to a solution of **16** (0.30 g, 1.0 mmol) in AcOEt (7 mL) and the reaction mixture was heated in a preheated oil bath at 80 °C for 6 h. The reaction mixture was cooled to rt, filtrated over silica and the filter cake was thoroughly washed with AcOEt. The combined filtrates were concentrated under vacuum to give the crude product. This was purified by column chromatography over silica gel (eluent: petroleum ether–AcOEt 80 : 20 to 70 : 30) to give the title product in 95% yield (0.28 g).

By Swern oxidation. To a solution of oxalyl chloride (0.32 mL, 3.8 mmol) in dry CH_2Cl_2 (10 mL) at −80 °C under argon, was added dry DMSO (0.27 mL, 3.8 mmol), and the mixture was stirred for 15 min at this temperature. A solution of the alcohol **16** (0.76 g, 2.5 mmol) in dry CH_2Cl_2 (5 mL) was then added dropwise, and the mixture was allowed to reach −40 °C in 0.5 h and kept at this temperature for an additional hour. Et_3N (1.7 mL, 12.5 mmol) was next added slowly, and the mixture was warmed up to rt before addition of H_2O (20 mL). The product was extracted with CH_2Cl_2 (2 × 20 mL). The organic layer was dried over $MgSO_4$. The solvent was removed under reduced pressure, and the residue was purified by column chromatography over silica gel (eluent: CH_2Cl_2) to give the title product in 98% yield (1.3 g).

Product 18. Attempts to deprotonate 3-(2-bromobenzoyl)-2-chloropyridine (**17**) in the presence of *t*BuSS*t*Bu (1 equiv.), by treatment with LiTMP (1.1 equiv.) in THF at −90 °C under argon, led to the poorly soluble product **18** which was identified by HRMS (ASAP; Maxis 4G): *m*/*z* = 590.8869 (0 ppm) found (calcd for $C_{24}H_{15}N_2O_2{}^{35}Cl_2{}^{79}Br_2$, $[M + H]^+$, requires 590.88718). However, its 500 MHz ^1H and 75 MHz ^{13}C NMR spectra recorded in $(CD_3)_2SO$ proved complex, probably due to impeded rotations around C–C bonds.

Synthesis of 3-benzoyl-2-chloro-4-(methylthio)pyridine (21) and 3-benzoyl-2-chloro-4-(methylsulfinyl)pyridine (22a)

2-Chloro-4-(methylthio)pyridine. It was prepared by treating 2-chloro-4-fluoropyridine with NaSMe (1 equiv.) in MeOH at 30 °C for 2.5 h. After removal of the solvent under reduced pressure and column chromatography over silica gel (eluent: petroleum ether–AcOEt–NEt$_3$ 80 : 18:2), the title product was obtained in 16% yield as a white solid: IR (ATR) ν 685, 726, 791, 807, 821, 858, 950, 984, 1081, 1113, 1130, 1148, 1230, 1281, 1318, 1369, 1437, 1454, 1522, 1568, 1920, 2927, 3052 cm^{-1}; ^1H NMR ($CDCl_3$, 300 K, 500 MHz) δ 2.48 (s, 3H, Me), 7.00 (dd, 1H, *J* = 5.4 and 1.6 Hz, H5), 7.08 (d, 1H, *J* = 1.4 Hz, H3), 8.15 (d, 1H, *J* = 5.4 Hz, H6) ppm; JMOD{^1H} NMR ($CDCl_3$, 300 K, 126 MHz) δ 13.9 (CH_3), 118.9 (CH, C5), 119.3 (CH, C3), 148.7 (CH, C6), 151.9 (C, C2), 153.7 (C, C4) ppm.

3-Benzoyl-2-chloro-4-(methylthio)pyridine (21). To a solution of 3-benzoyl-2-chloropyridine (0.635 g, 3.0 mmol) and MeSSMe (265 μL, 3.0 mmol) in THF (10 mL) under argon at −110 °C, was added a solution of LiTMP [prepared in THF at −10 °C by adding dropwise to TMPH (0.54 mL, 3.3 mmol) in THF (5 mL) a 1.5 M solution of *n*BuLi in hexane (1.9 mL, 3.0 mmol) followed by 5 min stirring] cooled to the same temperature. After 30 min at −110 °C, the reaction mixture was quenched with a concentrated THF solution of HCl (1 mL). After neutralization, extraction with AcOEt (2 × 20 mL), drying of the organic layer over $MgSO_4$ and removal of the solvent under reduced pressure, the product was purified by column chromatography over silica gel (eluent: Et_2O) to give the title product in 78% yield (0.61 g) as a yellow solid: R_f ($CHCl_3$) = 0.35; mp 110 °C; IR (ATR) ν 666, 683, 704, 766, 815, 925, 960, 1122, 1163, 1201, 1228, 1271, 1314, 1378, 1420, 1451, 1529, 1562, 1597, 1669, 2987 cm^{-1}; ^1H NMR ($CDCl_3$, 300 K, 500 MHz) δ 2.45 (s, 3H, Me), 7.14 (d, 1H, *J* = 5.5 Hz, H5), 7.48 (t, 2H, *J* = 7.8 Hz, H3′ and H5′), 7.63 (tt, 1H, *J* = 7.4 and 1.1 Hz, H4′), 7.83 (dd, 2H, *J* = 8.4 and 1.25 Hz, H2′ and H6′), 8.33 (d, 1H, *J* = 5.5 Hz, H6) ppm; JMOD{^1H} NMR ($CDCl_3$, 300 K, 126 MHz) δ 14.9 (CH_3), 118.0 (CH, C5), 129.2 (2CH, C3′ and C5′), 129.7 (2CH, C2′ and C6′), 132.0 (C, C3), 134.6 (CH, C4′), 135.3 (C, C1′), 147.1 (C, C2 or C4), 149.4 (CH, C6), 151.8 (C, C2 or C4), 192.8 (C, C=O) ppm.

3-Benzoyl-2-chloro-4-(methylsulfinyl)pyridine (22a). To **21** (0.61 g, 2.3 mmol) in CH_2Cl_2 (10 mL) at 0 °C, was slowly added a solution of *m*CPBA (77%; 0.52 g, 2.3 mmol) in CH_2Cl_2 (8 mL). After 0.5 h at 0 °C, the solution was washed with 10% aqueous $NaHCO_3$ (20 mL) and brine (20 mL). The organic layer was dried over $MgSO_4$ before removal of the solvent under reduced pressure. After purification by column chromatography over silica gel (eluent: Et_2O then AcOEt), the title product was isolated in 64% yield (0.32 g) as a white solid: R_f ($CHCl_3$) = 0.15; mp 104 °C; IR (ATR) ν 737, 808, 847, 926, 959, 1001, 1075, 1111, 1155, 1200, 1225, 1267, 1314, 1364, 1429, 1450, 1541, 1558, 1581, 1596, 1667, 3062 cm^{-1}; ^1H NMR ($CDCl_3$, 300 K, 500 MHz) δ 2.86 (s, 3H, Me), 7.50 (t, 2H, *J* = 7.8 Hz, H3′ and H5′), 7.67 (tt, 1H, *J* = 7.4 and 1.3 Hz, H4′), 7.77 (d, 2H, *J* = 7.9 Hz, H2′ and H6′), 8.07 (d, 1H, *J* = 5.1 Hz, H5), 8.77 (d, 1H, *J* = 5.1 Hz, H6) ppm; JMOD{^1H} NMR ($CDCl_3$, 300 K, 126 MHz) δ 44.2 (CH_3, S(O)Me), 117.0 (CH, C5), 129.3 (2CH, C3′ and C5′), 129.8 (2CH, C2′ and C6′), 130.7 (C, C3), 135.2 (CH, C4′), 135.3 (C, C1′), 147.7 (C, C2 or C4), 151.8 (CH, C6), 159.2 (C, C2 or C4), 191.9 (C, C=O) ppm. Note that the sulfone **22b** was similarly isolated in 4% yield (21 mg) as a white solid: IR (ATR) ν 736, 748, 780, 818, 847, 924, 962, 1001, 1070, 1111, 1147, 1201, 1265, 1317, 1359, 1450, 1560, 1596, 1670, 2925 cm^{-1}; ^1H NMR ($CDCl_3$, 300 K, 300 MHz) δ 3.16 (s, 3H, Me), 7.43–7.49 (m, 2H, H3′ and H5′), 7.68 (tt, 1H, *J* = 7.4 and 1.3 Hz, H4′), 7.73–7.76 (m, 2H, H2′ and H6′), 7.93 (d, 1H, *J* = 5.1 Hz, H5), 8.76 (d, 1H, *J* = 5.1 Hz, H6) ppm.

