Article

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2-(Substituted amino)-8-azachromones from 4,6-Diaryl-2-pyridones: a Synthetic Strategy toward Compounds of Broad Structural Diversity

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ABSTRACT

3-Acetoacetyl-4,6-diaryl-2-pyridones are synthesized in three steps from chalcones and then condense with carbon disulfide to afford 8-azachromones containing a methylthio group at C2. This leaving group offers an entry point for the insertion of more complex moieties via nucleophilic substitution. For this purpose, N-nucleophiles are explored according to their positions in the Mayr's nucleophilicity scale (*N* parameter), and three main classes are distinguished depending on whether the substitution takes place from their neutral forms, from their deprotonated anionic forms, or under nucleophilic catalysis. A broad range of primary and secondary amines may be inserted by this method, including enantiomerically pure amino acids, enabling us to explore structural diversity.

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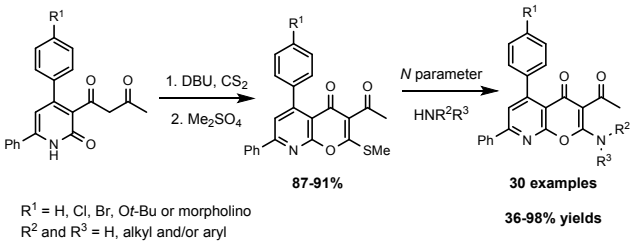
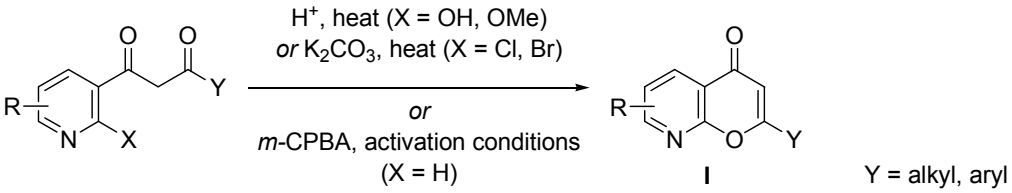


INTRODUCTION

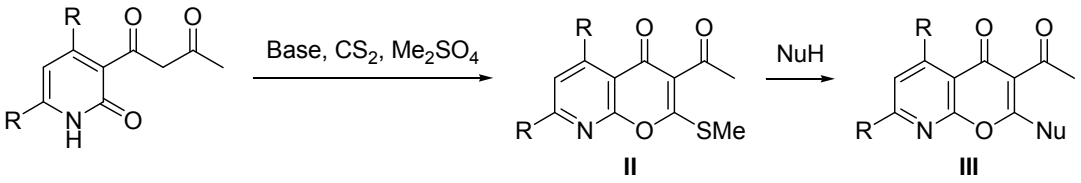
The 8-azachromone core was synthesized for the first time in 1967 from 1,3-diketone derivatives of 2-pyridones by an acid-catalyzed ring closure.[1] Since then, few methods have been developed in comparison with the isostere chromones,[2] although both scaffolds might have similar biological and pharmaceutical properties.[3] The electron-deficient nature of the pyridine ring is often pointed out as an issue to the challenging access to 8-azachromones. To date, most of the reported procedures still involve 1,3-diketones and fall into two approaches according to whether the ring closure takes place via intramolecular O-arylation or via condensation with carbon disulfide (Scheme 1). The intramolecular O-arylation has been the most explored and can be performed under acid catalysis for 2-pyridones[1,4] and 2-methoxypyridines,[5] under base catalysis for 2-halopyridines,[6] and via CH activation of *N*-oxides for 2-unsubstituted pyridine derivatives[7] (Scheme 1A). By contrast, the condensation with CS_2 was reported solely in the case of 4,6-dimethyl-2-pyridone derivatives (Scheme 1B)[8] and has not received further attention. Yet, the methylthio leaving group at the electrophilic site C2 on the cyclization product **II** would enable to access more complex derivatives **III** by simple nucleophilic substitution. Such derivatization would be more difficult from the O-arylation products **I**.

Scheme 1. Synthesis of 8-Azachromones from 1,3-Diketone Precursors.

A. Intramolecular O-arylations *(ref. 1, 4-7)*



B. Condensation with carbon disulfide and nucleophilic substitution
(R = methyl, ref. 8 ; R = aryl, this work)



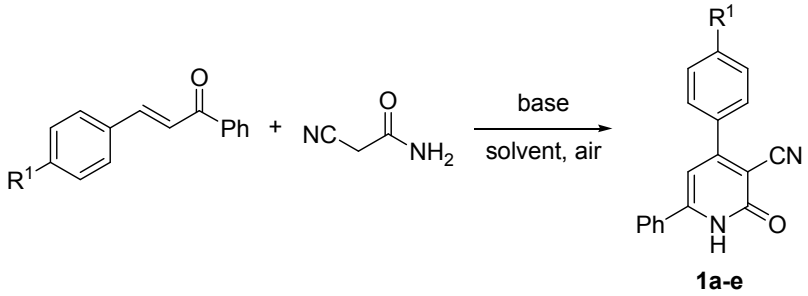
The present work revisits the condensation with CS_2 and further explores possibilities of nucleophilic substitution at C2 (Scheme 1B). We focus on 5,7-diaryl-8-azachromone derivatives because aryl substituents on the pyridine ring have not yet been considered by the synthetic methods mentioned above. We show that primary and secondary amines are well suited for the nucleophilic substitution and that they give rise to 2-(substituted amino)-8-azachromones under conditions that mainly depend on the nucleophile strength and position in the Mayr's nucleophilicity scale.[9] The synthesis of the 1,3-diketone cyclization precursors, namely 3-acetoacetyl-4,6-diaryl-2-pyridones, is also described, as they are not easily accessible.

RESULTS AND DISCUSSION

Synthesis of 3-Acetoacetyl-4,6-diaryl-2-pyridones. The 1,3-diketones cyclization precursors are commonly prepared by addition of a methyl Grignard reagent to the nitrile of 3-cyano-2-pyridones, followed by Claisen condensation of the resulting 3-acetyl-2-pyridones. This approach has been well described in the case of 4,5-dialkyl-2-pyridones but turned out to be more difficult with 4,5-diaryl derivatives.

Among the numerous methods for the synthesis of the starting material, 4,5-diaryl-3-cyano-2-pyridones **1**, we focused on the base-promoted condensation between chalcones and cyanoacetamide (Table 1). An effective reported procedure involves potassium *t*-butoxide in DMSO under oxygen atmosphere.[10] When conducted in open air, this procedure leads to a substantial amount of 3-unsubstituted 2-pyridones as by-products of decyanative aromatization, instead of the desired 3-cyano-2-pyridones.[11] This point is responsible for the modest yield of product **1a** (40%) obtained in open air (Table 1, entry 1), whereas an 88% yield was reported when using an oxygen atmosphere (data from ref. 10). As other procedures using ethanol as solvent with different bases, and without the need for oxygen atmosphere were reported,[12] we evaluated the effect of replacing DMSO with ethanol, 2-propanol, and *t*-butyl alcohol, together with the corresponding potassium alkoxide bases in open air (entries 2-5). Under these conditions, we did not observe the decyanative aromatization by-product. The reaction rate clearly depends on the base strength: although the reaction in ethanol/KOEt was still incomplete after 72 hours at room temperature (entries 2 and 3), a 96% yield of **1a** was obtained after 60 hours in 2-propanol/KO*i*-Pr (entry 4) and 92% after only 24 hours using the more basic *t*-butyl alcohol/KO*t*-Bu medium (entry 5). The desired product **1a** is initially formed as potassium salt, and is soluble neither in 2-propanol nor in *t*-butyl alcohol under this form. We took advantage of this insolubility to isolate and characterize **1a** as potassium salt **1a-K** in a simplified reaction work-up. According to the same procedure, we prepared 3-cyano-2-pyridones **1b-e-K** diversely substituted in the *para* position of the 4-phenyl ring (Table 1, entries 6-9).

Table 1. Synthesis of 3-Cyano-2-pyridones from 4-Substituted Chalcones and Cyanoacetamide.

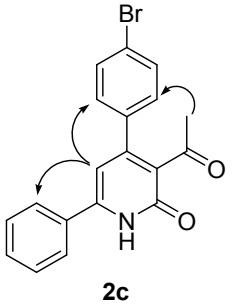


1a-e

Entry[a]	*R*[1]	*Solvent*	*Base*	*Temperature*	*Reaction time, h*	*Product*[b]	*Yield, %*[c]
1	H	DMSO	KO*t*-Bu	rt	2	**1a**	40
2	H	ethanol	KOEt	rt	20	**1a-K**	37
3	H	ethanol	KOEt	rt	72	**1a-K**	88
4	H	2-propanol	KO*i*-Pr	rt	60	**1a-K**	96
5	H	*t*-butyl alcohol	KO*t*-Bu	30 °C	24	**1a-K**	92
6	Cl	2-propanol	KO*i*-Pr	rt	60	**1b-K**	93
7	Br	2-propanol	KO*i*-Pr	rt	60	**1c-K**	96
8	O*t*-Bu	2-propanol	KO*i*-Pr	rt	60	**1d-K**	77
9	Morpholino	*t*-butyl alcohol	KO*t*-Bu	30 °C	48	**1e-K**	93

[a] Reaction conditions: 0.083 M chalcone, 1.1 equiv cyanoacetamide, 4 equiv base, open air. [b] **1a-e-K** refers to the potassium salts of products **1a-e**. [c] Yields of isolated products.

We assigned the position of the substituted phenyl ring on the basis of the probable reaction mechanism: the Michael addition of cyanoacetamide to the 4-substituted chalcone leads to a condensation product where the substituted phenyl ring would be adjacent to the 3-cyano group, i.e. at C4. This was later confirmed on the 3-acetyl derivative **2c** by the NOESY correlation between the acetyl group and the *ortho* protons of the bromo-substituted phenyl ring (Figure 1).



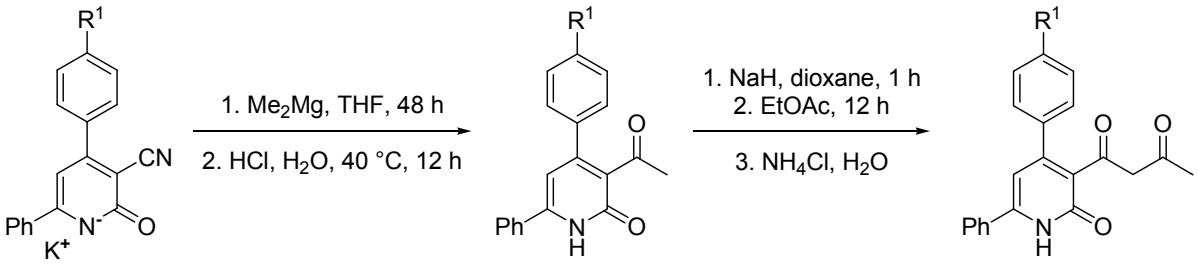
2c

Figure 1. Selected NOESY Correlations (Arrows) Showing the Position of the Substituted Phenyl Ring.

3-Acetyl-2-pyridones **2** might be obtained directly from chalcones by using acetoacetamide instead of cyanoacetamide in the procedure described above. However, the reaction requires heating under reflux and mainly gives the 3-unsubstituted products resulting from deacetylative aromatization. Therefore, the addition of a methyl Grignard reagent to 3-cyano-2-pyridones appears to be the most reliable strategy to access acetyl derivatives.

Alkyl-substituted cyanopyridones are known to give addition products with methylmagnesium bromide at room temperature.[13] For *aryl*-substituted derivatives **1a-e-K**, the use of a large excess of MeMgBr and heating (65 °C) were required to reach a significant conversion. However, under these conditions, halogenated derivatives **1b** (R^1 = Cl) and **1c** (R^1 = Br) gave rise to unidentified by-products due to a possible halogen-magnesium exchange. We obtained better results with the more reactive dimethylmagnesium generated in situ by the dioxane precipitation method: addition of 1,4-dioxane to MeMgBr precipitates $MgBr_2$ species as polymeric dioxane adducts and shifts the Schlenk equilibrium toward Me_2Mg.[14] Thus, 3-cyano-2-pyridones **1a-e-K** were converted to the corresponding 3-acetyl-2-pyridones **2a-e** at room temperature with 56-75% yields after hydrolysis of the imine intermediate products (Scheme 2). The hydrolysis does not need strong acidic conditions and can be performed at pH around 7-8, enabling to work with the acid-sensitive *t*-butyl ether derivative **2d**.

Scheme 2. Two-Step Synthesis of 1,3-Diketones 3 from 3-Cyano-2-pyridones 1-K.



1-K **2** **3**

1a-K, **2a**, **3a** : R^1 = H
1b-K, **2b**, **3b** : R^1 = Cl
1c-K, **2c**, **3c** : R^1 = Br
1d-K, **2d**, **3d** : R^1 = O*t*-Bu
1e-K, **2e**, **3e** : R^1 = Morpholino

2a, 75%
2b, 68%
2c, 65%
2d, 56%
2e, 61%

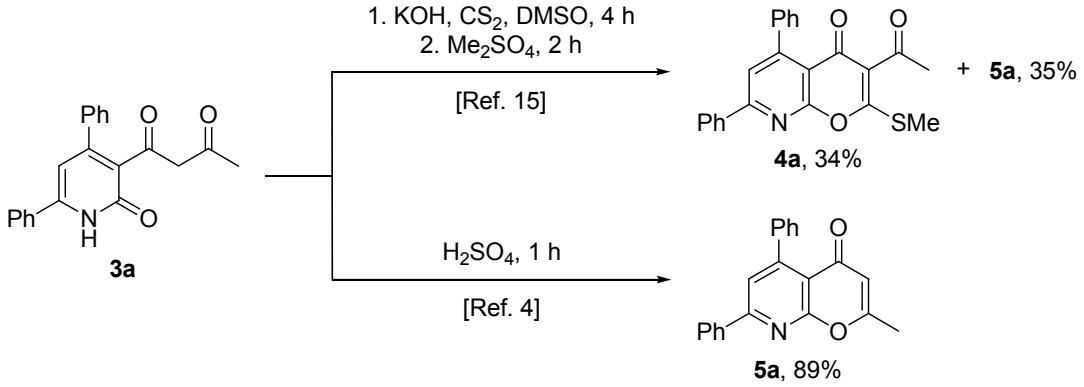
3a, 84%
3b, 79%
3c, 72%
3d, 83%
3e, 75%

Finally, the Claisen condensation between **2a-e** and ethyl acetate in dioxane led to the 1,3-diketone derivatives **3a-e** with yields of 72-84% (Scheme 2). These compounds were then considered as starting materials for their cyclization into 8-azachromones.