Synthesis of 11-(2-(methylsulfinyl)phenyl)benzofuro[2,3-*b*]1,8-naphthyridine (27)

2-Fluoro-3-(2-(methylthio)benzoyl)pyridine (24a). To a solution of TMPH (0.85 mL, 5.0 mmol) in THF (7 mL) at −10 °C under argon, was added dropwise a 1.4 M solution of *n*BuLi in hexane (3.7 mL, 5.0 mmol). After stirring for 5 min at this temperature, this solution of LiTMP was treated with CuCl (0.25 g, 2.5 mmol), and the resulting mixture was stirred for additional 15 min. 2-Fluoropyridine (0.215 mL, 2.5 mmol) was then introduced, and the mixture was stirred for 2 h at rt. 2-(Methylthio)benzoyl chloride (0.93 g, 5.0 mmol) in THF (15 mL) was next introduced, and the reaction mixture was stirred overnight at 40 °C. It was then cooled to rt, and quenched with aqueous 1 M NaOH (20 mL). The product was extracted with Et_2O (3 × 20 mL). The organic layer was washed with a saturated aqueous solution of NH_4Cl (10 mL), dried over $MgSO_4$ and concentrated under reduced pressure to afford, after purification by column chromatography over silica gel (eluent: petroleum ether–AcOEt 80 : 20; R_f = 0.14), the title ketone in 80% yield (0.51 g) as a yellow solid: mp 176 °C; IR (ATR) ν 669, 688, 741, 760, 784, 815, 849, 927, 963, 1047, 1098, 1130, 1171, 1210, 1261, 1313, 1429, 1458, 1567, 1586, 1597, 1647, 1736, 2927, 2984, 3063 cm^{-1}; ^1H NMR ($CDCl_3$, 300 K, 300 MHz) δ 2.29 (s, 3H, Me), 7.03 (ddd, 1H, *J* = 8.0, 7.2 and 1.2 Hz, H4′ or H5′), 7.21 (ddd, 1H, *J* = 7.4, 4.9 and 1.9 Hz, H5), 7.23 (dd, 1H, *J* = 8.1 and 1.2 Hz, H3′ or H6′), 7.29 (dtd, 1H, *J* = 7.8, 1.5 and 0.5 Hz, H3′ or H6′), 7.34 (ddd, 1H, *J* = 8.1, 7.2 and 1.5 Hz, H4′ or H5′), 7.90 (ddd, 1H, *J* = 9.4, 7.4 and 2.0 Hz, H4), 8.22 (ddd, 1H, *J* = 4.9, 2.1 and 1.1 Hz, H6) ppm; $^{13}C\{^1H\}$ NMR ($CDCl_3$, 300 K, 75 MHz) δ 15.8 (CH_3), 121.5 (d, CH, *J* = 4.6 Hz, C5), 121.6 (d, C, *J* = 28.6 Hz, C3), 123.7 (CH), 125.8 (CH), 131.4 (d, CH, *J* = 1.7 Hz, C5), 132.4 (CH), 134.7 (C), 141.6 (d, CH, *J* = 3.0 Hz, C4), 141.7 (C), 150.3 (d, CH, *J* = 15.0 Hz, C6), 159.8 (d, C, *J* = 244 Hz, C2, C–F), 191.2 (d, C, *J* = 4.9 Hz, C=O) ppm; $^{19}F\{^1H\}$ NMR ($CDCl_3$, 300 K, 282 MHz) δ −63.95 (d, *J* = 9.1 Hz) ppm.

2-Fluoro-3-(5-chloro-2-fluorobenzoyl)pyridine (24b). It was similarly prepared from 2-fluoropyridine (0.27 mL, 5.0 mmol) and 5-chloro-2-fluorobenzoyl chloride (0.7 mL, 5.3 mmol). The title ketone was isolated, after purification by column chromatography over silica gel (eluent: petroleum ether–AcOEt 80 : 20), in 74% yield (0.94 g) as a yellow oil: IR (ATR) ν 702, 743, 776, 818, 860, 895, 960, 1102, 1117, 1158, 1202, 1225, 1251, 1273, 1302, 1401, 1427, 1458, 1476, 1571, 1598, 1667, 3064 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 K, 500 MHz) δ 7.10 (dd, 1H, J = 9.7 and 8.8 Hz, H3′), 7.37 (ddd, 1H, J = 7.5, 4.9 and 1.9 Hz, H5), 7.53 (ddd, 1H, J = 8.8, 4.3 and 2.7 Hz, H4′), 7.72 (dd, 1H, J = 6.0 and 2.7 Hz, H6′), 8.18 (ddd, 1H, J = 9.3, 7.4 and 2.0 Hz, H4), 8.42 (ddd, 1H, J = 4.9, 2.1 and 1.1 Hz, H6) ppm; ^{13}C{^{1}H} NMR ($CDCl_3$, 300 K, 126 MHz) δ 118.0 (d, CH, J = 24.3 Hz, C3′), 121.8 (d, C, J = 1.0 Hz), 122.0 (d, CH, J = 4.5 Hz, C5), 127.7 (d, C, J = 13.9 Hz), 130.3 (d, C, J = 3.3 Hz), 130.5 (d, CH, J = 2.4 Hz, C6′), 134.7 (d, CH, J = 9.0 Hz, C4′), 141.8 (d, CH, J = 2.7 Hz, C4), 151.7 (d, CH, J = 15.5 Hz, C6), 159.7 (d, C, J = 256 Hz, C–F, C2′), 160.7 (d, C, J = 245 Hz, C–F, C2), 187.1 (d, C, J = 5.2 Hz, C=O) ppm; ^{19}F{^{1}H} NMR ($CDCl_3$, 300 K, 471 MHz) δ −114.5 (d, J = 2.5 Hz), −64.3 ppm.

2-Amino-3-(2-(methylthio)benzoyl)pyridine (23). A mixture of 2-fluoro-3-(2-methylthio)benzoylpyridine (**24a**; 0.51 g, 2.0 mmol) and 32% aqueous NH_4OH (65 mL) was heated overnight at 50 °C. It was next allowed to cool down to rt, and the precipitate was filtered. It was dissolved in CH_2Cl_2 (20 mL). The organic layer was dried over $MgSO_4$, and concentrated under reduced pressure to afford the title product in a quantitative yield (0.49 g) as a yellow powder: R_f (petroleum ether–AcOEt 80 : 20) = 0.32; mp not measured due to decomposition; IR (ATR) ν 740, 761, 844, 932, 971, 1066, 1126, 1240, 1302, 1354, 1430, 1549, 1585, 1618, 2974, 3142, 3406 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 K, 500 MHz) δ 2.42 (s, 3H, Me), 6.54 (dd, 1H, J = 7.8 and 4.7 Hz, H5), 6.98 (br s, 2H, NH_2), 7.23 (dd, 1H, J = 7.7 and 1.7 Hz, H3′ or H6′), 7.25 (td, 1H, J = 7.5 and 1.2 Hz, H4′ or H5′), 7.40 (d, 1H, J = 7.6 Hz, H3′ or H6′), 7.44 (ddd, 1H, J = 8.1, 6.4 and 2.2 Hz, H4′ or H5′), 7.52 (dd, 1H, J = 7.8 and 1.9 Hz, H4), 8.24 (dd, 1H, J = 4.7 and 1.9 Hz, H6) ppm; ^{13}C{^{1}H} NMR ($CDCl_3$, 300 K, 126 MHz) δ 17.1 (CH_3), 112.5 (CH, C5), 113.3 (C, C3), 125.3 (CH, C4′ or C5′), 127.9 (CH, C3′ or C6′), 128.1 (CH, C3′ or C6′), 130.5 (CH, C4′ or C5′), 136.8 (C), 139.6 (C), 143.3 (CH, C4), 154.7 (CH, C6), 159.6 (C, C2), 198.1 (C, C=O) ppm.

2-Amino-3-(5-chloro-2-fluorobenzoyl)pyridine (25). Similarly, 2-fluoro-3-(5-chloro-2-fluoro)benzoylpyridine (**24b**; 0.94 g, 3.7 mmol) was converted to the title product, which was obtained in 84% yield (0.77 g) as a yellow solid: R_f (petroleum ether–AcOEt 80 : 20) = 0.11; mp 174 °C; IR (ATR) ν 704, 782, 810, 880, 954, 1080, 1106, 1140, 1158, 1221, 1256, 1299, 1348, 1398, 1433, 1474, 1549, 1618, 3127, 3398 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 K, 500 MHz) δ 6.61 (dd, 1H, J = 7.9 and 4.7 Hz, H5), 7.06 (br s, 2H, NH_2), 7.11 (t, 1H, J = 8.8 Hz, H3′), 7.39 (dd, 1H, J = 5.8 and 2.7 Hz, H6′), 7.45 (ddd, 1H, J = 8.5, 4.4 and 2.8 Hz, H4′), 7.61 (dt, 1H, J = 8.1 and 2.4 Hz, H4), 8.28 (dd, 1H, J = 4.8 and 1.8 Hz, H6) ppm; ^{13}C{^{1}H} NMR ($CDCl_3$, 300 K, 126 MHz) δ 112.7 (CH, C5), 112.8 (C, C3), 117.8 (d, CH, J = 23.5 Hz, C3′), 129.0 (d, C, J = 18.6 Hz, C1′), 129.6 (d, CH, J = 3.8 Hz, C6′), 130.0 (d, C, J = 3.4 Hz, C5′), 132.2 (d, CH, J = 8.2 Hz, C4′), 143.0 (d, CH, J = 2.3 Hz, C4), 155.3 (CH, C6), 157.5 (d, C, J = 250 Hz, C–F, C2′), 159.5 (C, C2), 192.4 (C, C=O) ppm; ^{19}F NMR ($CDCl_3$, 300 K, 471 MHz) δ −115.7 ppm.