Cyclization into 2-(Methylthio)-8-azachromones. The reported procedure uses potassium hydroxide (two equivalents) as base to promote the condensation with CS_2 (three equivalents) in DMSO, followed by treatment with dimethyl sulfate (four equivalents).[8,15] Under these conditions, diketone **3a** gave rise to a mixture of the 2-(methylthio)-8-azachromone **4a** (34%) and of the 2-methyl derivative **5a** (35%) as intramolecular O-arylation by-product (Scheme 3). As discussed in the introduction, the O-arylation ring

closure of 2-pyridones has been mainly reported through dehydration under acidic conditions, and **5a** is indeed the main product observed (89%) after a one hour treatment of **3a** in sulfuric acid (Scheme 3).

Scheme 3. Cyclization of Diketone 3a into 8-Azachromones According to Reported Procedures.



With the aim of maximizing the formation of **4a**, the reaction conditions, including solvent nature, base strength, equivalents of the reagents, and reaction time were screened and revealed the following points. Firstly, the reaction requires polar solvents such as DMF, DMSO or acetonitrile. As solvent nucleophilicity may be problematic, anhydrous acetonitrile appears to be the solvent of choice, furthermore leading to the selective precipitation of product **4a** in the reaction mixture. Secondly, the use of two equivalents of a base at least as strong as K_3PO_4 is required. In this respect, DBU increases the solubility of the deprotonated anionic species in acetonitrile, resulting in higher reaction rates. The third point concerns the amount of CS_2. Although one equivalent would theoretically be enough for the reaction to proceed, we observed a decrease in the formation of the O-arylation by-product **5a** when using higher amounts of CS_2 (up to nine equivalents), thus resulting in a significant increase in the yield of **4a**. On the basis of these observations, we developed an improved procedure affording the 2-(methylthio)-8-azachromone derivatives **4a-e** with average yields of 87-91% (Scheme 4).

Scheme 4. Improved Conditions for the Cyclization of Diketones 3 into 2-(Methylthio)-8-azachromones 4.

*(Conditions: 0.1 M **3**, 2.2 equiv DBU, 9 equiv CS_2, 2.2 equiv Me_2SO_4, rt)*

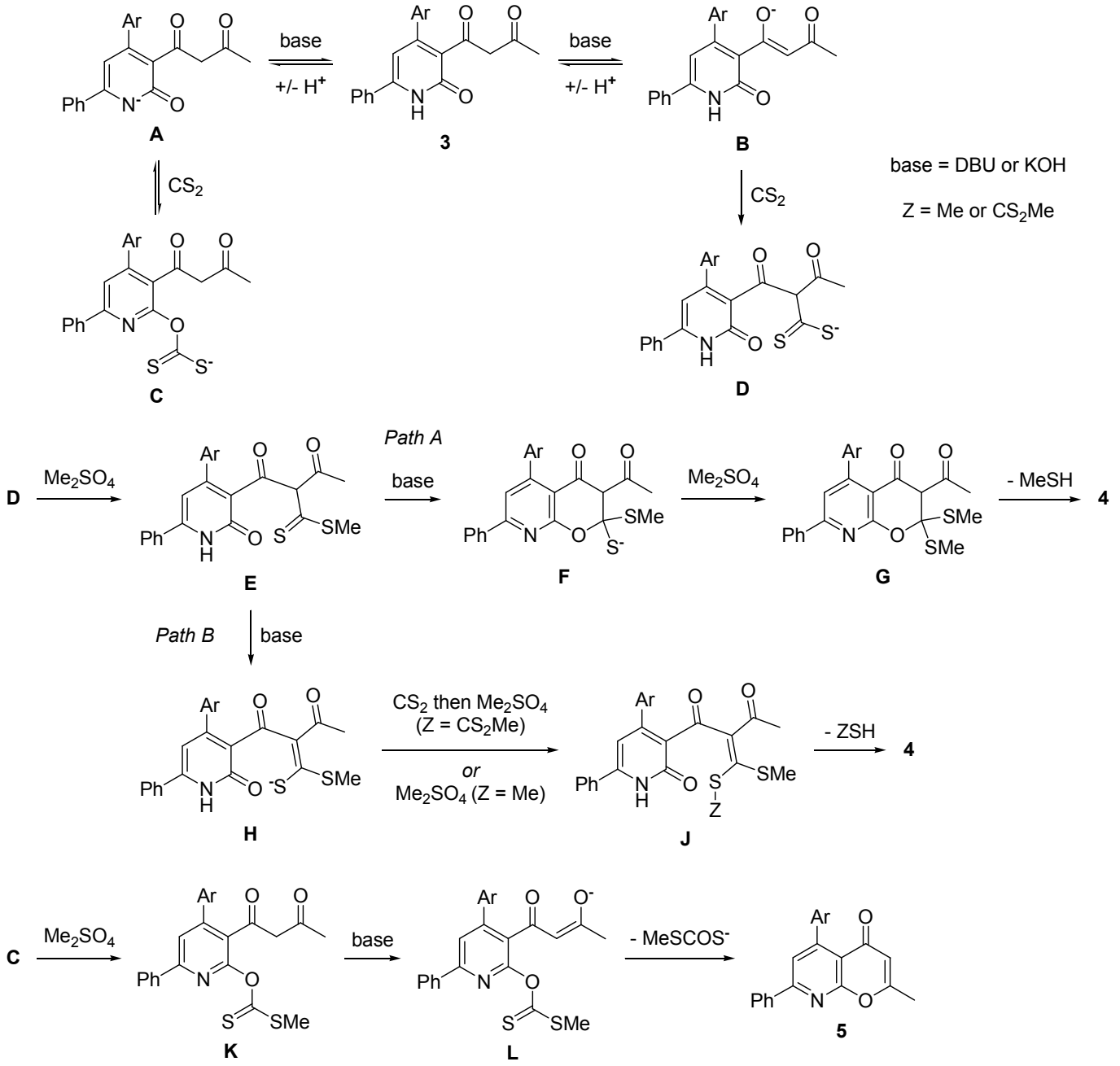
3a, **4a** : R^1 = H
3b, **4b** : R^1 = Cl
3c, **4c** : R^1 = Br
3d, **4d** : R^1 = O*t*-Bu
3e, **4e** : R^1 = Morpholino

4a, 91%
4b, 87%
4c, 88%
4d, 89%
4e, 89%

To explain the formation of both cyclization products **4** and **5**, we propose a mechanism in Scheme 5. This mechanism works on the assumption that dianionic species would not be formed under the conditions of Scheme 3 (KOH, DMSO) or Scheme 4 (DBU, acetonitrile). Deprotonation of diketone **3** gives rise to the multident nucleophilic species **A** and **B** in equilibrium. They may react with CS_2 through the oxygen atom of the pyridone ring or through the enolate, leading to species **C** and **D**, respectively (among other possible reactive sites and intermediate species). The reaction via the enolate carbon atom may be considered as thermodynamically favored, so that the whole equilibrium is shifted toward **D**, which would then lead to product **4** through two possible paths depending on whether the ring closure takes place via a 6-exo-trig (path A) or a 6-endo-trig reaction (path B). In path B, the thioenolate of **H** is first alkylated by either Me_2SO_4 or CS_2, the latter explaining the need for an excess of CS_2. Product **5**, however, would be formed from species **C** after methylation of the dithiocarbonate group, giving **K** and the corresponding anionic species **L**. The leaving group *S*-methyl dithiocarbonate at C2 enables the intramolecular O-arylation that leads to **5**. Actually, this mechanism might involve more complex intermediate species as the above assumption about the absence of dianionic species may not be valid.

Scheme 5. Plausible Reaction Mechanism for the Formation of Products 4 and 5.

(Counter ions and reversibility of reaction steps are not shown)



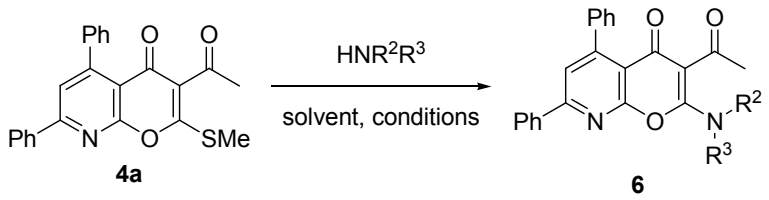
Nucleophilic Substitution of the Methylthio Group. Our approach to exploring the scope of the nucleophilic substitution is based on the Mayr's reactivity scales. These scales are constructed according to the equation log k = s (N + E), where the second-order rate constant k of a nucleophile-electrophile combination correlates with the nucleophilicity and electrophilicity parameters N and E of the reagents.[9] Values of N and E parameters of many reagents have been determined,[16] so that these scales allow predicting the feasibility of a wide variety of combinations. A given electrophile such as **4a** that reacts with a nucleophile referenced in the nucleophilicity scale (i.e. with a known N parameter), will be expected to react with other nucleophiles of similar or higher N parameters as well. Among the different π-, n- and σ-nucleophiles characterized in the Mayr's scales, we focused on neutral NH-type nucleophiles because they cover a wide range of nucleophilicity: basically, from N 7.69 for benzotriazole to N 18.52 for pyrrolidine

(data in acetonitrile, which was chosen as reference solvent for this work). This means roughly eleven units. In comparison, alcohols cover only six units and are significantly less nucleophilic.

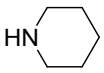
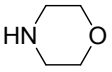
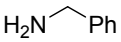
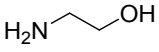
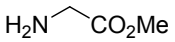
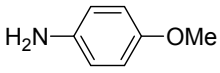
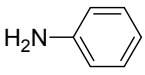
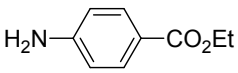
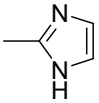
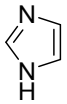
Therefore, we explored the reactivity of **4a** with some N-nucleophiles, starting from piperidine (*N* 17.35) and decreasing in nucleophilicity (Table 2). We observed the nucleophilic substitution in methylene chloride at room temperature until ethanolamine (*N* 14.11, entry 5) and glycine methyl ester (*N* 13.51 for potassium glycinate, data in water, entry 6). Under the same conditions, *p*-anisidine (*N* 13.42) only led to traces of the substitution product **6ag**, and weaker nucleophiles such as aniline (*N* 12.64) and benzocaine did not react at all, even upon heating at 65 °C in THF. Thus, a first limit in reactivity is reached for *N* value of approximately 13.5. Nucleophiles located above this limit give substitution products with **4a** whereas nucleophiles below do not, at least without further activation conditions.

To extend the scope of reactivity, we envisaged activation via nucleophilic catalysis. Because they show *N* parameter values above the limit of 13.5, DBU (*N* 15.29), DMAP (*N* 15.51) and DABCO (*N* 18.80) were expected to react with **4a** and to give rise to the corresponding positively charged intermediates of enhanced electrophile strengths. Indeed, all three catalysts enabled the nucleophilic substitution with *p*-anisidine and aniline, DMAP being the most effective with 90-91% yields of **6ag** and **6ah** after only two hours at 65 °C in THF (Table 2, entries 7 and 8). However, the efficacy of nucleophilic catalysis is quite limited as benzocaine required 36 hours at 100 °C in dioxane to afford 61% of the substitution product **6ai** (entry 9), and 2-methylimidazole (*N* 11.74) and imidazole (*N* 11.47) were completely unreactive under the same conditions (entries 10 and 11). Therefore, a second limit is reached for *N* value of about 12, above which the presence of DMAP enables the nucleophilic substitution.

Table 2. Nucleophilic Substitution of 4a with N-Nucleophiles Depending on the Nucleophilicity Parameter *N*.



4a **6**

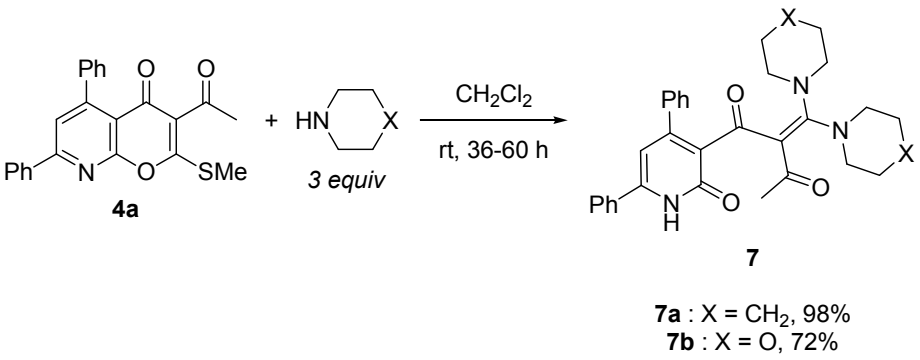
Entry[a]	*HNR²R³*	*N parameter*[b]	*Catalyst*	*Solvent*	*Temperature*	*Time, h*	*Product*	*Yield, %*[c]
1		17.35	none	DCM	rt	12	**6aa**	96
2		15.65	none	DCM	rt	12	**6ab**	93
3		15.19	none	DCM	rt	12	**6ac**	97
4		14.29	none	DCM	rt	12	**6ad**	94
5		14.11	none	DCM	rt	12	**6ae**	65
6[d]		13.51[e]	none	DCM	rt	12	**6af**	63
7[f]		13.42	DMAP	THF	65 °C	2	**6ag**	91
8[f]		12.64	DMAP	THF	65 °C	2	**6ah**	90
9[f]		n/a[g]	DMAP	dioxane	100 °C	36	**6ai**	61
10[f]		11.74	DMAP	dioxane	100 °C	12		0
11[f]		11.47	DMAP	dioxane	100 °C	12		0

[a] Reaction conditions: 0.1 M **4a** and 1.1 equiv Nu. [b] *N* parameters are given in acetonitrile, data from ref. 16. [c] Yields of isolated products. [d] Glycine methyl ester was generated from the corresponding hydrochloride (1.5 equiv) and Et_3N (1.1 equiv). [e] *N* parameter of the free carboxylate, data in water. [f] 0.05 M **4a**. [g] Data not yet available.

It is important to note that the products presented in Table 2 were obtained with one equivalent of nucleophile. With an excess, a second substitution takes place and leads to the 2-pyridone derivatives **7** by ring opening, due to the leaving group ability of the pyridone moiety. This second substitution works best

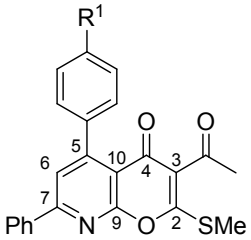
with cyclic secondary amines and becomes more difficult when the nucleophile strength decreases. In the presence of three equivalents of piperidine, **4a** was completely converted into the open-ring product **7a** after 36 hours, whereas with morpholine only 72% of **7b** were obtained after 60 hours (Scheme 6). The ring opening of the 8-azachromone scaffold in the presence of N-nucleophiles was reported in 2003 for 2-polyfluoroalkyl derivatives.[17] Curiously, in that case the reaction worked well with primary amines whereas piperidine and morpholine did not give open-ring products but the addition products 2-morpholino- and 2-piperidino- 8-azachromanones instead.

Scheme 6. Formation of Open-Ring Products by Two Consecutive Nucleophilic Substitutions.



The *N* values of 13.5 and 12 mentioned above allow predicting the nucleophilic substitution with a given nucleophile and were exemplified for the 5,7-diphenyl derivative **4a**, playing the role of constant electrophile strength. Nevertheless, these data may also be applied to the R^1-substituted derivatives **4b-e** as were observed that the presence of a *para* substituent on the 5-phenyl ring does not significantly affect the chemical properties of the azachromone core. This is revealed by comparing the ^{13}C chemical shifts of the azachromone scaffolds of compounds **4b-e** with those of **4a** (Table 3). Beside slight variations for carbon C5 (up to 1.3 ppm), the chemical shifts are almost identical, especially the chemical shifts of C2 and C4 (less than 0.4 ppm variations) which are directly connected to the electrophilicity. Therefore, compounds **4a-e** can be considered of similar electrophile strengths and the limits in reactivity that were determined for **4a** can be used with compounds **4b-e** as well.

Table 3. Influence of the R^1 Substituents on the ^{13}C NMR Data of the 8-Azachromone Scaffold.

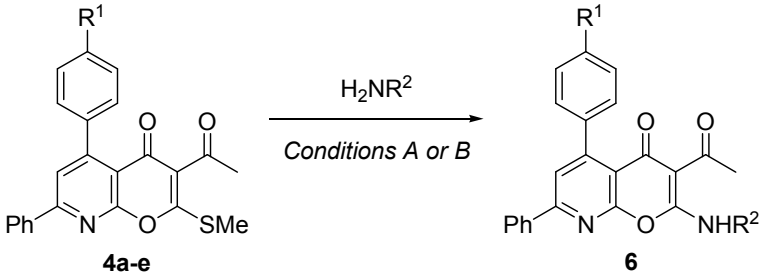


4a-e

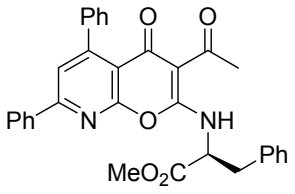
	^{13}C NMR ($CDCl_3$), δ_C, ppm							
R^1	*C2*	*C3*	*C4*	*C5*	*C6*	*C7*	*C9*	*C10*
H	**177.4**	**119.9**	**174.6**	**155.3**	**122.6**	**159.0**	**160.8**	**114.2**
Cl	177.6	119.8	174.6	154.0	122.4	159.3	160.8	114.1
Br	177.6	119.8	174.5	154.0	122.3	159.3	160.8	114.0
O*t*-Bu	177.1	119.9	174.7	155.1	122.7	158.9	160.9	114.2
Morpholino	177.1	119.9	175.0	155.1	122.5	158.8	161.1	114.0

Scheme 7 shows examples of substitution products that were obtained from **4a-e** according to the reaction conditions developed. Briefly, aliphatic primary amines were inserted in methylene chloride at room temperature (conditions A) whereas aromatic primary amines were inserted in dioxane at 85-100 °C in the presence of DMAP (conditions B). Enantiomerically pure amino acid methyl esters (phenylalanine, tyrosine, tryptophan and histidine) afforded substitution products according to conditions A with yields ranging from 43% to 81%. Under the conditions of Scheme 7, no significant racemization was observed and the products **6aj-am** and **6bb** can almost be considered as enantiomerically pure (see specific rotations in the experimental section). This feature is interesting because most of amino acids and peptides have primary amino groups of similar nucleophilicities[18] and, therefore, may be inserted to the 8-azachromone scaffold in this way without loss of optical activity.

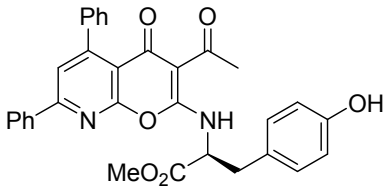
Scheme 7. Nucleophilic Substitution of 4a-e with Primary Aliphatic and Aromatic Amines.



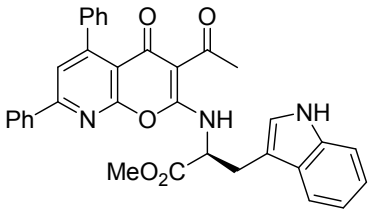
4a-e **6**



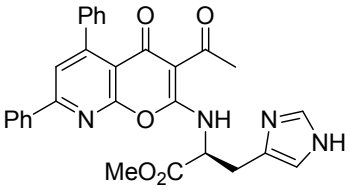
6aj, 71%[a,c]



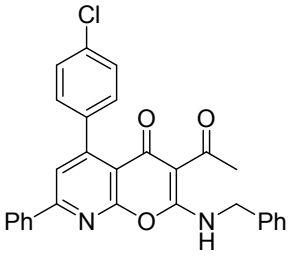
6ak, 75%[a,c]



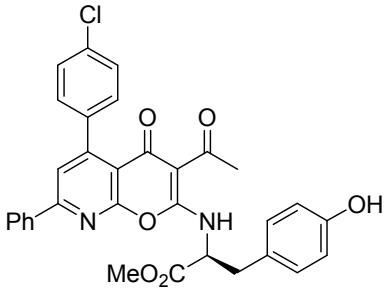
6al, 81%[a,c]



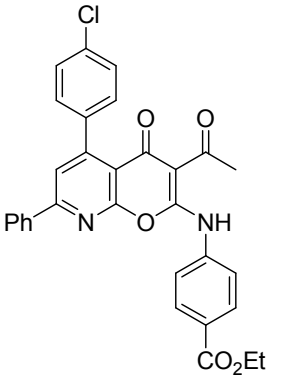
6am, 43%[a,d]



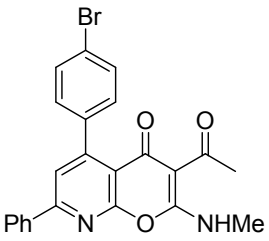
6ba, 98%[a]



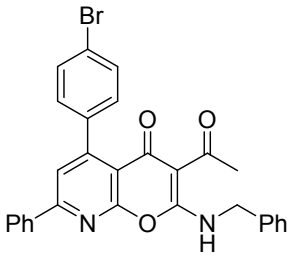
6bb, 74%[a,c]



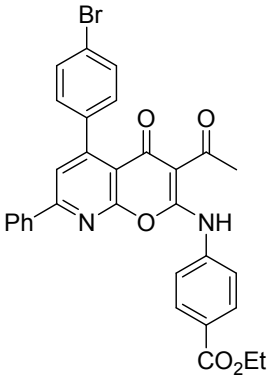
6bc, 61%[b]



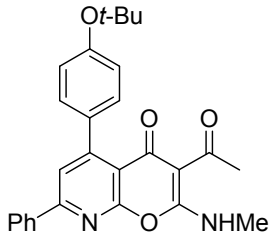
6ca, 91%[a]



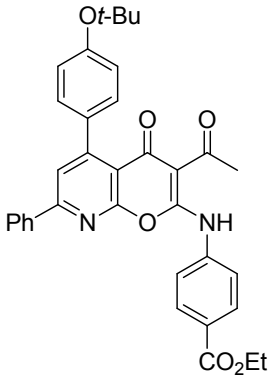
6cb, 89%[a]



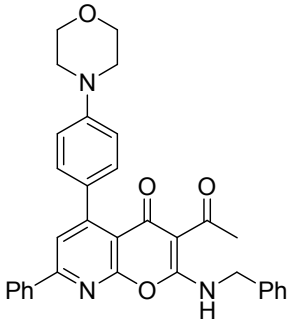
6cc, 67%[b]



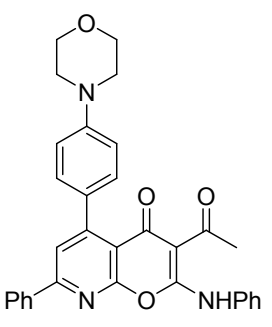
6da, 95%[a]



6db, 38%[b]



6ea, 81%[a]

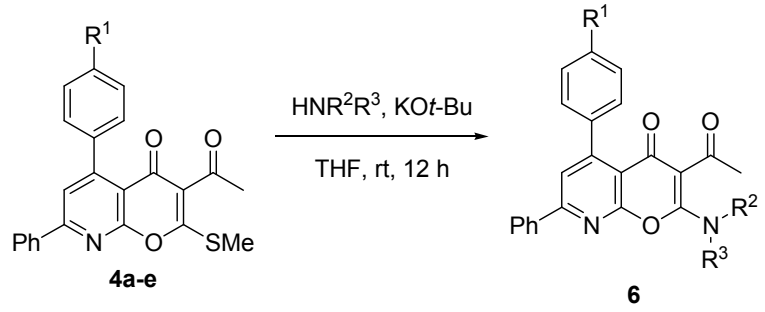


6eb, 89%[b]

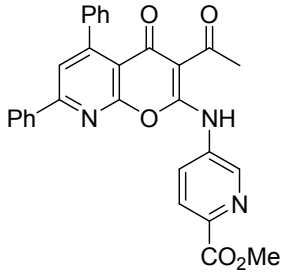
[a] Conditions A: 0.05-0.1 M **4**, 1.1 equiv amine, DCM, rt. [b] Conditions B: 0.05 M **4**, 1.1 equiv amine, 0.3 equiv DMAP, 1,4-dioxane, 85-100 °C. [c] Amino acid methyl ester generated from the corresponding hydrochloride (1.5 equiv) and Et_3N (1.1 equiv). [d] Histidine methyl ester generated from the dihydrochloride (1.2 equiv) and Et_3N (2 equiv).

So far, only N-nucleophiles at least as nucleophilic as benzocaine enabled the formation of substitution products. When the *N* value falls below the limit of *N* 12, the nucleophilic substitution does not take place. Accordingly, imidazole with *N* 11.47 is unreactive. However, imidazole is relatively acidic with a pKa of 18.6 in DMSO[19] and, under anionic form, shows a significant increase in nucleophilicity to *N* 21.09 (data in DMSO),[20] which is above the limit of reactivity. Thus, after deprotonation in the presence of KO*t*-Bu in THF, the potassium salt of imidazole indeed reacts with **4a** as predicted, but the product is quite unstable and unfortunately could not be isolated. However, primary amines of similar nucleophile strengths (i.e. unreactive under the conditions of Scheme 7), such as methyl and ethyl 5-aminopicolinate and 3-aminoisoxazole, also react with **4a** upon deprotonation by KO*t*-Bu in THF, but this time give stable products that were isolated and clearly identified as substitution products **6an-ap** (Scheme 8). The reaction is actually complicated by two distinctive features that cap the yields at 50%: on the first hand, deprotonation of the substitution product by the amine anion that would require two equivalents for a complete conversion, but on the other hand the fast ring opening of the substitution product that prevents the use of a second equivalent of amine anion. Nevertheless, this strategy enables the formation of substitution products that would not be possible under neutral conditions, and was successfully applied to the R^1-substituted derivatives **4b-e** (Scheme 8).

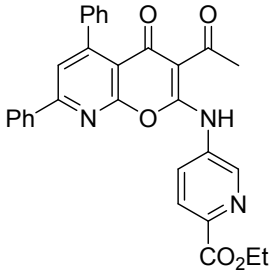
Scheme 8. Nucleophilic Substitution of 4a-e with Amine Anions.[a]



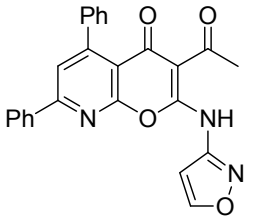
4a-e **6**



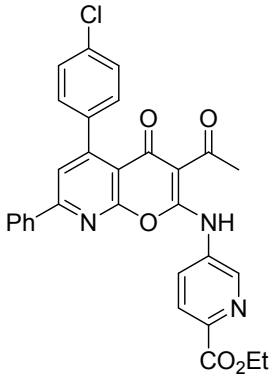
6an, 41%



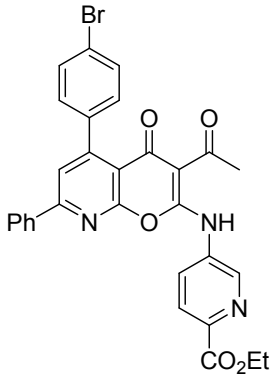
6ao, 47%



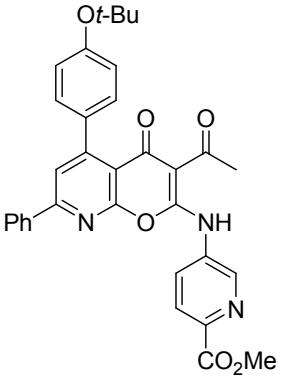
6ap, 38%



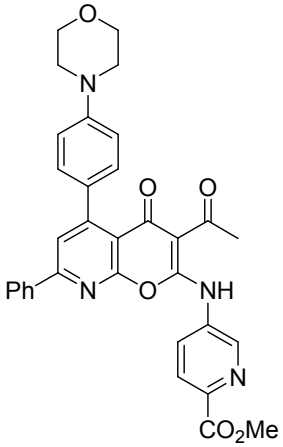
6bd, 46%



6cd, 48%



6dc, 49%



6ec, 36%

[a] Reaction conditions: 0.05 M **4**, 1.5 equiv amine, 1.1 equiv KO*t*-Bu, anhyd THF, rt, argon atm.

The activation via deprotonation, which is possible with N-nucleophiles, might not be effective for other classes of nucleophiles as the basicity of the reaction medium has to be taken into consideration. For example, the O-nucleophiles water (*N* 5.20) and methanol (*N* 7.54) would need deprotonation to give substitution products. However, the corresponding hydroxide and methoxide anions are much more basic than the amine anions used in Scheme 8, and thus deprotonate the 2-(methylthio)-8-azachromone starting materials, resulting in more difficult reactions. Nevertheless, neutral nucleophiles of any class with *N* values above 12 in the Mayr's nucleophilicity scale (e.g. enamines) should give the corresponding substitution products in the same way than N-nucleophiles do.