2-Iodobenzofuran[43]. To benzofuran (3.3 mL, 30 mmol) in THF (90 mL) at 0 °C under argon, was added dropwise a 1.4 M solution of *n*BuLi in hexane (53 mL, 75 mmol). After warming to rt, the resulting solution was stirred for 2 h. It was next cooled down to 0 °C before slow addition of a solution of I_2 (15.2 g, 60 mmol) in THF (20 mL). The resulting solution was warmed to rt and stirred for 2 h. It was then treated with 100 mL of a saturated solution of $Na_2S_2O_3$ and extracted with CH_2Cl_2 (3 × 50 mL). The organic layer was washed with brine (100 mL) and dried over $MgSO_4$. After removal of the solvent under reduced pressure, the product was purified by column chromatography over silica gel (eluent: petroleum ether). It was isolated in 67% yield (4.8 g) and identified by NMR: ^{1}H NMR ($CDCl_3$, 300 K, 300 MHz) δ 6.96 (s, 1H, H3), 7.20–7.25 (m, 2H), 7.48–7.53 (m, 2H) ppm. The amine **23** was directly involved in the tandem *N*-arylation-cyclization.

11-(2-(Methylthio)phenyl)benzofuro[2,3-b]1,8-naphthyridine (26). To 2-amino-3-(2-methylthio)benzoylpyridine (**23**; 0.37 g, 1.5 mmol) in degassed Bu_2O (2 mL) under argon, were added 2-iodobenzofuran (0.55 g, 2.25 mmol), activated Cu (18 mg, 0.30 mmol) and K_2CO_3 (0.415 g, 3.0 mmol). The reaction mixture was stirred for 16 h in a preheated oil bath at 160 °C while activated Cu (18 mg, 0.30 mmol) was added after 2 h, 4 h, 6 h and 8 h. After cooling to rt and filtration through Celite® to remove copper, H_2O (10 mL) was added before extraction with AcOEt (2 × 20 mL). The solvents were removed under reduced pressure. Purification was performed by column chromatography over silica gel (eluent: $CHCl_3$–AcOEt 50 : 50) to give the title product in 50% yield (0.255 g). This compound was identified by NMR: ^{1}H NMR ($CDCl_3$, 300 K, 500 MHz) δ 2.29 (s, 3H, Me), 6.94 (d, 1H, J = 7.5 Hz), 7.15 (t, 1H, J = 7.6 Hz), 7.30 (dd, 1H, J = 7.5 and 1.5 Hz), 7.41 (td, 1H, J = 7.5 and 1.3 Hz), 7.49 (ddd, 1H, J = 8.3, 7.8 and 1.0 Hz), 7.52 (d, 1H, J = 8.2 Hz), 7.46 (br s, 1H, H9), 7.62 (d, 1H, J = 7.1 Hz, H4), 7.64 (td, 1H, J = 7.7 and 1.25 Hz), 8.04 (br d, 1H, J = 7.3 Hz, H10), 9.17 (br s, 1H, H8) ppm; JMOD{^{1}H} NMR ($CDCl_3$, 300 K, 126 MHz) δ 15.7 (CH_3, Me), 112.1 (CH, C4), 117.5 (C), 121.8 (C), 123.0 (CH), 123.8 (CH), 125.6 (CH, C9), 126.0 (CH), 129.7 (CH), 129.9 (CH), 130.1 (C), 130.3 (CH), 132.6 (C), 135.4 (CH, C10), 138.5 (C), 142.5 (C), 153.2 (CH), 154.2 (C), 156.3 (C), 164.3 (C) ppm (1CH not seen).

11-(2-(Methylsulfinyl)phenyl)benzofuro[2,3-*b*]1,8-naphthyridine (27). To 11-(2-(methylthio)phenyl)benzofuro[2,3-*b*]quinoline (**26**; 0.235 g, 0.70 mmol) in CH_2Cl_2 (5 mL) at 0 °C, was slowly added a solution of *m*CPBA (77%; 0.195 g, 0.70 mmol) in CH_2Cl_2 (4 mL). After 6 h at 0 °C, the solution was washed with 10% aqueous NaOH (5 mL), 5% aqueous HCl (5 mL) and 10% aqueous $NaHCO_3$ (5 mL). The organic layer was dried over $MgSO_4$ before removal of the solvent under reduced pressure to give the title product in 79% yield (0.18 g) as a brown solid: IR (ATR) ν 677, 724, 751, 788, 819, 878, 910, 950, 1036, 1068, 1101, 1127, 1148, 1182, 1217, 1252, 1313, 1330, 1383, 1453, 1505, 1591, 2233, 2921, 3058, 3428 cm^{-1};

^{1}H NMR ($CDCl_3$, 300 K, 300 MHz; mixture of rotamers) δ 2.19 and 2.21 (s, 3H, Me), 6.80 and 6.93 (d, 1H, J = 7.7 Hz), 7.15 (td, 1H, J = 7.5 and 2.1 Hz), 7.47–7.62 (m, 4H), 7.82 (t, 1H, J = 7.4 Hz), 7.91–8.04 (m, 2H), 8.39 (d, 1H, J = 7.8 Hz), 9.12 (br s, 1H, H8) ppm; ^{1}H NMR ($(CD_3)_2SO$, 300 K, 500 MHz; mixture of rotamers) δ 2.22 and 2.26 (s, 3H, Me), 6.78 and 6.81 (d, 1H, J = 7.7 Hz), 7.30 and 7.31 (t, 1H, J = 7.6 Hz), 7.62–7.70 (m, 3H), 7.86 and 7.87 (d, 1H, J = 8.2 Hz), 7.92 (t, 1H, J = 7.5 Hz), 8.05 (t, 2H, J = 7.9 Hz), 8.29 and 8.30 (d, 1H, J = 7.9 Hz), 9.17 (br s, 1H, H8) ppm; ^{1}H NMR ($(CD_3)_2SO$, 375 K, 500 MHz; mixture of rotamers) δ 2.25 and 2.28 (s, 3H, Me), 6.83 and 6.86 (d, 1H, J = 7.8 Hz), 7.28 and 7.29 (t, 1H, J = 7.6 Hz), 7.59–7.67 (m, 3H, H3, H9), 7.81 (d, 1H, J = 8.4 Hz, H4), 7.91 (t, 1H, J = 7.5 Hz), 8.02–8.06 (m, 2H), 8.30 and 8.31 (d, 1H, J = 8.1 Hz), 9.11 and 9.16 (br s, 1H, H8) ppm; JMOD{^{1}H} NMR ($(CD_3)_2SO$, 375 K, 126 MHz; mixture of rotamers) δ 42.3 (CH_3, Me), 111.6/111.7 (CH, C4), 115.7/116.6 (C), 118.9/119.6 (C), 120.4/120.6 (C), 121.0 (CH), 121.5/121.6 (CH), 123.6/123.7 (CH), 123.8/123.9 (CH), 129.5/129.8 (CH), 129.9/129.9 (CH), 130.4/130.5 (C), 130.7/130.8 (CH), 131.4/131.6 (CH), 134.0/134.2 (CH), 139.1/139.3 (C), 145.4/145.5 (C), 152.9 (CH, C8), 153.1 (C), 155.2/155.3 (C), 162.7/162.8 (C) ppm; HRMS (ASAP; Maxis 4G), m/z = 359.0852 (1 ppm) found (calcd for $C_{21}H_{15}N_2O_2S$, $[M + H]^+$, requires 359.08487).

Attempt to prepare benzofuro[2,3-*b*]benzothiopyrano[4,3,2-*de*]-1,8-naphthyridine (28) from 27

By using Eaton's reagent. The sulfoxide **27** (0.10 g, 0.28 mmol) was dissolved under argon in Eaton's reagent (3.5 mL) and the viscous mixture was stirred for 2 days at rt. Ice-water (30 mL) was then added, and the brown sulfonium salt was isolated by filtration. Its demethylation was achieved by stirring for 8 h a solution in pyridine (18 mL) and H_2O (2 mL). After neutralization with a saturated aqueous solution of $NaHCO_3$ (20 mL) and extraction with CH_2Cl_2 (3 × 20 mL), the organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. However, the expected product was not detected in the crude.

By using triflic acid as solvent. As previously, but using triflic acid instead of the Eaton's reagent before demethylation. A complex mixture was similarly obtained.

By using triflic acid with dichloromethane. The sulfoxide **27** (0.18 g, 0.50 mmol) was dissolved under argon in dry CH_2Cl_2 (5 mL), and triflic acid (1 mL, 11 mmol) was slowly added at 0 °C. The reaction mixture was stirred for 24 h at rt, and poured slowly onto a solution of pyridine (27 mL) and H_2O (3 mL). The resulting solution was heated under reflux for 30 min and cooled down to rt. It was diluted with CH_2Cl_2 (20 mL), and washed with H_2O (20 mL) and brine (20 mL). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The starting material was recovered under these conditions.