CONCLUSION

We have developed an efficient strategy enabling the synthesis of 2-(substituted amino)-8-azachromones. This strategy relies on three main steps: the synthesis of 3-acetoacetyl derivatives of 4,6-diaryl-2-pyridones, their cyclization into 2-(methylthio)-8-azachromones via condensation with carbon disulfide, and finally the insertion of amines at C2 by nucleophilic substitution. Three main classes of amines have been distinguished according to the conditions promoting the nucleophilic substitution, which in turn depend on the nucleophile strength. The position of a given amine into one of those three classes is easily predicted by using the Mayr's nucleophilicity scale. Because the nucleophilic substitution is not altered by the presence of a *para* substituent on the 5-phenyl ring, numerous structural analogs can be designed. Our synthetic strategy paves the way for a greater access to new compounds of possible pharmaceutical interest. This may be driven by the pharmaceutical properties of many N-substituted 2-amino-chromones, including anti-platelet aggregation, kinase inhibition in anti-cancer therapies, anti-inflammatory and antibacterial drugs.[3a,21]

EXPERIMENTAL SECTION

General remarks. Commercially available reagents and solvents were used as purchased without further purification, unless otherwise indicated. ^{1}H and ^{13}C NMR spectra were recorded on 400 MHz, 500 MHz and 600 MHz instruments, and were calibrated using residual solvent signals as internal references: δ_H 7.26 ppm and δ_C 77.16 ppm for $CDCl_3$, δ_H 2.50 ppm and δ_C 39.52 ppm for DMSO-d_6. ^{1}H NMR data are reported as follows: chemical shift (ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad signal), coupling constants and integration. Proton-decoupled ^{13}C NMR data are reported in terms of chemical shifts with unresolved signals of chemically distinct carbons indicated. Structural assignments were made with additional information from gCOSY, gHSQC, and gHMBC experiments. High resolution mass spectra were recorded on a micrOTOF-Q instrument using electrospray ionization (ESI) in positive or negative ion polarity mode. Analytical thin-layer chromatography was performed with commercial plates of silica gel 60, visualized with short wavelength UV light (254 nm) and stained with a *p*-anisaldehyde solution in $EtOH/H_2SO_4$ with subsequent heating. Preparative flash chromatography was performed with silica gel 60. Reactions that required heating were performed in hot plate/heating block apparatus with internal temperature control.

General procedure for the synthesis of 4-susbtituted chalcones. To a stirred solution of 4-substituted benzaldehyde (6 mmol) and acetophenone (0.7 mL, 6 mmol) in absolute ethanol (18 mL), NaOH (15 M aq solution, 0.6 mL, 9 mmol) was added and the resulting reaction mixture was stirred 20 h at rt. After completion, the reaction mixture was diluted with absolute ethanol (18 mL) and cooled to 0 °C. The precipitated product was recovered by filtration, washed with cold absolute ethanol and dried under vacuum.

4-Chlorochalcone was commercially available.

4-Bromochalcone was prepared from 4-bromobenzaldehyde according to the general procedure. 1.33 g (4.63 mmol, 77% yield), pale yellow solid. The spectroscopic data were consistent with those reported.[22]

4-*t*-Butoxychalcone was prepared from 4-*t*-butoxybenzaldehyde according to the general procedure. 1.63 g (5.81 mmol, 97% yield), pale yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 – 7.98 (m, 2H), 7.79 (d, *J* = 15.7 Hz, 1H), 7.61 – 7.54 (m, 3H), 7.53 – 7.48 (m, 2H), 7.44 (d, *J* = 15.7 Hz, 1H), 7.03 (dm, *J* = 8.6 Hz, 2H), 1.40 (s, 9H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 190.8, 158.3, 144.8, 138.6, 132.8, 129.8, 129.6, 128.7, 128.6, 123.9, 120.8, 79.6, 29.1. HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{19}H_{21}O_2$ 281.1536, found 281.1528.

4-Morpholinochalcone was prepared from 4-morpholinobenzaldehyde according to the general procedure. 1.54 g (5.25 mmol, 87% yield), yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 – 7.96 (m, 2H), 7.78 (d, *J* = 15.6 Hz, 1H), 7.62 – 7.53 (m, 3H), 7.53 – 7.46 (m, 2H), 7.39 (d, *J* = 15.6 Hz, 1H), 6.92 (dm, *J* = 8.8 Hz, 2H), 3.91 – 3.84 (m, 4H), 3.31 – 3.25 (m, 4H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 190.8, 152.7, 145.1, 138.9, 132.6, 130.3, 128.7, 128.5, 126.2, 119.0, 115.0, 66.7, 48.3. HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{19}H_{20}NO_2$ 294.1494, found 294.1494.

General procedure for the synthesis of 4,6-diaryl-3-cyano-2-pyridones 1a-e-K (Table 1). To a stirred solution of chalcone (2 mmol) and cyanoacetamide (185 mg, 2.2 mmol) in the indicated alcohol (*t*-butyl alcohol or 2-propanol, 24 mL), KO*t*-Bu (898 mg, 8 mmol) was added in one portion and the resulting reaction mixture was stirred in open air under the indicated conditions. After completion, 2-propanol (24 mL) was added and the stirring was kept 15 min at rt. The precipitated product was recovered by filtration, washed with successively 2-propanol (3 x 24 mL), cyclohexane (3 x 12 mL) and Et_2O (3 x 12 mL), and dried under vacuum. The products were characterized as potassium salts. The neutral forms **1a**,[23,24] **1b**[23,25] and **1c**[25,26] have been reported.

3-Cyano-4,6-diphenyl-2(1*H*)-pyridone, potassium salt (1a-K) was prepared from *trans*-chalcone according to the general procedure (2-propanol, rt, 60 h). 595 mg (1.92 mmol, 96% yield), pale yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.97 (dm, *J* = 6.9 Hz, 2H), 7.57 (dm, *J* = 6.9 Hz, 2H), 7.51 – 7.32 (m, 6H), 6.53 (s, 1H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 172.2, 158.9, 154.6, 140.3, 139.3, 128.5, 128.3 (2C), 128.2, 128.0, 126.8, 121.5, 101.8, 91.2. HRMS (ESI/Q-TOF) *m/z*: $[M - K]^-$ calcd for $C_{18}H_{11}N_2O$ 271.0871, found 271.0871.

4-(4-Chlorophenyl)-3-cyano-6-phenyl-2(1*H*)-pyridone, potassium salt (1b-K) was prepared from 4-chlorochalcone according to the general procedure (2-propanol, rt, 60 h). 643 mg (1.86 mmol, 93% yield), pale yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.00 – 7.93 (m, 2H), 7.59 (dm, *J* = 8.6 Hz, 2H), 7.53 (dm, *J* = 8.6 Hz, 2H), 7.43 – 7.32 (m, 3H), 6.52 (s, 1H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 172.0,

159.1, 153.3, 140.2, 138.1, 133.1, 129.9, 128.6, 128.4, 128.2, 126.8, 121.3, 101.6, 91.0. HRMS (ESI/Q-TOF) *m/z*: $[M - K]^-$ calcd for $C_{18}H_{10}ClN_2O$ 305.0482, found 305.0477.

4-(4-Bromophenyl)-3-cyano-6-phenyl-2(1*H*)-pyridone, potassium salt (1c-K) was prepared from 4-bromochalcone according to the general procedure (2-propanol, rt, 60 h). 747 mg (1.92 mmol, 96% yield), pale yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.00 – 7.93 (m, 2H), 7.66 (dm, J = 8.5 Hz, 2H), 7.52 (dm, J = 8.5 Hz, 2H), 7.43 – 7.32 (m, 3H), 6.53 (s, 1H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 172.3, 159.5, 153.8, 140.1, 138.4, 131.6, 130.4, 129.0, 128.5, 127.1, 122.1, 121.2, 102.7, 91.4. HRMS (ESI/Q-TOF) *m/z*: $[M - K]^-$ calcd for $C_{18}H_{10}$ $^{79}BrN_2O$ 348.9982, found 348.9992 ; calcd for $C_{18}H_{10}$ $^{81}BrN_2O$ 350.9956, found 350.9980.

4-(4-*t*-Butoxyphenyl)-3-cyano-6-phenyl-2(1*H*)-pyridone, potassium salt (1d-K) was prepared from 4-*t*-butoxychalcone according to the general procedure (2-propanol, rt, 60 h). 589 mg (1.54 mmol, 77% yield), white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.00 – 7.94 (m, 2H), 7.51 (dm, J = 8.6 Hz, 2H), 7.43 – 7.31 (m, 3H), 7.05 (dm, J = 8.6 Hz, 2H), 6.51 (s, 1H), 1.35 (s, 9H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 172.2, 158.8, 155.4, 154.1, 140.4, 133.7, 128.8, 128.4, 128.1, 126.8, 122.9, 121.7, 101.7, 91.1, 78.3, 28.6. HRMS (ESI/Q-TOF) *m/z*: $[M - K]^-$ calcd for $C_{22}H_{19}N_2O_2$ 343.1447, found 343.1443.

3-Cyano-4-(4-morpholinophenyl)-6-phenyl-2(1*H*)-pyridone, potassium salt (1e-K) was prepared from 4-morpholinochalcone according to the general procedure (*t*-butyl alcohol, 30 °C, 48 h). 734 mg (1.86 mmol, 93% yield), pale yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.01 – 7.91 (m, 2H), 7.49 (d, J = 8.8 Hz, 2H), 7.43 – 7.31 (m, 3H), 7.01 (d, J = 8.8 Hz, 2H), 6.50 (s, 1H), 3.79 – 3.73 (m, 4H), 3.22 – 3.15 (m, 4H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 172.4, 158.7, 154.4, 151.1, 140.5, 129.5, 128.8, 128.4, 128.1, 126.8, 121.9, 114.4, 101.6, 90.9, 66.1, 48.0. HRMS (ESI/Q-TOF) *m/z*: $[M - K]^-$ calcd for $C_{22}H_{18}N_3O_2$ 356.1405, found 356.1408.

General procedure for the synthesis of 3-acetyl-4,6-diaryl-2-pyridones 2a-e (Scheme 2). To a stirred suspension of 3-cyano-2-pyridone **1-K** (2 mmol) in anhydrous THF (10 mL) under argon atmosphere, anhydrous 1,4-dioxane (1 mL, 12 mmol) was added and the mixture was cooled to 0 °C. Then, MeMgBr (3 M solution in Et_2O, 4 mL, 12 mmol) was slowly added and the resulting reaction mixture was stirred 48 h while allowed to reach rt. After completion, 4 mL H_2O were added dropwise at 0 °C followed by 14 mL of 1 N aq HCl (14 mmol HCl). The resulting mixture was stirred 12 h at 40 °C. Finally, most of the THF was evaporated under reduced pressure, an excess volume of 0.1 N aq HCl was added and the product was extracted with DCM. The combined organic layers were washed with successively 0.1 N aq HCl, H_2O and brine, dried over Na_2SO_4 and concentrated. The crude product containing 4-8% of the starting 3-cyano-2-pyridone (neutral form) was precipitated in petroleum ether, recovered by filtration, dried under vacuum and used without further purification (analytical samples were obtained by flash chromatography on silica gel).

3-Acetyl-4,6-diphenyl-2(1*H*)-pyridone (2a) was prepared from **1a-K** according to the general procedure. 434 mg (1.5 mmol, 75% yield), orange solid. An analytical sample was obtained by flash chromatography (DCM/EtOAc 85:15 then DCM/EtOAc/EtOH 85:10:5). The spectroscopic data were consistent with those reported.[27]

3-Acetyl-4-(4-chlorophenyl)-6-phenyl-2(1*H*)-pyridone (2b) was prepared from **1b-K** according to the general procedure. 440 mg (1.36 mmol, 68% yield), yellowish solid. An analytical sample was obtained by flash chromatography (DCM/EtOAc 80:20 then DCM/EtOAc/EtOH 80:15:5). ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.36 (br s, 1H), 7.82 – 7.77 (m, 2H), 7.54 – 7.48 (m, 3H), 7.41 (dm, *J* = 8.5 Hz, 2H), 7.30 (dm, *J* = 8.5 Hz, 2H), 6.54 (s, 1H), 2.43 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 202.0, 162.9, 152.6, 148.1, 136.8, 135.4, 132.7, 131.1, 129.42, 129.36, 129.1, 127.8 (br), 127.0, 107.6, 32.0. HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{19}H_{15}ClNO_2$ 324.0791, found 324.0792.

3-Acetyl-4-(4-bromophenyl)-6-phenyl-2(1*H*)-pyridone (2c) was prepared from **1c-K** according to the general procedure. 479 mg (1.30 mmol, 65% yield), yellowish solid. An analytical sample was obtained by flash chromatography (DCM/EtOAc 80:20 then DCM/EtOAc/EtOH 80:15:5). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.03 (br s, 1H), 7.90 – 7.80 (m, 2H), 7.63 (dm, *J* = 8.5 Hz, 2H), 7.53 – 7.48 (m, 3H), 7.35 (dm, *J* = 8.5 Hz, 2H), 6.62 (br s, 1H), 2.42 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6) δ 202.4, 161.2, 150.2, 148.0 (br), 137.3, 133.0 (br), 131.6, 130.4 (2C), 130.2, 128.9, 127.4, 122.3, 106.7 (br), 31.8. HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{19}H_{15}$ $^{79}BrNO_2$ 368.0286, found 368.0288.

3-Acetyl-4-(4-*t*-butoxyphenyl)-6-phenyl-2(1*H*)-pyridone (2d) was prepared from **1d-K** according to the general procedure. 405 mg (1.12 mmol, 56% yield), yellowish solid. An analytical sample was obtained by flash chromatography (DCM/EtOAc 80:20 then DCM/EtOAc/EtOH 80:15:5). ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.90 (br s, 1H), 7.88 – 7.81 (m, 2H), 7.53 – 7.46 (m, 3H), 7.29 (dm, *J* = 8.6 Hz, 2H), 7.04 (dm, *J* = 8.6 Hz, 2H), 6.62 (s, 1H), 2.35 (s, 3H), 1.39 (s, 9H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 202.5, 163.2, 156.8, 152.9, 147.6, 133.0, 132.8, 130.8, 129.3, 129.0, 127.8, 127.2, 123.9, 107.8, 79.2, 31.8, 29.0. HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{23}H_{24}NO_3$ 362.1751, found 362.1759.

3-Acetyl-4-(4-morpholinophenyl)-6-phenyl-2(1*H*)-pyridone (2e) was prepared from **1e-K** according to the general procedure. 454 mg (1.21 mmol, 61% yield), orange solid. An analytical sample was obtained by flash chromatography (DCM/EtOAc 70:30 then DCM/EtOAc/EtOH 70:25:5). ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.58 (br s, 1H), 7.86 – 7.78 (m, 2H), 7.54 – 7.46 (m, 3H), 7.31 (dm, *J* = 8.8 Hz, 2H), 6.92 (dm, *J* = 8.8 Hz, 2H), 6.60 (s, 1H), 3.90 – 3.84 (m, 4H), 3.29 – 3.19 (m, 4H), 2.38 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 202.9, 163.1, 152.8, 151.8, 147.5, 133.1, 130.7, 129.4, 129.3, 128.8, 127.3, 127.1, 115.1, 107.7, 66.9, 48.5, 31.9. HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{23}H_{23}N_2O_3$ 375.1703, found 375.1692.

General procedure for the synthesis of 1,3-diketones 3a-e (Scheme 2). 3-Acetyl-2-pyridone **2** (2 mmol) and NaH (60% dispersion in mineral oil, 12 mmol, 480 mg) were suspended in anhydrous 1,4-dioxane (8 mL) under argon atmosphere, and stirred 1 h at rt. Then, EtOAc (2 mL, 20.5 mmol, *see note below*) was added and the resulting reaction mixture was stirred 12 h at rt. After completion, the reaction was diluted with EtOAc and quenched at 0 °C by slow addition of an excess volume of saturated aq NH_4Cl. The organic layer was separated and the aqueous layer was extracted again with EtOAc. The combined organic layers were washed with saturated aq NH_4Cl, dried over Na_2SO_4 and concentrated. The product was isolated by chromatography on silica gel and then precipitated by addition of the indicated solvent. Enol/keto ratios were determined by ^{1}H NMR in $CDCl_3$. *Note: commercial grade EtOAc was dried over $CaCl_2$ overnight, then filtered through a cotton plug and stored over 4 Å molecular sieves until used.*

3-Acetoacetyl-4,6-diphenyl-2(1*H*)-pyridone (3a) was prepared from **2a** according to the general procedure and was isolated by flash chromatography (DCM/EtOAc 85:15 then DCM/EtOAc/EtOH 85:10:5). 557 mg (1.68 mmol, 84% yield), yellowish solid (cyclohexane). Ratio enol/keto 3.6:1. ^{1}H NMR (400 MHz, $CDCl_3$, enol form) δ 15.41 (br s, 1H), 12.80 (br s, 1H), 7.89 – 7.80 (m, 2H), 7.56 – 7.36 (m, 8H), 6.63 (s, 1H), 5.86 (s, 1H), 2.02 (s, 3H). ^{1}H NMR (400 MHz, $CDCl_3$, keto form) δ 12.80 (br s, 1H), 7.89 – 7.80 (m, 2H), 7.56 – 7.36 (m, 8H), 6.60 (s, 1H), 3.96 (s, 2H), 2.00 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$, enol form) δ 191.4, 184.9, 163.1, 154.9, 147.8, 139.0, 132.9, 130.9, 129.3, 129.0 (2C), 128.7, 127.9, 127.2, 108.1, 104.2, 25.3. HRMS (ESI/Q-TOF) *m/z*: $[M - H]^-$ calcd for $C_{21}H_{16}NO_3$ 330.1130, found 330.1123.

3-Acetoacetyl-4-(4-chlorophenyl)-6-phenyl-2(1*H*)-pyridone (3b) was prepared from **3b** according to the general procedure and was isolated by flash chromatography (DCM/EtOAc 80:20 then DCM/EtOAc/EtOH 80:15:5). 578 mg (1.58 mmol, 79% yield), yellowish solid (cyclohexane). Ratio enol/keto 3.7:1. ^{1}H NMR (400 MHz, $CDCl_3$, enol form) δ 15.40 (br s, 1H), 12.60 (br s, 1H), 7.86 – 7.76 (m, 2H), 7.55 – 7.45 (m, 3H), 7.43 – 7.32 (m, 4H), 6.56 (s, 1H), 5.90 (s, 1H), 2.05 (s, 3H). ^{1}H NMR (400 MHz, $CDCl_3$, keto form) δ 12.60 (br s, 1H), 7.86 – 7.76 (m, 2H), 7.55 – 7.45 (m, 3H), 7.43 – 7.32 (m, 4H), 6.53 (s, 1H), 4.00 (s, 2H), 2.00 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$, enol form) δ 191.6, 184.5, 162.9, 153.7, 148.0, 137.4, 135.2, 132.7, 131.0, 129.4, 129.3, 129.0, 127.4, 127.1, 107.7, 104.1, 25.4. HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{21}H_{17}ClNO_3$ 366.0897, found 366.0894.

3-Acetoacetyl-4-(4-bromophenyl)-6-phenyl-2(1*H*)-pyridone (3c) was prepared from **2c** according to the general procedure and was isolated by flash chromatography (DCM/EtOAc 80:20 then DCM/EtOAc/EtOH 80:15:5). 591 mg (1.44 mmol, 72% yield), yellowish solid (cyclohexane). Ratio enol/keto 3.4:1. ^{1}H NMR (400 MHz, $CDCl_3$, enol form) δ 15.38 (br s, 1H), 11.94 (br s, 1H), 7.82 – 7.73 (m, 2H), 7.55 (dm, *J* = 8.5 Hz, 2H), 7.58 – 7.46 (m, 3H), 7.30 (dm, *J* = 8.5 Hz, 2H), 6.55 (s, 1H), 5.89 (s, 1H), 2.05 (s, 3H). ^{1}H NMR (400 MHz, $CDCl_3$, keto form) δ 11.94 (br s, 1H), 7.82 – 7.73 (m, 2H), 7.58 – 7.46 (m, 5H), 7.33 – 7.24 (m, 2H), 6.51 (s, 1H), 4.01 (s, 2H), 2.04 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$, enol form) δ 191.7, 184.5, 162.6, 153.7, 147.9, 137.9, 132.7, 131.9, 131.1, 129.51, 129.48, 127.2, 127.0, 123.5,

107.6, 104.1, 25.4. HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{21}H_{17}{}^{79}BrNO_3$ 410.0386, found 410.0388 ; calcd for $C_{21}H_{17}{}^{81}BrNO_3$ 412.0372, found 412.0370.

3-Acetoacetyl-4-(4-*t*-butoxyphenyl)-6-phenyl-2(1*H*)-pyridone (3d) was prepared from **2d** according to the general procedure and was isolated by flash chromatography (DCM/EtOAc 80:20 then DCM/EtOAc/EtOH 80:15:5). 670 mg (1.66 mmol, 83% yield), yellowish solid (cyclohexane). Ratio enol/keto 3.8:1. ^{1}H NMR (400 MHz, $CDCl_3$, enol form) δ 15.43 (br s, 1H), 12.58 (br s, 1H), 7.87 – 7.80 (m, 2H), 7.53 – 7.44 (m, 3H), 7.34 (dm, *J* = 8.6 Hz, 2H), 7.01 (dm, *J* = 8.6 Hz, 2H), 6.63 (s, 1H), 5.72 (s, 1H), 1.99 (s, 3H), 1.39 (s, 9H). ^{1}H NMR (400 MHz, $CDCl_3$, keto form) δ 12.58 (br s, 1H), 7.87 – 7.80 (m, 2H), 7.53 – 7.44 (m, 3H), 7.31 (dm, *J* = 8.6 Hz, 2H), 7.01 (dm, *J* = 8.6 Hz, 2H), 6.60 (s, 1H), 3.90 (s, 2H), 2.02 (s, 3H), 1.39 (s, 9H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$, enol form) δ 191.3, 185.4, 163.0, 156.6, 154.2, 147.7, 133.4, 133.0, 130.8, 129.3 (2C), 128.9, 127.1, 123.8, 107.9, 104.1, 79.2, 29.0, 25.3. HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{25}H_{26}NO_4$ 404.1862, found 404.1859.

3-Acetoacetyl-4-(4-morpholinophenyl)-6-phenyl-2(1*H*)-pyridone (3e) was prepared from **2e** according to the general procedure and was isolated by flash chromatography (DCM/EtOAc 70:30 then DCM/EtOAc/EtOH 70:25:5). 624 mg (1.50 mmol, 75% yield), orange solid (cyclohexane). Ratio enol/keto 3.9:1. ^{1}H NMR (400 MHz, $CDCl_3$, enol form) δ 15.49 (br s, 1H), 12.56 (br s, 1H), 7.85 – 7.78 (m, 2H), 7.52 – 7.44 (m, 3H), 7.38 (dm, *J* = 8.8 Hz, 2H), 6.91 (dm, *J* = 8.8 Hz, 2H), 6.62 (s, 1H), 5.85 (s, 1H), 3.91 – 3.83 (m, 4H), 3.31 – 3.19 (m, 4H), 2.05 (s, 3H). ^{1}H NMR (400 MHz, $CDCl_3$, keto form) δ 12.56 (br s, 1H), 7.85 – 7.78 (m, 2H), 7.52 – 7.44 (m, 3H), 7.33 (dm, *J* = 8.8 Hz, 2H), 6.91 (dm, *J* = 8.8 Hz, 2H), 6.59 (s, 1H), 3.93 (s, 2H), 3.91 – 3.83 (m, 4H), 3.31 – 3.19 (m, 4H), 2.04 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$, enol form) δ 191.5, 185.7, 163.1, 154.2, 151.7, 147.4, 133.0, 130.7, 129.32, 129.28, 129.24, 127.1, 122.3, 114.9, 107.8, 104.2, 66.9, 48.5, 25.4. HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{25}H_{25}N_2O_4$ 417.1809, found 417.1808.

2-Methyl-5,7-diphenyl-4*H*-pyrano[2,3-*b*]pyridin-4-one (5a) (Scheme 3). 1,3-Diketone **3a** (33 mg, 0.1 mmol) was dissolved in H_2SO_4 (1 mL) and the resulting mixture was stirred 1 h at rt. The reaction mixture was then diluted with chloroform (3 mL), cooled to 0 °C, and quenched under vigorous stirring by dropwise addition of an excess volume of cold H_2O. The organic layer was separated and the aqueous layer was extracted again with chloroform. The combined organic layers were washed with successively H_2O, aq $NaHCO_3$ and brine, then dried over Na_2SO_4 and concentrated. The product was isolated by flash chromatography on silica gel (DCM/EtOAc 97:3). 28 mg (0.089 mmol, 89% yield), white solid (cyclohexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 – 8.08 (m, 2H), 7.66 (s, 1H), 7.55 – 7.48 (m, 3H), 7.48 – 7.42 (m, 3H), 7.42 – 7.36 (m, 2H), 6.10 (d, *J* = 0.5 Hz, 1H), 2.45 (d, *J* = 0.5 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 178.3, 165.1, 162.2, 159.1, 154.6, 139.1, 137.0, 130.8, 129.1, 128.41, 128.38, 127.9, 127.8, 121.6, 114.1, 112.3, 20.4. HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{21}H_{16}NO_2$ 314.1181, found 314.1180.

General procedure for the synthesis of 2-(methylthio)-azachromones 4a-e (Scheme 4). To a suspension of 1,3-diketone **3** (1 mmol) in anhydrous acetonitrile (10 mL) under argon atmosphere, DBU (0.33 mL, 2.2 mmol) was added and the resulting mixture was stirred 30 min at rt while the starting diketone dissolved. Then, carbon disulfide (0.54 mL, 9 mmol) was first added, followed after 4 h by dimethyl sulfate (0.21 mL, 2.2 mmol). The reaction mixture was stirred 12 h at rt while product **4** slowly precipitated. After completion, 10 mL acetonitrile and 20 mL H_2O were added, resulting in the complete precipitation of the product. After 15 min of additional stirring, the product was recovered by filtration, washed with successively H_2O/acetonitrile mixture (1:1 v/v) and petroleum ether, and dried under vacuum.

3-Acetyl-2-(methylthio)-5,7-diphenyl-4*H*-pyrano[2,3-*b*]pyridin-4-one (4a) was prepared from **3a** according to the general procedure. 353 mg (0.91 mmol, 91% yield), pale yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 – 8.11 (m, 2H), 7.69 (s, 1H), 7.56 – 7.44 (m, 6H), 7.43 – 7.37 (m, 2H), 2.71 (s, 3H), 2.58 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 197.9, 177.4, 174.6, 160.8, 159.0, 155.3, 139.0, 136.7, 131.1, 129.2, 128.7, 128.3, 128.1, 127.8, 122.6, 119.9, 114.2, 32.2, 14.6. HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{23}H_{18}NO_3S$ 388.1007, found 388.1008.

3-Acetyl-5-(4-chlorophenyl)-2-(methylthio)-7-phenyl-4*H*-pyrano[2,3-*b*]pyridin-4-one (4b) was prepared from **3b** according to the general procedure. 367 mg (0.87 mmol, 87% yield), pale yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 – 8.08 (m, 2H), 7.65 (s, 1H), 7.58 – 7.49 (m, 3H), 7.45 (dm, *J* = 8.5 Hz, 2H), 7.34 (dm, *J* = 8.5 Hz, 2H), 2.71 (s, 3H), 2.58 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 197.8, 177.6, 174.6, 160.8, 159.3, 154.0, 137.4, 136.6, 134.9, 131.2, 129.7, 129.3, 128.5, 127.8, 122.4, 119.8, 114.1, 32.2, 14.6. HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{23}H_{17}ClNO_3S$ 422.0612, found 422.0619.

3-Acetyl-5-(4-bromophenyl)-2-(methylthio)-7-phenyl-4*H*-pyrano[2,3-*b*]pyridin-4-one (4c) was prepared from **3c** according to the general procedure. 410 mg (0.88 mmol, 88% yield), pale yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 – 8.09 (m, 2H), 7.65 (s, 1H), 7.60 (dm, *J* = 8.5 Hz, 2H), 7.55 – 7.50 (m, 3H), 7.28 (dm, *J* = 8.5 Hz, 2H), 2.71 (s, 3H), 2.57 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 197.7, 177.6, 174.5, 160.8, 159.3, 154.0, 137.9, 136.5, 131.4, 131.2, 130.0, 129.2, 127.8, 123.1, 122.3, 119.8, 114.0, 32.2, 14.6. HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{23}H_{17}{}^{79}BrNO_3S$ 466.0107, found 466.0119 ; calcd for $C_{23}H_{17}{}^{81}BrNO_3S$ 468.0092, found 468.0103.