Synthesis of 5-methyl-10-(methylsulfinyl)-11-phenylindolo[2,3-*b*]-1,8-naphthyridine (34)

***tert*-Butyl *N*-(2-pyridyl)carbamate.** Di-*tert*-butyl dicarbonate (22 g, 0.10 mol) was added portionwise to a solution of 2-aminopyridine (9.4 g, 0.10 mol) and I_2 (0.25 g, 1.0 mmol) in *tert*-butanol (100 mL) at 45 °C. After addition, the reaction mixture was stirred at 45 °C for 14 h. Aqueous saturated $Na_2S_2O_3$ (10 mL) and H_2O (200 mL) were added to the reaction mixture which was extracted with AcOEt (3 × 100 mL). The combined organic layers were dried over $MgSO_4$, filtrated and concentrated under reduced pressure to give the crude product. It was purified by column chromatography over silica gel (eluent: petroleum ether–AcOEt 80 : 20 to 70 : 30) to give the title product in 60% yield as a white solid (11.6 g): R_f (petroleum ether–AcOEt 70 : 30) = 0.89; mp 95–96 °C; IR (ATR) ν 735, 753, 773, 804, 840, 902, 993, 1027, 1049, 1063, 1111, 1152, 1167, 1234, 1256, 1267, 1292, 1308, 1365, 1390, 1468, 1531, 1586, 1715, 2982, 3183 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 K, 500 MHz) δ 1.54 (s, 9H, *t*Bu), 6.93 (ddd, 1H, J = 7.4, 5.0 and 1.1 Hz, H5), 7.65 (ddd, 1H, J = 8.9, 7.3 and 2.0 Hz, H4), 8.00 (d, 1H, J = 8.5 Hz, H3), 8.35 (ddd, 1H, J = 5.0, 2.1 and 0.9 Hz, H6), 9.54 (br s, 1H, NH) ppm; JMOD{^{1}H} NMR ($CDCl_3$, 300 K, 126 MHz) δ 28.5 ($3CH_3$, C*Me*$_3$), 80.8 (C, *C*Me$_3$), 112.7 (CH, C3), 118.1 (CH, C5), 138.4 (CH, C4), 147.8 (CH, C6), 152.9 (C, C2 or C=O), 153.0 (C, C2 or C=O) ppm. These data are as described previously.[84]

2-(*tert*-Butoxycarbonylamino)-3-((1-phenyl)hydroxymethyl)-pyridine (29). To a solution of *tert*-butyl *N*-(2-pyridyl)carbamate (1.9 g, 10 mmol) in dry THF (25 mL) under argon at −80 °C, was added dropwise a 1.6 M pentane solution of *t*BuLi (15 mL, 24 mmol). The reaction mixture was stirred at −80 °C for 15 min before being warmed to −20 °C. The reaction mixture was stirred at −20 °C for 2.5 h and was then cooled to −40 °C. A solution of benzaldehyde (1.3 mL, 13 mmol) in THF (8 mL) was added dropwise and the reaction mixture was then warmed to −20 °C. It was quenched by H_2O (20 mL) and the layers were separated. The product remaining in the aqueous phase was extracted with AcOEt (3 × 30 mL). The combined organic layers were washed with brine (10 mL) and dried over $MgSO_4$. After removal of the solvents under reduced pressure, the residue was purified by chromatography over silica gel (eluent: AcOEt–petroleum ether 50 : 50; R_f = 0.36) to give the title product in 31% yield (0.93 g) as a white solid: mp 168–169 °C; IR (ATR) ν 727, 756, 773, 793, 821, 843, 879, 920, 1023, 1046, 1148, 1229, 1254, 1322, 1369, 1392, 1445, 1460, 1515, 1591, 1731, 2974, 3223 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 K, 500 MHz) δ 1.49 (s, 9H, *t*Bu), 4.31 (br s, 1H, OH), 5.96 (s, 1H, C*H*(OH)), 7.02 (dd, 1H, J = 7.7 and 4.8 Hz, H5), 7.25–7.29 (m, 1H, H4′), 7.31–7.37 (m, 4H, H2′, H3′, H5′ and H6′), 7.45 (dd, 1H, J = 7.7 and 1.8 Hz, H4), 7.81 (br s, 1H, NH), 8.32 (dd, 1H, J = 4.8 and 1.8 Hz, H6) ppm; JMOD{^{1}H} NMR ($CDCl_3$, 300 K, 126 MHz) δ 28.4 ($3CH_3$, C*Me*$_3$), 72.0 (CH, CH(OH)), 81.4 (C, *C*Me$_3$), 120.8 (CH, C5), 126.4 (2CH, C2′ and C6′), 127.6 (CH, C4′), 128.5 (2CH, C3′ and C5′), 131.7 (C, C3), 138.7 (CH, C4), 141.9 (C, C1′), 147.8 (CH, C6), 149.3 (C, C2), 154.2 (C, C=O) ppm.

2-((*tert*-Butoxycarbonyl)(methoxymethyl)amino)pyridine. To a solution of *tert*-butyl *N*-(2-pyridyl)carbamate (1.9 g, 10 mmol) in dry THF (50 mL) and DMF (5 mL) under argon at rt was added NaH (1.3 g, 30 mmol) portionwise. After 5 min at rt, $ClCH_2OMe$ (MOMCl; 0.91 mL, 12 mmol) was added dropwise and the reaction mixture was stirred at rt for 15 min before addition of H_2O (100 mL). After extraction with AcOEt (2 × 30 mL), drying of the organic layer over $MgSO_4$ and removal of the solvent under reduced pressure, the product was purified by column chromatography over silica gel (eluent: petroleum ether–AcOEt 80 : 20 to 70 : 30) to give the title product in 88% yield (2.1 g) as a colorless oil: R_f (petroleum ether–AcOEt 80 : 20) = 0.48; IR (ATR) ν 744, 757, 786, 813, 857, 913, 976, 993, 1073, 1094, 1143, 1253, 1281, 1310, 1367, 1402, 1435, 1472, 1573, 1589, 1707, 2935, 2978 cm^{-1}; ^1H NMR ($CDCl_3$, 300 K, 500 MHz) δ 1.49 (s, 9H, *t*Bu), 3.38 (s, 3H, CH_2OMe), 5.32 (s, 2H, CH_2OMe), 7.06 (ddd, 1H, *J* = 7.5, 4.9 and 1.1 Hz, H5), 7.47 (d, 1H, *J* = 8.2 Hz, H3), 7.64 (ddd, 1H, *J* = 8.2, 7.4 and 2.0 Hz, H4), 8.41 (dd, 1H, *J* = 4.9 and 1.3 Hz, H6) ppm; JMOD{^1H} NMR ($CDCl_3$, 300 K, 126 MHz) δ 28.3 ($3CH_3$, CMe_3), 56.5 (CH_3, OMe), 78.5 (CH_2), 81.8 (C, CMe_3), 120.6 (CH, C5), 120.9 (CH, C3), 137.3 (CH, C4), 148.2 (CH, C6), 154.0 (C, C2 or C═O), 154.1 (C, C2 or C═O) ppm.

3-Benzoyl-2-(*tert*-butoxycarbonylamino)pyridine (30). To the alcohol **29** (0.75 g, 2.5 mmol) in dry CH_2Cl_2 (30 mL), was added Dess–Martin periodinane (DMP; 1.6 g, 3.8 mmol). The reaction mixture was stirred at rt for 15 min before being quenched with H_2O (10 mL). The product was extracted with CH_2Cl_2 (3 × 10 mL). The organic layer was dried over $MgSO_4$. The solvent was removed under reduced pressure, and the residue was purified by column chromatography over silica gel (eluent: AcOEt–petroleum ether 50 : 50; R_f = 0.57) to give the title product in a quantitative yield (745 mg) as a white solid: mp 175–176 °C; IR (ATR) ν 708, 745, 763, 771, 788, 814, 839, 902, 931, 939, 960, 1028, 1051, 1066, 1087, 1148, 1221, 1272, 1308, 1367, 1395, 1444, 1517, 1579, 1593, 1670, 1726, 2989, 3069, 3172 cm^{-1}; ^1H NMR ($CDCl_3$, 300 K, 500 MHz) δ 1.46 (s, 9H, *t*Bu), 7.02 (dd, 1H, *J* = 7.8 and 4.8 Hz, H5), 7.47 (t, 2H, *J* = 7.7 Hz, H3′ and H5′), 7.58 (tt, 1H, *J* = 7.5 and 1.3 Hz, H4′), 7.68 (dd, 2H, *J* = 8.3 and 1.4 Hz, H2′ and H6′), 7.86 (dd, 1H, *J* = 7.8 and 1.9 Hz, H4), 8.60 (dd, 1H, *J* = 4.8 and 1.9 Hz, H6), 9.69 (br s, 1H, NH) ppm; JMOD{^1H} NMR ($CDCl_3$, 300 K, 126 MHz) δ 28.3 ($3CH_3$, CMe_3), 81.3 (C, CMe_3), 117.3 (CH, C5), 119.5 (C, C3), 128.5 (2CH, C3′ and C5′), 129.8 (2CH, C2′ and C6′), 132.8 (CH, C4′), 137.8 (C, C1′), 141.6 (CH, C4), 151.3 (C, C2 or N–C═O), 152.1 (C, C2 or N–C═O), 152.5 (CH, C6), 197.0 (C, C═O) ppm. Swern oxidation gave **30** in 7% yield due to competitive cyclization between the alcohol and the carbamate of **27** giving 1,4-dihydro-4-phenylpyrido[2,3-*d*][1,3]2-oxazinone: ^1H NMR ($CDCl_3$, 300 K, 300 MHz) δ 6.36 (s, 1H, *CH*-Ph), 7.00 (dd, 1H, *J* = 7.6 and 5.0 Hz, H5), 7.19 (d, 1H, *J* = 7.5 Hz, H4), 7.35–7.38 (m, 2H, Ph), 7.41–7.45 (m, 3H, Ph), 8.36 (dd, 1H, *J* = 5.2 and 1.7 Hz, H6), 9.55 (br s, 1H, NH) ppm.