3-Acetyl-5-(4-*t*-butoxyphenyl)-2-(methylthio)-7-phenyl-4*H*-pyrano[2,3-*b*]pyridin-4-one (4d) was prepared from **3d** according to the general procedure. 409 mg (0.89 mmol, 89% yield), pale yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 – 8.10 (m, 2H), 7.70 (s, 1H), 7.56 – 7.48 (m, 3H), 7.33 (dm, *J* = 8.6 Hz, 2H), 7.08 (dm, *J* = 8.6 Hz, 2H), 2.71 (s, 3H), 2.59 (s, 3H), 1.45 (s, 9H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 197.9, 177.1, 174.7, 160.9, 158.9, 156.4, 155.1, 136.8, 133.2, 131.0, 129.4, 129.2, 127.8, 123.0, 122.7, 119.9, 114.2, 79.0, 32.1, 29.1, 14.6. HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{27}H_{26}NO_4S$ 460.1577, found 460.1591.

3-Acetyl-2-(methylthio)-5-(4-morpholinophenyl)-7-phenyl-4*H*-pyrano[2,3-*b*]pyridin-4-one (4e) was prepared from **3e** according to the general procedure. 421 mg (0.89 mmol, 89% yield), yellowish solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 – 8.08 (m, 2H), 7.69 (s, 1H), 7.57 – 7.47 (m, 3H), 7.38 (dm, *J* = 8.7 Hz, 2H), 6.98 (dm, *J* = 8.7 Hz, 2H), 3.95 – 3.82 (m, 4H), 3.36 – 3.21 (m, 4H), 2.71 (s, 3H), 2.61 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 198.0, 177.1, 175.0, 161.1, 158.8, 155.1, 151.5, 136.9, 130.9, 130.0, 129.3, 129.2, 127.7, 122.5, 119.9, 114.4, 114.0, 67.0, 48.5, 32.3, 14.6. HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{27}H_{25}N_2O_4S$ 473.1530, found 473.1528.

General procedures for the synthesis of 2-(substituted amino)-8-azachromones 6aa-am, 6ba-bc, 6ca-cc, 6da-db and 6ea-eb (Table 2 and Scheme 7). *Note: safety precautions must be taken due to the release of toxic methanethiol.* **Procedure A:** 2-(Methylthio)-8-azachromone **4** (0.1 mmol) and amine (amount indicated) were dissolved in anhydrous DCM (volume indicated) under argon atmosphere, and the resulting mixture was stirred under the indicated conditions. After completion, the crude reaction mixture was applied on top of a silica gel column and the product was eluted with the indicated solvent. **Procedure B:** 2-(Methylthio)-8-azachromone **4** (0.1 mmol), amine (0.11 mmol) and DMAP (4 mg, 0.03 mmol) were dissolved in the indicated anhydrous solvent (THF or 1,4-dioxane, 2 mL), and the resulting mixture was stirred in open air under the indicated conditions. After completion, the reaction mixture was cooled to rt and the product was precipitated by addition of the indicated solvents. After 15 min of additional stirring, the product was recovered by filtration, washed with the indicated solvents, and dried under vacuum.

3-Acetyl-5,7-diphenyl-2-(piperidin-1-yl)-4*H*-pyrano[2,3-*b*]pyridin-4-one (6aa) was prepared from **4a** and piperidine (11 μL, 0.11 mmol) according to procedure A (1 mL DCM, rt, 12 h), and was eluted with DCM/EtOAc 85:15. 41 mg (0.096 mmol, 96% yield), white solid (cyclohexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 – 8.06 (m, 2H), 7.57 (s, 1H), 7.54 – 7.37 (m, 8H), 3.56 – 3.49 (m, 4H), 2.54 (s, 3H), 1.83 – 1.70 (m, 6H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 197.9, 176.7, 163.3, 158.5, 158.2, 154.6, 139.8, 137.3, 130.5, 129.1, 128.34, 128.29, 127.9, 127.6, 121.8, 114.0, 103.8, 50.3, 33.0, 26.0, 23.9. HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{27}H_{25}N_2O_3$ 425.1860, found 425.1877.

3-Acetyl-2-morpholino-5,7-diphenyl-4*H*-pyrano[2,3-*b*]pyridin-4-one (6ab) was prepared from **4a** and morpholine (10 μL, 0.11 mmol) according to procedure A (1 mL DCM, rt, 12 h), and was eluted with DCM/EtOAc 4:1. 40 mg (0.093 mmol, 93% yield), white solid (cyclohexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 – 8.01 (m, 2H), 7.60 (s, 1H), 7.54 – 7.37 (m, 8H), 3.93 – 3.82 (m, 4H), 3.65 – 3.54 (m, 4H), 2.54 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 197.9, 176.8, 163.0, 158.4 (2C), 154.7, 139.5, 137.1, 130.6, 129.1, 128.4, 128.3, 128.0, 127.6, 122.0, 113.9, 104.1, 66.5, 49.3, 33.1. HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{26}H_{23}N_2O_4$ 427.1652, found 427.1665.

3-Acetyl-2-(methylamino)-5,7-diphenyl-4*H*-pyrano[2,3-*b*]pyridin-4-one (6ac) was prepared from **4a** and methylamine (8.03 M solution in absolute ethanol, 14 μL, 0.11 mmol) according to procedure A (1 mL DCM, rt, 12 h), and was eluted with DCM/EtOAc 19:1. 36 mg (0.097 mmol, 97% yield), white solid

(cyclohexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.49 (br q, 1H), 8.16 – 8.04 (m, 2H), 7.61 (s, 1H), 7.55 – 7.43 (m, 6H), 7.42 – 7.35 (m, 2H), 3.31 (d, *J* = 5.1 Hz, 3H), 2.59 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 199.8, 175.3, 165.8, 158.03, 157.97, 155.2, 139.9, 137.0, 130.7, 129.1, 128.3, 128.2, 128.0, 127.6, 122.4, 114.0, 100.2, 32.6, 28.0. HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{23}H_{19}N_2O_3$ 371.1390, found 371.1409.

3-Acetyl-2-(benzylamino)-5,7-diphenyl-4*H*-pyrano[2,3-*b*]pyridin-4-one (6ad) was prepared from **4a** and benzylamine (12 μL, 0.11 mmol) according to procedure A (1 mL DCM, rt, 12 h), and was eluted with DCM/EtOAc 19:1. 42 mg (0.094 mmol, 94% yield), white solid (cyclohexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.91 (br t, *J* = 5.4 Hz, 1H), 8.17 – 8.05 (m, 2H), 7.61 (s, 1H), 7.55 – 7.37 (m, 12H), 7.37 – 7.32 (m, 1H), 4.91 (d, *J* = 5.8 Hz, 2H), 2.60 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 199.8, 175.4, 164.9, 158.0, 157.9, 155.1, 139.9, 137.0, 136.3, 130.7, 129.16, 129.13, 128.3, 128.23, 128.19, 127.98, 127.95, 127.6, 122.4, 114.0, 100.1, 45.5, 32.7. HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{29}H_{23}N_2O_3$ 447.1709, found 447.1710.

3-Acetyl-2-(2-hydroxyethylamino)-5,7-diphenyl-4*H*-pyrano[2,3-*b*]pyridin-4-one (6ae) was prepared from **4a** and ethanolamine (7 μL, 0.11 mmol) according to procedure A (1 mL DCM, rt, 12 h). After completion, the precipitated product was recovered by filtration and washed with DCM. 26 mg (0.065 mmol, 65% yield), white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.40 (br t, 1H), 8.25 – 8.19 (m, 2H), 7.80 (s, 1H), 7.58 – 7.50 (m, 3H), 7.42 (br s, 5H), 5.13 (t, *J* = 4.6 Hz, 1H), 3.76 – 3.66 (m, 4H), 2.41 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 197.4, 174.7, 164.4, 157.5, 156.7, 154.2, 139.6, 136.2, 130.8, 129.1, 128.5, 127.8, 127.54, 127.45, 121.6, 113.5, 99.3, 59.2, 43.5, 32.1. HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{24}H_{21}N_2O_4$ 401.1501, found 401.1498.

Methyl 2-(3-acetyl-4-oxo-5,7-diphenyl-4*H*-pyrano[2,3-*b*]pyridin-2-ylamino)acetate (6af) was prepared from **4a** according to procedure A (1 mL DCM, rt, 12 h) using glycine methyl ester hydrochloride (19 mg, 0.15 mmol) and triethylamine (15 μL, 0.11 mmol), and was eluted with DCM/EtOAc 9:1. 27 mg (0.063 mmol, 63% yield), white solid (cyclohexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.88 (br t, *J* = 5.3 Hz, 1H), 8.12 – 8.05 (m, 2H), 7.61 (s, 1H), 7.55 – 7.43 (m, 6H), 7.42 – 7.35 (m, 2H), 4.51 (d, *J* = 5.6 Hz, 2H), 3.87 (s, 3H), 2.62 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 200.0, 175.3, 168.7, 165.2, 158.2, 157.8, 155.2, 139.7, 136.9, 130.8, 129.2, 128.4, 128.2, 128.0, 127.6, 122.5, 114.1, 100.4, 53.0, 43.0, 32.6. HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{25}H_{21}N_2O_5$ 429.1445, found 429.1437.

3-Acetyl-2-(4-methoxyphenylamino)-5,7-diphenyl-4*H*-pyrano[2,3-*b*]pyridin-4-one (6ag) was **p**repared from **4a** and *p*-anisidine according to procedure B (2 mL THF, 65 °C, 2 h). The product was precipitated by addition of cyclohexane (4 mL), recovered by filtration, and washed with cyclohexane/THF 2:1 and petroleum ether. 42 mg (0.091 mmol, 91% yield), white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.49 (s, 1H), 8.13 – 8.06 (m, 2H), 7.63 (s, 1H), 7.53 (dm, *J* = 9.0 Hz, 2H), 7.51 – 7.45 (m, 6H), 7.44 – 7.38 (m, 2H), 7.02 (dm, *J* = 9.0 Hz, 2H), 3.88 (s, 3H), 2.67 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 200.1, 175.5,

162.6, 158.2, 158.1, 157.9, 155.0, 139.8, 136.8, 130.8, 129.1, 128.40, 128.36, 128.2, 128.0, 127.6, 124.8, 122.3, 114.8, 114.1, 100.1, 55.7, 32.8. HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{29}H_{23}N_2O_4$ 463.1652, found 463.1643.

3-Acetyl-5,7-diphenyl-2-(phenylamino)-4*H*-pyrano[2,3-*b*]pyridin-4-one (6ah) was prepared from **4a** and aniline according to procedure B (2 mL THF, 65 °C, 2 h). The product was precipitated by addition of cyclohexane (4 mL), recovered by filtration, and washed with cyclohexane/THF 2:1 and petroleum ether. 39 mg (0.09 mmol, 90% yield), pale yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.61 (s, 1H), 8.15 – 8.08 (m, 2H), 7.67 – 7.61 (m, 2H), 7.64 (s, 1H), 7.54 – 7.46 (m, 8H), 7.44 – 7.38 (m, 2H), 7.32 (tm, *J* = 7.4 Hz, 1H), 2.68 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 200.3, 175.6, 162.8, 158.3, 157.9, 155.0, 139.7, 136.8, 135.8, 130.8, 129.7, 129.1, 128.4, 128.2, 128.0, 127.7, 126.4, 123.2, 122.4, 114.2, 100.3, 32.8. HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{28}H_{21}N_2O_3$ 433.1547, found 433.1551.

Ethyl 4-(3-acetyl-4-oxo-5,7-diphenyl-4H-pyrano[2,3-b]pyridin-2-ylamino)benzoate (6ai) was prepared from **4a** and ethyl 4-aminobenzoate according to procedure B (2 mL dioxane, 100 °C, 36 h). The product was precipitated by addition of dioxane (2 mL) and cyclohexane (8 mL), recovered by filtration, and washed with cyclohexane/dioxane 2:1 and petroleum ether. 31 mg (0.061 mmol, 61% yield), white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.80 (s, 1H), 8.18 (dm, *J* = 8.7 Hz, 2H), 8.16 – 8.11 (m, 2H), 7.74 (dm, *J* = 8.7 Hz, 2H), 7.67 (s, 1H), 7.56 – 7.45 (m, 6H), 7.44 – 7.38 (m, 2H), 4.42 (q, *J* = 7.1 Hz, 2H), 2.69 (s, 3H), 1.43 (t, *J* = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 200.7, 175.5, 166.0, 162.7, 158.5, 157.8, 155.1, 139.8, 139.5, 136.6, 131.3, 131.0, 129.2, 128.5, 128.2, 128.1, 127.8, 127.7, 122.5, 122.3, 114.1, 100.7, 61.3, 32.8, 14.5. HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{31}H_{25}N_2O_5$ 505.1758, found 505.1732.

(*S*)-Methyl 2-(3-acetyl-4-oxo-5,7-diphenyl-4*H*-pyrano[2,3-*b*]pyridin-2-ylamino)-3-phenylpropanoate (6aj) was prepared from **4a** according to procedure A (1 mL DCM, rt, 84 h) using L-phenylalanine methyl ester hydrochloride (32 mg, 0.15 mmol) and triethylamine (15 μL, 0.11 mmol), and was eluted with DCM/EtOAc 49:1. 37 mg (0.071 mmol, 71% yield), white solid (MeOH). $[\alpha]_D^{20}$ +13.2° (*c* 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.91 (d, *J* = 7.8 Hz, 1H), 8.11 – 8.05 (m, 2H), 7.58 (s, 1H), 7.55 – 7.42 (m, 6H), 7.39 – 7.28 (m, 6H), 7.25 – 7.20 (m, 1H), 5.21 (td, *J* = 8.0, 5.0 Hz, 1H), 3.83 (s, 3H), 3.41 (dd, *J* = 13.9, 5.0 Hz, 1H), 3.24 (dd, *J* = 13.9, 8.1 Hz, 1H), 2.58 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 199.8, 175.3, 170.6, 164.6, 157.9, 157.6, 155.0, 139.7, 136.9, 135.4, 130.7, 129.5, 129.1, 129.0, 128.3, 128.2, 128.0, 127.60, 127.55, 122.3, 113.9, 100.2, 56.0, 53.1, 39.0, 32.7. HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{32}H_{27}N_2O_5$ 519.1914, found 519.1915.