3-Benzoyl-2-((*tert*-butoxycarbonyl)(methoxymethyl)amino)pyridine (31). To a solution of 3-benzoyl-2-(*tert*-butoxycarbonylamino)pyridine (**30**; 2.2 g, 7.5 mmol) in THF (50 mL) and DMF (5 mL) at rt under argon was added NaH (0.98 g, 22.5 mmol) portionwise. After 5 min at rt, $ClCH_2OMe$ (MOMCl; 0.68 mL, 9.0 mmol) was added dropwise and the reaction mixture was stirred at rt for 15 min before addition of H_2O (100 mL). After extraction with AcOEt (2 × 30 mL), drying of the organic layer over $MgSO_4$ and removal of the solvent under reduced pressure, the product was purified by column chromatography over silica gel (eluent: petroleum ether–AcOEt 60 : 40) to give the title product in 91% yield (2.35 g) as a colorless oil: R_f (petroleum ether–AcOEt 50 : 50) = 0.58; IR (ATR) ν 705, 764, 787, 824, 853, 923, 977, 1001, 1082, 1111, 1151, 1199, 1254, 1271, 1295, 1367, 1400, 1431, 1449, 1581, 1598, 1669, 1704, 2976 cm^{-1}; ^1H NMR ($CDCl_3$, 300 K, 500 MHz) δ 1.30 (s, 9H, *t*Bu), 3.41 (s, 3H, CH_2OMe), 5.20 (br s, 2H, CH_2OMe), 7.24 (dd, 1H, *J* = 7.6 and 4.8 Hz, H5), 7.44 (t, 2H, *J* = 7.8 Hz, H3′ and H5′), 7.57 (tt, 1H, *J* = 7.4 and 1.3 Hz, H4′), 7.76 (dd, 1H, *J* = 7.7 and 1.9 Hz, H4), 7.80 (dd, 2H, *J* = 8.0 and 1.5 Hz, H2′ and H6′), 8.59 (dd, 1H, *J* = 5.0 and 1.9 Hz, H6) ppm; JMOD{^1H} NMR ($CDCl_3$, 300 K, 126 MHz) δ 28.1 ($3CH_3$, CMe_3), 57.2 (CH_3, OMe), 79.7 (CH_2), 82.2 (C, CMe_3), 120.9 (CH, C5), 128.4 (2CH, C3′ and C5′), 130.2 (2CH, C2′ and C6′), 131.0 (C, C3), 133.2 (CH, C4′), 138.4 (CH, C4), 150.2 (CH, C6), 136.5 (C, C1’), 152.1 (C, C2), 154.0 (C, N–C═O), 194.1 (C, C═O) ppm.

3-Benzoyl-2-((*tert*-butoxycarbonyl)(methoxymethyl)amino)-4-(methylthio)pyridine (32). To a solution of 3-benzoyl-2-((*tert*-butoxycarbonyl)(methoxymethyl)amino)pyridine (**31**; 0.34 g, 1.0 mmol) and MeSSMe (0.18 mL, 2.0 mmol) in THF (3 mL) under argon at −50 °C, was added a solution of LiTMP [prepared in THF at −10 °C by adding dropwise to TMPH (0.34 mL, 2.0 mmol) in THF (3 mL) a 1.4 M solution of *n*BuLi in hexane (1.4 mL, 2.0 mmol) followed by 5 min stirring] cooled to the same temperature. After 15 min at −50 °C, the reaction mixture was quenched with MeOH (1 mL) then H_2O (15 mL). After extraction with AcOEt (2 × 20 mL), drying of the organic layer over $MgSO_4$ and removal of the solvent under reduced pressure, the product was purified by column chromatography over silica gel (eluent: AcOEt–petroleum ether 50 : 50 to 60 : 40) to give the title product in 62% yield (0.24 g) as a white solid: R_f (AcOEt–petroleum ether 50 : 50) = 0.27; mp 121–122 °C; IR (ATR) ν 709, 773, 794, 805, 858, 914, 927, 991, 1036, 1081, 1110, 1147, 1208, 1221, 1269, 1290, 1302, 1364, 1400, 1430, 1537, 1559, 1582, 1594, 1663, 1703, 2930, 2981 cm^{-1}; ^1H NMR ($CDCl_3$, 300 K, 500 MHz) δ 1.27 (s, 9H, *t*Bu), 2.44 (s, 3H, SMe), 3.24 (s, 3H, CH_2OMe), 4.86 (br s, 2H, CH_2OMe), 7.15 (d, 1H, *J* = 5.4 Hz, H5), 7.42 (t, 2H, *J* = 7.8 Hz, H3′ and H5′), 7.56 (tt, 1H, *J* = 7.4 and 1.3 Hz, H4′), 7.78 (d, 2H, *J* = 7.7 Hz, H2′ and H6′), 8.48 (d, 1H, *J* = 5.4 Hz, H6) ppm; JMOD{^1H} NMR ($CDCl_3$, 300 K, 126 MHz) δ 15.2 (CH_3, SMe), 28.0 ($3CH_3$, CMe_3), 56.7 (CH_3, OMe), 80.5 (CH_2), 81.8 (C, CMe_3), 118.1 (CH, C5), 128.6 (2CH, C3′ and C5′), 129.9 (2CH, C2′ and C6′), 131.2 (C, C3), 134.0 (CH, C4′), 136.2 (C, C1′), 149.2 (CH, C6), 150.8 (C, C4), 151.1 (C, C2), 154.0 (C, N–C═O), 193.9 (C, C═O) ppm.

2-Amino-3-benzoyl-4-(methylthio)pyridine (20). Deprotection of the amino group was performed by treating a solution of 3-benzoyl-2-((*tert*-butoxycarbonyl)(methoxymethyl)amino)-4-(methylthio)pyridine (**32**; 0.66 g, 1.7 mmol) in THF (5.5 mL) with aqueous HCl (6 M, 2.8 mL, 17 mmol) at 50 °C overnight. After neutralization using aqueous saturated $NaHCO_3$ (10 mL), NaCl was added until saturation. After extraction with AcOEt (3 × 15 mL), drying of the organic layer over $MgSO_4$ and removal of the solvent under reduced pressure, the product was purified by column chromatography over silica gel (eluent: AcOEt–petroleum ether 70 : 30; R_f = 0.36) to give the title product in 93% yield (0.39 mg) as a white solid: mp 140–141 °C; IR (ATR) ν 752, 776, 794, 921, 969, 1001, 1025, 1070, 1123, 1149, 1174, 1208, 1243, 1265, 1310, 1357, 1436, 1459, 1540, 1558, 1594, 1636, 1659, 2928, 3133, 3303, 3420 cm^{-1}; ^{1}H NMR (CDCl$_3$, 300 K, 500 MHz) δ 2.35 (s, 3H, SMe), 4.86 (br s, 2H, NH$_2$), 6.60 (d, 1H, J = 5.5 Hz, H5), 7.47 (t, 2H, J = 7.9 Hz, H3′ and H5′), 7.61 (tt, 1H, J = 7.1 and 1.3 Hz, H4′), 7.83 (dd, 2H, J = 8.3 and 1.4 Hz, H2′ and H6′), 8.05 (d, 1H, J = 5.6 Hz, H6) ppm; JMOD{^{1}H} NMR (CDCl$_3$, 300 K, 126 MHz) δ 15.6 (CH$_3$, SMe), 110.5 (CH, C5), 116.0 (C, C3), 129.0 (2CH, C3′ and C5′), 129.7 (2CH, C2′ and C6′), 134.0 (CH, C4′), 137.4 (C, C1′), 149.5 (CH, C6), 150.9 (C, C4), 156.2 (C, C2), 197.0 (C, C═O) ppm. Upon storage with or without solvent, it was observed that this compound could be converted to a tautomeric form **20′**. This tautomer was separated by chromatography over silica gel (eluent: AcOEt–petroleum ether 70 : 30) and identified as being 3-benzoyl-2-imino-4-(methylthio)-1,2-dihydropyridine on the basis of its NMR data: ^{1}H NMR (CDCl$_3$, 300 K, 300 MHz) δ 2.33 (s, 3H, SMe), 4.92 (t, 1H, J = 6.4 Hz, NH), 6.04 (t, 1H, J = 6.5 Hz, =NH), 6.50 (d, 1H, J = 5.6 Hz, H5), 7.37 (tt, 2H, J = 7.6 and 1.7 Hz, H3′ and H5′), 7.53 (tt, 1H, J = 7.4 and 1.4 Hz, H4′), 7.73–7.77 (m, 2H, H2′ and H6′), 7.91 (d, 1H, J = 5.5 Hz, H6) ppm; JMOD{^{1}H} NMR (CDCl$_3$, 300 K, 126 MHz) δ 15.5 (CH$_3$, SMe), 109.9 (CH, C5), 117.2 (C, C3), 128.9 (2CH, C3′ and C5′), 129.6 (2CH, C2′ and C6′), 133.9 (CH, C4′), 137.1 (C, C1′), 148.9 (CH, C6), 149.8 (C, C4), 155.1 (C, C2), 196.6 (C, C═O) ppm.

5-Methyl-10-(methylthio)-11-phenylindolo[2,3-*b*]1,8-naphthyridine (33). To 2-amino-3-benzoyl-4-(methylthio)pyridine (**20**; 0.30 g, 1.2 mmol) in degassed Bu$_2$O (1.5 mL) under argon, were added 2-iodo-*N*-methylindole (0.50 g, 1.9 mmol), activated Cu (18 mg, 0.30 mmol) and K$_2$CO$_3$ (0.415 g, 3.0 mmol). The reaction mixture was stirred for 16 h in a preheated oil bath at 160 °C while activated Cu (18 mg, 0.30 mmol) was added after 2 h, 4 h, 6 h and 8 h. After cooling to rt and filtration through Celite® to remove copper, H$_2$O (7 mL) was added before extraction with AcOEt (2 × 15 mL). The solvents were removed under reduced pressure. Purification was performed by column chromatography over silica gel (eluent: AcOEt–petroleum ether 70 : 30 to 100 : 0) to give the title product in 58% yield (0.25 g) as a brown solid: R_f (AcOEt) = 0.09; mp 190 °C (dec.); IR (ATR) ν 666, 702, 744, 799, 814, 867, 981, 1023, 1110, 1160, 1243, 1272, 1315, 1345, 1366, 1394, 1424, 1473, 1506, 1552, 1571, 1594, 1626, 1732, 2919, 3049 cm^{-1}; ^{1}H NMR (CDCl$_3$, 300 K, 500 MHz) δ 2.34 (s, 3H, SMe), 4.07 (s, 3H, NMe), 6.55 (d, 1H, J = 7.8 Hz, H1), 6.96 (t, J = 7.4 Hz, 1H, H2), 7.05 (br s, 1H, H9), 7.41 (d, 1H, J = 7.5 Hz, H4), 7.48 (t, 1H, J = 7.5 Hz, H3), 7.50 (d, 2H, J = 7.2 Hz, H2′ and H6′), 7.59 (t, 2H, J = 7.4 Hz, H3′ and H5′), 7.66 (t, J = 7.4 Hz, 1H, H4′), 8.84 (br s, 1H, H8) ppm; JMOD{^{1}H} NMR (CDCl$_3$, 300 K, 126 MHz) δ 17.3 (CH$_3$, SMe), 27.9 (CH$_3$, NMe), 108.7 (CH, C4), 120.3 (CH, C2), 120.7 (C), 123.4 (CH, C1), 126.7 (CH), 128.3 (CH), 128.9 (4CH, C2′, C3′, C5′ and C6′), 129.4 (CH), 129.8 (CH), 139.9 (C), 143.2 (C), 148.1 (C), 153.2 (C) ppm (4C not seen).

5-Methyl-10-(methylsulfinyl)-11-phenylindolo[2,3-*b*]1,8-naphthyridine (34) and putative 10-methyl-5-phenyl-1,10-dihydro-4*H*-indolo[2,3-*b*]1,8-naphthyridin-4-one (34′). To **33** (0.25 g, 0.70 mmol) in CH$_2$Cl$_2$ (5 mL) at 0 °C, was slowly added a solution of *m*CPBA (77%; 0.16 g, 0.70 mmol) in CH$_2$Cl$_2$ (4 mL). After 1 h at 0 °C, the solution was washed with 10% aqueous Na$_2$CO$_3$ (10 mL). The organic layer was dried over MgSO$_4$ before removal of the solvent under reduced pressure to give 5-methyl-10-(methylsulfinyl)-11-phenylindolo[2,3-*b*]1,8-naphthyridine (**34**) in 50% yield (0.12 g) as a yellow solid which was purified by preparative silica TLC (eluent: AcOEt–MeOH 95 : 5): R_f (AcOEt) = 0.05; mp 250 °C (dec.); IR (ATR) ν 663, 682, 707, 727, 746, 773, 798, 814, 841, 876, 954, 1023, 1044, 1087, 1134, 1161, 1205, 1275, 1316, 1341, 1394, 1427, 1473, 1505, 1564, 1595, 1624, 2921, 3050, 3273 cm^{-1}; ^{1}H NMR (CDCl$_3$, 300 K, 300 MHz) δ 2.42 (s, 3H, S(O)Me), 4.10 (s, 3H, NMe), 6.75 (d, 1H, J = 7.6 Hz), 7.02 (ddd, 1H, J = 8.0, 7.6 and 1.1 Hz), 7.44–7.61 (m, 4H), 7.64–7.76 (m, 3H, H3′, H4′ and H5′), 8.29 (d, 1H, J = 4.5 Hz, H9), 9.29 (d, 1H, J = 4.1 Hz, H8) ppm; ^{1}H NMR ((CD$_3$)$_2$SO, 300 K, 500 MHz) δ 2.44 (s, 3H, S(O)Me), 3.98 (s, 3H, NMe), 6.60 (d, 1H, J = 7.8 Hz), 7.04 (td, 1H, J = 7.6 and 1.0 Hz), 7.54 (d, 1H, J = 7.5 Hz), 7.58 (td, 1H, J = 7.6 and 1.2 Hz), 7.68–7.78 (m, 5H, H4, H2′, H6′), 8.15 (d, 1H, J = 4.4 Hz, H9), 9.26 (br s, 1H, H8) ppm; JMOD{^{1}H} NMR ((CD$_3$)$_2$SO, 300 K, 126 MHz) δ 27.7 (CH$_3$, NMe), 45.5 (CH$_3$, S(O)Me), 109.9 (CH, C4), 113.4 (CH, C9), 113.6 (C), 117.7 (C), 119.4 (C), 120.5 (CH), 122.6 (CH), 129.0 (CH), 129.2 (CH), 129.3 (CH), 129.6 (CH), 130.0 (CH), 130.2 (CH), 136.5 (C), 141.1 (C), 143.0 (C), 151.8 (CH), 152.9 (C), 154.0 (C), 159.3 (C) ppm; ^{1}H NMR ((CD$_3$)$_2$SO, 375 K, 500 MHz) δ 2.43 (s, 3H, S(O)Me), 4.02 (s, 3H, NMe), 6.69 (d, 1H, J = 7.8 Hz, H1), 7.03 (t, 1H, J = 7.6 Hz, H2), 7.52 (d, 1H, J = 7.7 Hz, H4), 7.57 (td, 1H, J = 7.6 and 1.2 Hz), 7.66 (d, 1H, J = 8.1 Hz), 7.67–7.72 (m, 2H), 7.73–7.78 (m, 2H), 8.18 (d, 1H, J = 4.5 Hz, H9), 9.26 (d, 1H, J = 4.5 Hz, H8) ppm; JMOD{^{1}H} NMR ((CD$_3$)$_2$SO, 375 K, 126 MHz) δ 27.1 (CH$_3$, NMe), 45.2 (CH$_3$, S(O)Me), 109.2 (CH, C4), 112.9 (CH, C9), 113.3 (C), 119.1 (C), 119.9 (CH), 122.2 (CH, C1), 128.4 (CH), 128.6 (CH), 129.0 (CH), 129.1 (CH), 129.4 (CH), 129.8 (CH), 136.1 (C), 140.5 (C), 142.8 (C), 151.1 (CH, C8), 152.8 (C), 159.3 (C), 163.2 (C) ppm (1C not seen). During the NMR experiment (several hours in deuterated DMSO at 375 K), the product was quantitatively converted into what could be 10-methyl-5-phenyl-1,10-dihydro-4*H*-indolo[2,3-*b*]1,8-naphthyridin-4-one (**34′**), on the basis of its NMR spectra and HRMS: ^{1}H NMR ((CD$_3$)$_2$SO, 375 K, 500 MHz) δ 3.95 (s, 3H, NMe), 6.37 (d, 1H, J = 7.0 Hz), 6.56 (d, 1H, J = 7.9 Hz), 6.99 (t, 1H, J = 7.6 Hz), 7.36–7.38 (m, 2H), 7.49 (t, 1H, J = 7.7 Hz), 7.54–7.55 (m, 3H), 7.62 (d, 1H, J = 8.1 Hz), 8.10 (d, 1H, J = 7.1 Hz) ppm (NH not unambiguously seen); ^{1}H NMR ((CD$_3$)$_2$SO, 300 K, 500 MHz) δ 3.96 (s, 3H, NMe), 6.48 (d, 1H, J = 7.8 Hz, H6), 6.63 (d, 1H, J = 7.0 Hz, H3), 6.99 (td, 1H, J = 7.6 and 1.0 Hz, H7), 7.39–7.40 (m, 2H, H2′ and H6′), 7.54 (ddd, 1H, J = 8.2, 7.4 and 1.3 Hz, H8), 7.56–7.59 (m, 3H, H3′, H4′ and H5′), 7.69 (d, 1H, J = 8.1 Hz, H9), 8.40 (d, 1H, J = 7.0 Hz, H2) ppm; JMOD{^{1}H} NMR (CDCl$_3$, 300 K, 126 MHz) δ 28.0 (CH$_3$, NMe), 106.8 (CH, C4), 109.9 (C), 110.3 (CH, C9), 116.4 (C), 119.9 (C), 121.1 (CH, C7), 122.2 (CH, C6), 127.0 (2CH, C2′ and C6′), 127.8 (CH), 128.3 (CH), 128.4 (2CH, C3′ and C5′), 138.5 (C), 141.7 (CH, C2), 141.9 (C), 144.8

(C), 149.2 (C), 152.8 (C), 174.6 (C, C═O) ppm; HRMS (ESI; Maxis 4G), *m*/*z* = 326.1286 (1 ppm) found (calcd for $C_{21}H_{16}N_3O$, $[M + H]^+$, requires 326.12879).