(*S*)-Methyl 2-(3-acetyl-4-oxo-5,7-diphenyl-4*H*-pyrano[2,3-*b*]pyridin-2-ylamino)-3-(4-hydroxyphenyl)propanoate (6ak) was prepared from **4a** according to procedure A (1 mL DCM, rt, 84 h) using L-tyrosine methyl ester hydrochloride (35 mg, 0.15 mmol) and triethylamine (15 μL, 0.11 mmol), and was eluted with DCM/EtOAc 85:15. 40 mg (0.075 mmol, 75% yield), white solid (cyclohexane). $[\alpha]_D^{20}$

+29.8° (*c* 1.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 11.80 (d, *J* = 7.8 Hz, 1H), 8.12 – 8.03 (m, 2H), 7.59 (s, 1H), 7.54 – 7.48 (m, 3H), 7.47 – 7.41 (m, 3H), 7.39 – 7.33 (m, 2H), 7.11 (dm, *J* = 8.5 Hz, 2H), 6.72 (dm, *J* = 8.5 Hz, 2H), 5.93 (br s, 1H), 5.17 (td, *J* = 7.7, 4.9 Hz, 1H), 3.82 (s, 3H), 3.31 (dd, *J* = 14.1, 4.9 Hz, 1H), 3.18 (dd, *J* = 14.1, 7.7 Hz, 1H), 2.58 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 200.2, 175.4, 170.7, 164.6, 158.1, 157.7, 155.6, 155.1, 139.7, 136.9, 130.8, 130.7, 129.2, 128.4, 128.2, 128.0, 127.6, 126.8, 122.5, 115.9, 113.9, 100.3, 56.2, 53.1, 38.0, 32.5. HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{32}H_{27}N_2O_6$ 535.1864, found 535.1864.

(*S*)-Methyl 2-(3-acetyl-4-oxo-5,7-diphenyl-4*H*-pyrano[2,3-*b*]pyridin-2-ylamino)-3-(1*H*-indol-3-yl)propanoate (6al) was prepared from **4a** according to procedure A (1 mL DCM, rt, 60 h) using L-tryptophan methyl ester hydrochloride (38 mg, 0.15 mmol) and triethylamine (15 µL, 0.11 mmol), and was eluted with DCM/EtOAc 9:1. 45 mg (0.081 mmol, 81% yield), pale yellow solid (MeOH). $[\alpha]_D^{20}$ −19.8° (*c* 1.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 11.88 (d, *J* = 7.5 Hz, 1H), 8.20 (br s, 1H), 8.11 – 8.04 (m, 2H), 7.71 – 7.67 (m, 1H), 7.57 (s, 1H), 7.54 – 7.48 (m, 3H), 7.48 – 7.42 (m, 3H), 7.38 – 7.33 (m, 2H), 7.33 – 7.29 (m, 1H), 7.23 (br d, *J* = 2.4 Hz, 1H), 7.20 – 7.12 (m, 2H), 5.26 (td, *J* = 7.3, 5.2 Hz, 1H), 3.78 (s, 3H), 3.55 (dd, *J* = 14.8, 5.2 Hz, 1H), 3.49 (dd, *J* = 14.8, 7.2 Hz, 1H), 2.57 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 199.8, 175.4, 171.1, 164.7, 157.9, 157.7, 155.0, 139.8, 136.9, 136.4, 130.7, 129.1, 128.3, 128.2, 128.0, 127.6, 127.1, 123.7, 122.5, 122.2, 119.9, 118.7, 113.9, 111.5, 109.4, 100.3, 55.3, 53.1, 32.6, 28.9. HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{34}H_{28}N_3O_5$ 558.2023, found 558.2017.

(*S*)-Methyl 2-(3-acetyl-4-oxo-5,7-diphenyl-4*H*-pyrano[2,3-*b*]pyridin-2-ylamino)-3-(1*H*-imidazol-4-yl)propanoate (6am) was prepared from **4a** according to procedure A (1 mL DCM, rt, 72 h) using L-histidine methyl ester dihydrochloride (29 mg, 0.12 mmol) and triethylamine (28 µL, 0.2 mmol), and was eluted with DCM/EtOH 93:7. 22 mg (0.043 mmol, 43% yield), yellowish solid (Et_2O). $[\alpha]_D^{20}$ −3.4° (*c* 0.5, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 11.85 (d, *J* = 7.6 Hz, 1H), 8.09 – 8.03 (m, 2H), 7.56 – 7.53 (m, 2H), 7.52 – 7.34 (m, 9H), 6.93 (s, 1H), 5.30 – 5.22 (m, 1H), 3.84 (s, 3H), 3.38 (dd, *J* = 15.0, 5.9 Hz, 1H), 3.30 (dd, *J* = 15.0, 4.9 Hz, 1H), 2.55 (s, 3H). $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 199.8, 175.5, 170.7, 164.6, 158.1, 157.8, 155.1, 139.7, 136.8, 135.6, 130.8, 129.1, 128.4 (2C), 128.2 (2C), 128.0, 127.6, 122.4, 113.9, 100.4, 54.6, 53.2, 32.6, 30.5. HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{29}H_{25}N_4O_5$ 509.1819, found 509.1825.

3-Acetyl-2-(benzylamino)-5-(4-chlorophenyl)-7-phenyl-4*H*-pyrano[2,3-*b*]pyridin-4-one (6ba) was prepared from **4b** and benzylamine (12 µL, 0.11 mmol) according to procedure A (2 mL DCM, rt, 24 h), and was eluted with DCM/EtOAc 49:1. 47 mg (0.098 mmol, 98% yield), white solid (DCM). ^1H NMR (400 MHz, $CDCl_3$) δ 11.93 (br t, *J* = 5.5 Hz, 1H), 8.14 – 8.07 (m, 2H), 7.57 (s, 1H), 7.55 – 7.49 (m, 3H), 7.48 – 7.38 (m, 6H), 7.37 – 7.30 (m, 3H), 4.91 (d, *J* = 5.8 Hz, 2H), 2.60 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 199.8, 175.3, 164.9, 158.3, 157.9, 153.8, 138.2, 136.8, 136.3, 134.5, 130.8, 129.6, 129.2 (2C),

128.3 (2C), 128.0, 127.6, 122.2, 113.9, 100.1, 45.5, 32.7. HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{29}H_{22}ClN_2O_3$ 481.1313, found 481.1308.

(*S*)-Methyl 2-(3-acetyl-5-(4-chlorophenyl)-4-oxo-7-phenyl-4*H*-pyrano[2,3-*b*]pyridin-2-ylamino)-3-(4-hydroxyphenyl)propanoate (6bb) was prepared from **4b** according to procedure A (2 mL DCM, rt, 120 h) using L-tyrosine methyl ester hydrochloride (35 mg, 0.15 mmol) and triethylamine (15 µL, 0.11 mmol), and was eluted with DCM/EtOAc 8:1. 42 mg (0.074 mmol, 74% yield), white solid (cyclohexane). $[\alpha]_D^{20}$ +33.7° (*c* 0.5, DMSO). ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.84 (d, *J* = 7.8 Hz, 1H), 8.11 – 8.04 (m, 2H), 7.54 (s, 1H), 7.53 – 7.49 (m, 3H), 7.41 (dm, *J* = 8.5 Hz, 2H), 7.29 (dm, *J* = 8.5 Hz, 2H), 7.12 (dm, *J* = 8.5 Hz, 2H), 6.74 (dm, *J* = 8.5 Hz, 2H), 5.49 (br s, 1H), 5.16 (td, *J* = 7.8, 4.9 Hz, 1H), 3.82 (s, 3H), 3.32 (dd, *J* = 14.1, 4.9 Hz, 1H), 3.18 (dd, *J* = 14.1, 7.8 Hz, 1H), 2.58 (s, 3H). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.55 (d, *J* = 7.3 Hz, 1H), 9.30 (s, 1H), 8.25 – 8.19 (m, 2H), 7.83 (s, 1H), 7.59 – 7.52 (m, 3H), 7.49 (dm, *J* = 8.7 Hz, 2H), 7.44 (dm, *J* = 8.7 Hz, 2H), 7.06 (dm, *J* = 8.5 Hz, 2H), 6.68 (dm, *J* = 8.5 Hz, 2H), 5.13 – 5.07 (m, 1H), 3.77 (s, 3H), 3.23 (dd, *J* = 14.1, 5.5 Hz, 1H), 3.17 (dd, *J* = 14.1, 6.6 Hz, 1H), 2.40 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 197.8, 174.6, 170.3, 163.9, 157.1, 156.9, 156.5, 152.8, 138.2, 136.0, 132.7, 130.8, 130.4, 130.3, 129.1, 127.46, 127.42, 125.4, 121.6, 115.3, 113.4, 99.4, 55.6, 52.7, 36.8, 31.9. HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{32}H_{26}ClN_2O_6$ 569.1479, found 569.1479.

Ethyl 4-(3-acetyl-5-(4-chlorophenyl)-4-oxo-7-phenyl-4*H*-pyrano[2,3-*b*]pyridin-2-ylamino)benzoate (6bc) was prepared from **4b** and ethyl 4-aminobenzoate according to procedure B (2 mL dioxane, 100 °C, 36 h). The product was precipitated by addition of dioxane (2 mL) and cyclohexane (4 mL), recovered by filtration, and washed with cyclohexane/dioxane 1:1 and petroleum ether. 33 mg (0.061 mmol, 61% yield), white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.81 (s, 1H), 8.18 (dm, *J* = 8.7 Hz, 2H), 8.15 – 8.09 (m, 2H), 7.73 (dm, *J* = 8.7 Hz, 2H), 7.62 (s, 1H), 7.55 – 7.50 (m, 3H), 7.45 (dm, *J* = 8.5 Hz, 2H), 7.34 (dm, *J* = 8.5 Hz, 2H), 4.42 (q, *J* = 7.1 Hz, 2H), 2.69 (s, 3H), 1.43 (t, *J* = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 200.6, 175.5, 166.0, 162.7, 158.7, 157.8, 153.8, 139.7, 137.9, 136.4, 134.7, 131.3, 131.1, 129.6, 129.2, 128.4, 128.0, 127.7, 122.3 (2C), 114.0, 100.7, 61.3, 32.9, 14.5. HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{31}H_{24}ClN_2O_5$ 539.1368, found 539.1370.

3-Acetyl-5-(4-bromophenyl)-2-(methylamino)-7-phenyl-4*H*-pyrano[2,3-*b*]pyridin-4-one (6ca) was prepared from **4c** and methylamine (8.03 M solution in absolute ethanol, 14 µL, 0.11 mmol) according to procedure A (2 mL DCM, rt, 24 h), and was eluted with DCM/EtOAc 24:1. 41 mg (0.091 mmol, 91% yield), pale yellow solid (cyclohexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.51 (br q, 1H), 8.13 – 8.06 (m, 2H), 7.58 (dm, *J* = 8.5 Hz, 2H), 7.56 (s, 1H), 7.54 – 7.47 (m, 3H), 7.26 (dm, *J* = 8.5 Hz, 2H), 3.31 (d, *J* = 5.1 Hz, 3H), 2.60 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 199.7, 175.2, 165.8, 158.3, 158.0, 153.8, 138.8, 136.9, 131.2, 130.8, 129.9, 129.2, 127.6, 122.7, 122.1, 113.8, 100.1, 32.7, 28.1. HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{23}H_{18}{}^{79}BrN_2O_3$ 449.0495, found 449.0496 ; calcd for $C_{23}H_{18}{}^{81}BrN_2O_3$ 451.0481, found 451.0479.

3-Acetyl-2-(benzylamino)-5-(4-bromophenyl)-7-phenyl-4*H*-pyrano[2,3-*b*]pyridin-4-one (6cb) was prepared from **4c** and benzylamine (12 µL, 0.11 mmol) according to procedure A (2 mL DCM, rt, 24 h), and was eluted with DCM/EtOAc 99:1. 47 mg (0.089 mmol, 89% yield), white solid (cyclohexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.93 (br t, *J* = 5.6 Hz, 1H), 8.13 – 8.07 (m, 2H), 7.58 (dm, *J* = 8.5 Hz, 2H), 7.57 (s, 1H), 7.54 – 7.49 (m, 3H), 7.47 – 7.38 (m, 4H), 7.34 (tm, *J* = 7.1 Hz, 1H), 7.26 (dm, *J* = 8.5 Hz, 2H), 4.91 (d, *J* = 5.8 Hz, 2H), 2.60 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 199.8, 175.3, 164.9, 158.3, 157.9, 153.8, 138.8, 136.8, 136.3, 131.2, 130.9, 129.9, 129.2 (2C), 128.3, 128.0, 127.6, 122.7, 122.1, 113.9, 100.0, 45.5, 32.7. HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{29}H_{22}{}^{79}BrN_2O_3$ 525.0808, found 525.0821 ; calcd for $C_{29}H_{22}{}^{81}BrN_2O_3$ 527.0794, found 527.0806.

Ethyl 4-(3-acetyl-5-(4-bromophenyl)-4-oxo-7-phenyl-4*H*-pyrano[2,3-*b*]pyridin-2-ylamino)benzoate (6cc) was prepared from **4c** and ethyl 4-aminobenzoate according to procedure B (2 mL dioxane, 100 °C, 36 h). The product was precipitated by addition of dioxane (2 mL) and cyclohexane (4 mL), recovered by filtration, and washed with cyclohexane/dioxane 1:1 and petroleum ether. 39 mg (0.067 mmol, 67% yield), pale yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.81 (s, 1H), 8.18 (dm, *J* = 8.7 Hz, 2H), 8.15 – 8.09 (m, 2H), 7.73 (dm, *J* = 8.7 Hz, 2H), 7.62 (s, 1H), 7.60 (dm, *J* = 8.4 Hz, 2H), 7.56 – 7.50 (m, 3H), 7.28 (dm, *J* = 8.4 Hz, 2H), 4.42 (q, *J* = 7.1 Hz, 2H), 2.69 (s, 3H), 1.43 (t, *J* = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 200.6, 175.5, 166.0, 162.7, 158.7, 157.8, 153.8, 139.7, 138.4, 136.4, 131.3 (2C), 131.1, 129.9, 129.2, 128.0, 127.7, 122.9, 122.32, 122.26, 113.9, 100.6, 61.3, 32.9, 14.5. HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{31}H_{24}{}^{79}BrN_2O_5$ 583.0863, found 583.0854 ; calcd for $C_{31}H_{24}{}^{81}BrN_2O_5$ 585.0848, found 585.0841.

3-Acetyl-5-(4-*t*-butoxyphenyl)-2-(methylamino)-7-phenyl-4*H*-pyrano[2,3-*b*]pyridin-4-one (6da) was prepared from **4d** and methylamine (8.03 M solution in absolute ethanol, 14 µL, 0.11 mmol) according to procedure A (1 mL DCM, rt, 12 h), and was eluted with DCM/EtOAc 9:1. 42 mg (0.095 mmol, 95% yield), white solid (cyclohexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.46 (br q, *J* = 4.9 Hz, 1H), 8.14 – 8.07 (m, 2H), 7.61 (s, 1H), 7.54 – 7.45 (m, 3H), 7.31 (dm, *J* = 8.6 Hz, 2H), 7.05 (dm, *J* = 8.6 Hz, 2H), 3.30 (d, *J* = 5.1 Hz, 3H), 2.61 (s, 3H), 1.44 (s, 9H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 199.7, 175.4, 165.7, 158.1, 157.9, 156.0, 155.0, 137.1, 134.2, 130.6, 129.2, 129.1, 127.6, 122.9, 122.5, 113.9, 100.2, 78.9, 32.5, 29.1, 28.0. HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{27}H_{27}N_2O_4$ 443.1965, found 443.1960.