Synthesis of benzofuro- and benzothieno[2,3-*b*]benzothiopyrano-[4,3,2-*de*]1,8-naphthyridine (28 and 39), and attempt to prepare 10-methylbenzothiopyrano[4,3,2-*de*]indolo[2,3-*b*]1,8-naphthyridine, from 2-chloro-4-fluoropyridine

2-Chloro-4-fluoro-3-(1-(2-fluorophenyl)hydroxymethyl)pyridine (36). To a solution of TMPH (2.2 mL, 13 mmol) in THF (40 mL) at −80 °C under argon, was added dropwise a 1.35 M solution of *n*BuLi in hexane (8.9 mL, 12 mmol). The mixture was stirred for 15 min at this temperature before slow addition of 2-chloro-4-fluoropyridine (0.95 mL, 10 mmol). After 1 h at −80 °C, 2-fluorobenzaldehyde (1.3 mL, 12 mmol) was slowly added to the formed pyridyllithium. After warming to −10 °C, H_2O (20 mL) was added to the reaction mixture. The product was extracted with AcOEt (3 × 30 mL). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure to afford, after purification by column chromatography over silica gel (eluent: petroleum ether–AcOEt 80 : 20), the title product in 76% yield (1.95 g) as a white solid: R_f ($CHCl_3$) = 0.25; R_f (petroleum ether–AcOEt 60 : 40) = 0.37; mp 112 °C; IR (ATR) ν 762, 804, 831, 855, 870, 918, 949, 1031, 1044, 1067, 1105, 1167, 1191, 1221, 1267, 1385, 1452, 1460, 1482, 1569, 1591, 3198 cm^{-1}; ^1H NMR ($CDCl_3$, 300 K, 500 MHz) δ 3.52 (d, 1H, *J* = 6.7 Hz, OH), 6.54 (d, 1H, *J* = 6.1 Hz, C*H*(OH)), 6.96–7.00 (m, 2H, H5 and H3′), 7.18 (td, 1H, *J* = 7.55 and 0.65 Hz, H4′ or H5′), 7.28 (tdd, 1H, *J* = 7.45, 5.4 and 1.6 Hz), 7.67 (t, 1H, *J* = 7.7 Hz), 8.25 (dd, 1H, *J* = 7.7 and 5.6 Hz, H6) ppm; JMOD{^1H} NMR ($CDCl_3$, 300 K, 126 MHz) δ 65.4 (t, CH, *J* = 2.4 Hz, CH(OH)), 112.2 (d, CH, *J* = 19.4 Hz, C5 or C3′), 115.4 (d, CH, *J* = 21.1 Hz, C5 or C3′), 124.1 (d, CH, *J* = 3.4 Hz, C4′ or C5′), 125.1 (d, C, *J* = 11.3 Hz, C3 or C1′), 127.7 (d, C, *J* = 12.8 Hz, C3 or C1′), 127.9 (t, CH, *J* = 3.2 Hz), 129.7 (d, CH, *J* = 8.2 Hz), 150.4 (d, CH, *J* = 9.8 Hz, C6), 151.7 (d, C, *J* = 6.2 Hz, C2), 159.7 (d, C, *J* = 247 Hz, C–F, C4 or C2′), 168.2 (d, C, *J* = 268 Hz, C–F, C4 or C2′) ppm; ^{19}F\{^1H\} NMR ($CDCl_3$, 300 K, 471 MHz) δ −116.4 (d, *J* = 6.5 Hz), −100.0 (d, *J* = 6.5 Hz). *Crystal data for* **36**: $C_{12}H_8ClF_2NO$, *M* = 255.64, monoclinic, $P\,2_1/c$, *a* = 13.651(2), *b* = 5.9725(11), *c* = 13.013(2) Å, β = 90.997(6) °, *V* = 1060.8(3) $Å^3$, *Z* = 4, *d* = 1.601 g cm^{-3}, μ = 0.368 mm^{-1}. A final refinement on F^2 with 2387 unique intensities and 157 parameters converged at $\omega R(F^2)$ = 0.0746 ($R(F)$ = 0.0283) for 2290 observed reflections with $I > 2\sigma(I)$. CCDC 2204835.†

2-Chloro-4-fluoro-3-(2-fluorobenzoyl)pyridine (37). To a solution of oxalyl chloride (0.30 mL, 3.6 mmol) in dry CH_2Cl_2 (10 mL) at −80 °C, was added dry DMSO (0.25 mL, 3.6 mmol), and the mixture was stirred for 15 min at this temperature. A solution of the alcohol **36** (0.61 g, 2.4 mmol) in dry CH_2Cl_2 (5 mL) was then added dropwise, and the mixture was allowed to reach −40 °C in 0.5 h. Et_3N (1.65 mL, 12 mmol) was next added slowly, and the mixture was warmed up to rt before addition of H_2O (20 mL). The product was extracted with CH_2Cl_2 (2 × 20 mL). The organic layer was dried over $MgSO_4$. The solvent was removed under reduced pressure, and the residue was purified by column chromatography over silica gel (eluent: petroleum ether–AcOEt 80 : 20; R_f = 0.29) to give the title product in 98% yield (0.58 g) as an orange oil: IR (ATR) ν 750, 828, 915, 1233, 1292, 1381, 1454, 1482, 1560, 1594, 1607, 1675 cm^{-1}; ^1H NMR ($CDCl_3$, 300 K, 300 MHz) δ 7.08 (ddd, 1H, *J* = 11.1, 8.3 and 1.1 Hz, H3′), 7.10 (dd, 1H, *J* = 8.0, 5.7 Hz, 1H, H5), 7.27 (td, 1H, *J* = 7.6 and 1.1 Hz), 7.59 (dddd, 1H, *J* = 8.3, 7.0, 5.0 and 1.8 Hz, H4′), 7.91 (td, 1H, *J* = 7.7 and 1.9 Hz), 8.42 (dd, 1H, *J* = 8.1 and 5.7 Hz, H6) ppm; JMOD{^1H} NMR ($CDCl_3$, 300 K, 75 MHz) δ 111.3 (d, CH, *J* = 17.8 Hz, C5), 117.0 (d, CH, *J* = 22.5 Hz, C3′), 124.5 (d, C, *J* = 9.0 Hz, C3), 124.9 (d, CH, *J* = 3.7 Hz), 125.9 (dd, C, *J* = 17.5 and 1.4 Hz, C1′), 131.2 (CH), 136.6 (d, CH, *J* = 9.4 Hz, C4′), 148.5 (dd, C, *J* = 5.7 and 2.0 Hz, C2), 151.8 (d, CH, *J* = 8.5 Hz, C6), 162.3 (d, C, *J* = 259 Hz, C–F, C4 or C2′), 165.9 (dd, C, *J* = 267 and 2.0 Hz, C–F, C4 or C2′), 185.1 (C, C═O) ppm; ^{19}F\{^1H\} NMR ($CDCl_3$, 300 K, 282 MHz) δ −111.3 (d, *J* = 1.7 Hz), −102.7 (d, *J* = 2.0 Hz). This ketone was directly involved in the cyclization step below.

1-Chlorobenzothiopyrano[3,2-*c*]pyridin-10-one (19) and 1-aminobenzothiopyrano[3,2-*c*]pyridin-10-one (38). To **37** (0.50 g, 2.0 mmol) in NMP (15 mL) under argon, was added Na_2S (0.185 g, 2.4 mmol). The mixture was stirred at 60 °C for 3 h and poured onto ice-water (75 mL). The product was extracted with AcOEt (3 × 20 mL), and the organic layer washed with brine (10 mL). The organic layer was dried over $MgSO_4$ before removal of the solvents under reduced pressure. The crude product was washed with CH_2Cl_2 (5 mL) to give 1-chlorobenzothiopyrano[3,2-*c*]pyridin-10-one (**19**), which was directly involved in the next step. To **19** in NMP (2.5 mL) was added 32% aqueous NH_4OH (2.5 mL). The mixture was heated at 110 °C for 24 h and cooled down to rt. The precipitate was collected by filtration, washed with H_2O and dried to give 1-aminobenzothiopyrano[3,2-*c*]-pyridin-10-one (**38**) in 40% yield (185 mg) for 2 steps as a green solid: mp > 260 °C (deg.); IR (ATR) ν 721, 750, 778, 811, 902, 922, 961, 1015, 1036, 1085, 1178, 1284, 1355, 1435, 1522, 1555, 1592, 1636, 2918 cm^{-1}; ^1H NMR ($CDCl_3$, 300 K, 500 MHz; poorly soluble) δ 5.47 (br s, 2H, NH_2), 6.53 (d, 1H, *J* = 5.6 Hz), 7.31–7.46 (m, 3H), 7.84 (d, 1H, *J* = 5.6 Hz), 8.43 (dd, 1H, *J* = 7.9 and 1.3 Hz) ppm. A one pot procedure could also be used to access **38**.

General procedure for the tandem coupling-cyclization from 38. To 1-aminobenzothiopyrano[3,2-*c*]pyridin-10-one (**38**; 93 mg, 0.40 mmol) in degassed DMSO (1.5 mL) under argon, were added the aromatic iodide (0.80 mmol), activated Cu (5 mg, 80 μmol) and K_2CO_3 (115 mg, 0.80 mmol). The reaction mixture was stirred for 16 h in a preheated oil bath at 170 °C while activated Cu (5 mg, 80 μmol) was added after 2 h, 4 h, 6 h and 8 h. After cooling to rt and filtration through Celite® to remove copper, H_2O (7 mL) was added before extraction with AcOEt (2 × 15 mL). The solvents were removed under reduced pressure. Purification was performed by column chromatography over silica gel (eluent given in the product description).

Benzofuro[2,3-*b*]benzothiopyrano[4,3,2-*de*]1,8-naphthyridine (28). The general procedure using 2-iodobenzofuran (0.20 g) gave (eluent: CH_2Cl_2–AcOEt 90 : 10) the title product in 25% yield (35 mg) as a yellow solid: R_f (AcOEt–petroleum ether 80 : 20) = 0.31; mp 228 °C; IR (ATR) ν 707, 731, 749, 836, 850, 879, 890, 991, 1030, 1095, 1127, 1190, 1226, 1246, 1262, 1324, 1372, 1448, 1458, 1490, 1552, 1593, 2851, 2920 cm^{-1}; ^1H NMR ($CDCl_3$, 300 K, 500 MHz) δ 7.32–7.35 (m, 2H, H6), 7.46–7.59 (m, 4H), 7.68 (d, 1H, *J* = 8.2 Hz), 8.23 (d, 1H, *J* = 7.8 Hz), 8.55 (dd, 1H, *J* = 7.6 and 1.05 Hz), 8.80 (br s, 1H, H7) ppm; JMOD{^{1}H} NMR ($CDCl_3$, 300 K, 126 MHz) δ 112.3 (C), 112.5 (CH), 114.6 (CH, C6), 117.6 (C), 122.2 (C), 123.3 (CH), 123.7 (CH), 127.0 (CH), 127.4 (CH), 128.3 (C), 129.7 (CH), 129.9 (CH), 131.2 (CH), 133.3 (C), 137.8 (C), 143.3 (C), 151.4 (CH, C7), 154.7 (C), 156.3 (C), 166.1 (C) ppm; HRMS (ASAP; Maxis 4G), *m*/*z* = 327.0589 (1 ppm) found (calcd for $C_{20}H_{11}N_2OS$, $[M + H]^+$, requires 327.05866).

Benzothieno[2,3-*b*]benzothiopyrano[4,3,2-*de*]1,8-naphthyridine (39). The general procedure using 2-iodobenzothiophene (0.21 g) gave (eluent: CH_2Cl_2–AcOEt 100 : 0 to 85 : 15) the title product in 5% yield (7 mg) as a yellow solid: R_f (AcOEt–petroleum ether 80 : 20) = 0.34; mp 232 °C; ^{1}H NMR ($CDCl_3$, 300 K, 500 MHz) δ 7.28 (t, 1H, *J* = 7.6 Hz), 7.33 (t, 1H, *J* = 7.6 Hz), 7.38 (br s, 1H, H6), 7.47–7.50 (m, 2H), 7.58 (dd, 1H, *J* = 7.9, 0.9 Hz), 7.85 (d, 1H, *J* = 8.0 Hz), 8.26 (d, 1H, *J* = 8.2 Hz), 8.34 (d, 1H, *J* = 7.9 Hz), 8.83 (br s, 1H, H7) ppm; JMOD{^{1}H} NMR ($CDCl_3$, 300 K, 126 MHz) δ 114.8 (CH), 119.3 (CH), 123.4 (CH), 124.2 (CH), 125.4 (CH), 126.9 (CH), 128.0 (CH), 128.3 (C), 128.6 (CH), 131.0 (CH), 132.6 (C), 133.3 (C), 137.1 (C), 139.1 (C), 151.4 (CH, C7), 154.3 (C), 169.0 (C) ppm (3C not seen); HRMS (ASAP; Maxis 4G), *m*/*z* = 343.0357 (0 ppm) found (calcd for $C_{20}H_{11}N_2S_2$, $M^{+\cdot}$, requires 343.03582).

10-Methylbenzothiopyrano[4,3,2-*de*]indolo[2,3-*b*]1,8-naphthyridine (35). The general procedure (but at a 0.50 mmol scale, and using only 0.10 mmol of activated Cu (7 mg) instead of 0.50 mmol) using 2-iodo-*N*-methylindole (0.19 g) gave (eluent: CH_2Cl_2–AcOEt 90 : 10) the title product in 20% yield (34 mg) as a yellow solid: R_f ($CHCl_3$) = 0.10; mp 78 °C; IR (ATR) ν 734, 747, 803, 816, 879, 989, 1083, 1124, 1159, 1241, 1263, 1315, 1345, 1365, 1392, 1427, 1474, 1543, 1585, 1618, 2851, 2921 cm^{-1}; ^{1}H NMR ($(CD_3)_2SO$, 300 K, 500 MHz) δ 3.94 (br s, 3H, NMe), 7.15 (t, 1H, *J* = 7.6 Hz), 7.43 (t, 1H, *J* = 7.6 Hz), 7.54 (t, 2H, *J* = 7.5 Hz), 7.59 (d, 1H, *J* = 8.1 Hz), 7.64 (d, 1H, *J* = 7.8 Hz), 8.07 (d, 1H, *J* = 7.9 Hz), 8.37 (d, 1H, *J* = 7.9 Hz) ppm (H6 and H7 not seen at this temperature due to very large signals); ^{1}H NMR ($(CD_3)_2SO$, 375 K, 500 MHz) δ 3.96 (s, 3H, NMe), 7.22 (t, 1H, *J* = 7.5 Hz, H12), 7.38 (br s, 1H, H6), 7.50 (t, 1H, *J* = 7.6 Hz), 7.57 (t, 1H, *J* = 7.5 Hz), 7.60 (t, 1H, *J* = 7.4 Hz), 7.63 (d, 1H, *J* = 8.0 Hz, H11), 7.67 (d, 1H, *J* = 7.8 Hz), 8.23 (d, 1H, *J* = 8.0 Hz), 8.50 (d, 1H, *J* = 8.0 Hz), 8.74 (br s, 1H, H7) ppm; JMOD{^{1}H} NMR ($(CD_3)_2SO$, 375 K, 126 MHz) δ 27.3 (CH_3, NMe), 109.3 (CH, C11), 111.5 (C), 112.4 (CH, C6), 114.2 (C), 119.0 (C), 119.5 (CH, C12), 122.6 (CH), 126.5 (CH), 126.8 (CH), 127.5 (C), 128.1 (CH), 129.6 (CH), 130.4 (CH), 131.8 (C), 134.6 (C), 141.4 (C), 142.6 (C), 149.7 (CH, C7), 153.4 (C), 155.0 (C) ppm; HRMS (ESI; Maxis 4G), *m*/*z* = 340.0901 (1 ppm) found (calcd for $C_{21}H_{14}N_3S$, $[M + H]^+$, requires 340.09029).

Photophysical measurements

Measurements were performed on freshly-prepared air-equilibrated solutions contained in quartz cells of 1 cm path-length at room temperature (25 °C). UV-Vis absorption spectra were recorded on a Jasco V-770 spectrophotometer. Steady-state measurements were performed using a Jasco FP-8300 fluorimeter equipped with a 150 W Xenon lamp and a Hamamatsu R928 photomultiplier tube. Fully corrected emission spectra were obtained, for each compound, after excitation at the wavelength of the absorption maximum, with $A_{\lambda_{ex}} < 0.1$ to minimize internal absorption. Quinine bisulfate in 0.5 M H_2SO_4 (Φ = 0.546 at λ_{ex} = 346 nm) was used as a standard. Fluorescence lifetimes were measured by time correlated single-photon counting (TCSPC) by using an Edinburgh Instrument (FLS920) fluorimeter. Excitation at 375 nm was achieved by a pulsed laser diode EDEPL375. The instrument response (FWHM *ca.* 1 ns) was determined by measuring the light scattered by a toluene suspension. The TCSPC traces were analyzed by standard iterative reconvolution methods implemented in the software of the fluorimeter. All compounds displayed strictly monoexponential fluorescence decays.

Protein kinase assays

Kinase enzymatic activities were assayed in 384-well plates using the ADP-Glo™ assay kit (Promega, Madison, WI) according to the recommendations of the manufacturer. In order to determine the half maximal inhibitory concentration (IC_{50}), the assays were performed in duplicate in the absence or presence of increasing doses of the tested compounds. ATP concentration used in the kinase assays was 10 μM. PIM1 (human proto-oncogene, recombinant, expressed in bacteria) and PIM2 (human proto-oncogene, recombinant, expressed by baculovirus in Sf9 insect cells) were assayed in kinase buffer ''A'' with 630 μM of PIMtide peptide (ARKRRRHPSGPPTA) as substrate. Peptide substrates were obtained from Proteogenix (Schiltigheim, France). Kinase buffer ''A'': 10 mM $MgCl_2$, 1 mM EGTA, 1 mM DTT, 25 mM Tris-HCl pH 7.5, 50 μg mL^{-1} heparin.

Molecular modeling experiments

After geometric optimization of the compounds **MN34-20**, **39**, **NM-049** and **NM65-45** structures using Gaussian 16 at DFT B3LYP level and 6-31g orbital basis sets,[85] the docking studies were performed with AutoDock Vina version 1.1.2.[76] Files for the docking were prepared from 3JPV PIM1 structure after removing of water molecules and pdbqt files prepared with Chimera software.[77] Apolar hydrogen atoms were removed and Gasteiger charges were added. Docking experiments were performed using the default AutoDock Vina parameters.

Author contributions

Conceptualization, F. M., W. E., J. P. H., N. M.; investigation, N. M., W. E., M. M., T. R., L. N., O. M., L. P., T. R.; supervision, F. M., W. E., J. P. H.; writing initial draft, F. M., P. M., O. M.; writing – review and editing, W. E., N. M., S. B., P. M., L. N., J. P. H., T. R., L. P., V. T.

Conflicts of interest

There are no conflicts of interest to declare.

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