Ethyl 4-(3-acetyl-5-(4-*t*-butoxyphenyl)-4-oxo-7-phenyl-4*H*-pyrano[2,3-*b*]pyridin-2-ylamino)benzoate (6db) was prepared from **4d** and ethyl 4-aminobenzoate according to procedure B (2 mL dioxane, 100 °C, 36 h). The product was precipitated by addition of dioxane (2 mL) and cyclohexane (8 mL), recovered by filtration, and washed with cyclohexane/dioxane 2:1 and petroleum ether. 22 mg (0.038 mmol, 38% yield), white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.77 (s, 1H), 8.18 (dm, *J* = 8.7 Hz, 2H), 8.16 – 8.11 (m, 2H), 7.73 (dm, *J* = 8.7 Hz, 2H), 7.67 (s, 1H), 7.56 – 7.49 (m, 3H), 7.33 (dm, *J* = 8.6 Hz, 2H), 7.08 (dm, *J* = 8.6 Hz, 2H), 4.41 (q, *J* = 7.1 Hz, 2H), 2.69 (s, 3H), 1.45 (s, 9H), 1.43 (t, *J* = 7.1 Hz, 3H). ^{13}C{^{1}H}

NMR (101 MHz, $CDCl_3$) δ 200.7, 175.7, 166.0, 162.6, 158.3, 157.9, 156.1, 155.0, 139.8, 136.7, 133.8, 131.2, 130.9, 129.3, 129.1, 127.8, 127.7, 123.0, 122.6, 122.2, 114.0, 100.7, 78.9, 61.3, 32.7, 29.1, 14.5. HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{35}H_{33}N_2O_6$ 577.2333, found 577.2342.

3-Acetyl-2-(benzylamino)-5-(4-morpholinophenyl)-7-phenyl-4*H*-pyrano[2,3-*b*]pyridin-4-one (6ea) was prepared from **4e** and benzylamine (12 μL, 0.11 mmol) according to procedure A (2 mL DCM, rt, 24 h), and was eluted with DCM/EtOAc 9:1. 43 mg (0.081 mmol, 81% yield), bright yellow solid (cyclohexane). ^1H NMR (400 MHz, $CDCl_3$) δ 11.87 (t, *J* = 5.7 Hz, 1H), 8.12 – 8.07 (m, 2H), 7.61 (s, 1H), 7.55 – 7.31 (m, 10H), 6.97 (dm, *J* = 8.8 Hz, 2H), 4.91 (d, *J* = 5.8 Hz, 2H), 3.92 – 3.85 (m, 4H), 3.31 – 3.24 (m, 4H), 2.63 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 199.8, 175.7, 164.8, 158.1, 157.8, 154.9, 151.2, 137.1, 136.3, 130.6, 130.3, 129.8, 129.14, 129.10, 128.2, 127.9, 127.5, 122.4, 114.4, 113.7, 100.1, 67.0, 48.6, 45.4, 32.7. HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{33}H_{30}N_3O_4$ 532.2231, found 532.2229.

3-Acetyl-5-(4-morpholinophenyl)-7-phenyl-2-(phenylamino)-4*H*-pyrano[2,3-*b*]pyridin-4-one (6eb) was prepared from **4e** and aniline according to procedure B (2 mL dioxane, 85 °C, 12 h). The product was precipitated by addition of dioxane (2 mL) and cyclohexane (8 mL), recovered by filtration, and washed with cyclohexane/dioxane 2:1 and petroleum ether. 46 mg (0.089 mmol, 89% yield), yellowish solid. ^1H NMR (400 MHz, $CDCl_3$) δ 13.58 (s, 1H), 8.13 – 8.08 (m, 2H), 7.64 (s, 1H), 7.65 – 7.61 (m, 2H), 7.53 – 7.47 (m, 5H), 7.38 (dm, *J* = 8.8 Hz, 2H), 7.31 (tm, *J* = 7.4 Hz, 1H), 6.98 (dm, *J* = 8.8 Hz, 2H), 3.93 – 3.86 (m, 4H), 3.32 – 3.26 (m, 4H), 2.71 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 200.3, 175.9, 162.7, 158.2, 158.1, 154.9, 151.3, 137.0, 135.7, 130.7, 130.1, 129.9, 129.7, 129.1, 127.6, 126.4, 123.2, 122.4, 114.4, 113.9, 100.4, 67.0, 48.7, 32.8. HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{32}H_{28}N_3O_4$ 518.2074, found 518.2074.

General procedure for the formation of open-ring products 7a-b (Scheme 6). 2-(Methylthio)-8-azachromone **4a** (39 mg, 0.1 mmol) and secondary cyclic amine (0.3 mmol) were dissolved in anhydrous DCM (1 mL) under argon atmosphere, and the resulting mixture was stirred under the indicated conditions. After completion, the reaction mixture was diluted with an excess volume of DCM, washed with H_2O (3 x) and brine, then dried over Na_2SO_4 and concentrated. The product was isolated by flash chromatography on silica gel and then precipitated by addition of the indicated solvent. *Note: safety precautions must be taken due to the release of toxic methanethiol.*

3-(2-(Di(piperidin-1-yl)methylene)-1,3-dioxobutyl)-4,6-diphenyl-2(1*H*)-pyridone (7a) was prepared from **4a** and piperidine according to the general procedure (rt, 36 h), and was isolated by flash chromatography (DCM/MeOH 9:1). 50 mg (0.098 mmol, 98%), yellowish solid (hexane). ^1H NMR (400 MHz, $CDCl_3$) δ 11.76 (br s, 1H), 7.74 – 7.67 (m, 2H), 7.59 – 7.53 (m, 2H), 7.49 – 7.38 (m, 3H), 7.35 – 7.27 (m, 3H), 6.52 (s, 1H), 3.43 (br s, 4H), 3.01 (br s, 4H), 2.02 (s, 3H), 1.78 – 1.28 (m, 12H). $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 190.7, 184.7, 173.9, 163.0, 149.2, 144.6, 139.4, 133.7, 133.2, 129.9, 129.3, 128.6,

128.2 (2C), 126.6, 109.8, 107.6, 51.7 (br, 2C), 28.5, 25.5 (2C), 24.33, 24.28. HRMS (ESI/Q-TOF) *m/z*: $[M - H]^-$ calcd for $C_{32}H_{34}N_3O_3$ 508.2600, found 508.2599.

3-(2-(Dimorpholinomethylene)-1,3-dioxobutyl)-4,6-diphenyl-2(1*H*)-pyridone (7b) was prepared from **4a** and morpholine according to the general procedure (rt, 60 h), and was isolated by flash chromatography (DCM/MeOH 9:1). 37 mg (0.072 mmol, 72%), yellowish solid (hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.86 (br s, 1H), 7.73 – 7.64 (m, 2H), 7.58 – 7.51 (m, 2H), 7.51 – 7.42 (m, 3H), 7.38 – 7.28 (m, 3H), 6.52 (s, 1H), 4.09 – 2.82 (m, 16H), 2.09 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 190.5, 184.6, 173.6, 162.9, 149.7, 145.2, 139.2, 133.6, 132.4, 130.2, 129.4, 128.5 (2C), 128.4, 126.7, 108.9, 107.7, 65.8 (2C), 51.2 (br, 2C), 28.4. HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{30}H_{32}N_3O_5$ 514.2336, found 514.2330.

General procedure for the synthesis of 2-(substituted amino)-8-azachromones 6an-ap, 6bd, 6cd, 6dc and 6ec (Scheme 8). 2-(Methylthio)-8-azachromone **4** (0.1 mmol), amine (0.15 mmol) and KO*t*-Bu (12 mg, 0.11 mmol) were dissolved in anhydrous THF (2 mL) under argon atmosphere, and the resulting mixture was stirred 12 h at rt. After completion, an excess volume of DCM was added and the medium was neutralized with saturated aq NH_4Cl. The organic layer was separated and the aqueous layer was extracted again with DCM. The combined organic layers were washed with saturated aq NH_4Cl (4 x), dried over Na_2SO_4 and concentrated. The product was isolated by flash chromatography on silica gel and then precipitated by addition of the indicated solvent. *Note: safety precautions must be taken due to the release of toxic methanethiol.*

Methyl 5-(3-acetyl-4-oxo-5,7-diphenyl-4*H*-pyrano[2,3-*b*]pyridin-2-ylamino)pyridine-2-carboxylate (6an) was prepared from **4a** and methyl 5-aminopicolinate according to the general procedure, and was isolated by flash chromatography (DCM/MeOH 99:1). 20 mg (0.041 mmol, 41% yield), white solid (cyclohexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.98 (s, 1H), 9.09 (d, *J* = 2.6 Hz, 1H), 8.30 (d, *J* = 8.6 Hz, 1H), 8.20 (dd, *J* = 8.6, 2.6 Hz, 1H), 8.17 – 8.11 (m, 2H), 7.69 (s, 1H), 7.56 – 7.44 (m, 6H), 7.43 – 7.36 (m, 2H), 4.06 (s, 3H), 2.70 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 201.1, 175.4, 165.2, 163.0, 158.7, 157.7, 155.3, 144.4, 143.5, 139.3, 136.4, 136.0, 131.2, 129.6, 129.2, 128.6, 128.2, 128.1, 127.7, 126.2, 122.6, 114.1, 101.1, 53.2, 32.7. HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{29}H_{22}N_3O_5$ 492.1559, found 492.1560.

Ethyl 5-(3-acetyl-4-oxo-5,7-diphenyl-4*H*-pyrano[2,3-*b*]pyridin-2-ylamino)pyridine-2-carboxylate (6ao) was prepared from **4a** and ethyl 5-aminopicolinate according to the general procedure, and was isolated by flash chromatography (DCM/MeOH 99:1). 24 mg (0.047 mmol, 47% yield), white solid (cyclohexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.97 (s, 1H), 9.09 (d, *J* = 2.6 Hz, 1H), 8.30 (d, *J* = 8.6 Hz, 1H), 8.19 (dd, *J* = 8.6, 2.6 Hz, 1H), 8.17 – 8.11 (m, 2H), 7.69 (s, 1H), 7.55 – 7.46 (m, 6H), 7.43 – 7.36 (m, 2H), 4.53 (q, *J* = 7.1 Hz, 2H), 2.70 (s, 3H), 1.48 (t, *J* = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 201.1, 175.4, 164.7, 163.0, 158.7, 157.7, 155.3, 144.8, 143.6, 139.3, 136.4, 135.9, 131.1, 129.6, 129.2,

128.6, 128.2, 128.1, 127.7, 126.2, 122.7, 114.1, 101.1, 62.3, 32.7, 14.5. HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{30}H_{24}N_3O_5$ 506.1716, found 506.1719.

3-Acetyl-2-(isoxazol-3-ylamino)-5,7-diphenyl-4*H*-pyrano[2,3-*b*]pyridin-4-one (6ap) was prepared from **4a** and 3-aminoisoxazole according to the general procedure, and was isolated by flash chromatography (DCM/EtOAc 99:1). 16 mg (0.038 mmol, 38% yield), pale yellow solid (cyclohexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.90 (s, 1H), 8.50 (d, *J* = 1.7 Hz, 1H), 8.18 – 8.11 (m, 2H), 7.70 (s, 1H), 7.55 – 7.47 (m, 6H), 7.43 – 7.38 (m, 2H), 7.24 (d, *J* = 1.7 Hz, 1H), 2.67 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 200.6, 175.4, 162.2, 160.1, 158.6, 157.9, 156.0, 155.4, 139.2, 136.5, 131.1, 129.2, 128.6, 128.20, 128.14, 127.7, 122.7, 114.1, 101.1, 100.8, 32.8. HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{25}H_{18}N_3O_4$ 424.1297, found 424.1298.

Ethyl 5-(3-acetyl-5-(4-chlorophenyl)-4-oxo-7-phenyl-4*H*-pyrano[2,3-*b*]pyridin-2-ylamino)pyridine-2-carboxylate (6bd) was prepared from **4b** and ethyl 5-aminopicolinate according to the general procedure, and was isolated by flash chromatography (DCM/MeOH 99:1). 25 mg (0.046 mmol, 46% yield), pale yellow solid (cyclohexane). ^{1}H NMR (500 MHz, $CDCl_3$) δ 13.98 (s, 1H), 9.09 (d, *J* = 2.4 Hz, 1H), 8.30 (d, *J* = 8.5 Hz, 1H), 8.17 (dd, *J* = 8.5, 2.6 Hz, 1H), 8.15 – 8.10 (m, 2H), 7.64 (s, 1H), 7.55 – 7.50 (m, 3H), 7.45 (dm, *J* = 8.5 Hz, 2H), 7.33 (dm, *J* = 8.5 Hz, 2H), 4.52 (q, *J* = 7.1 Hz, 2H), 2.70 (s, 3H), 1.48 (t, *J* = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 201.0, 175.3, 164.7, 162.9, 158.9, 157.7, 154.0, 144.9, 143.6, 137.6, 136.1, 135.7, 134.7, 131.3, 129.67, 129.62, 129.2, 128.4, 127.7, 126.2, 122.5, 113.9, 101.0, 62.3, 32.8, 14.5. HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{30}H_{23}ClN_3O_5$ 540.1321, found 540.1314.

Ethyl 5-(3-acetyl-5-(4-bromophenyl)-4-oxo-7-phenyl-4*H*-pyrano[2,3-*b*]pyridin-2-ylamino)pyridine-2-carboxylate (6cd) was prepared from **4c** and ethyl 5-aminopicolinate according to the general procedure, and was isolated by flash chromatography (DCM/MeOH 99:1). 28 mg (0.048 mmol, 48% yield), pale yellow solid (cyclohexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.99 (s, 1H), 9.10 (d, *J* = 2.5 Hz, 1H), 8.30 (d, *J* = 8.5 Hz, 1H), 8.18 (dd, *J* = 8.6, 2.6 Hz, 1H), 8.16 – 8.10 (m, 2H), 7.64 (s, 1H), 7.61 (dm, *J* = 8.4 Hz, 2H), 7.56 – 7.50 (m, 3H), 7.28 (dm, *J* = 8.4 Hz, 2H), 4.53 (q, *J* = 7.1 Hz, 2H), 2.70 (s, 3H), 1.48 (t, *J* = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 201.0, 175.3, 164.7, 163.0, 159.0, 157.7, 154.0, 144.9, 143.6, 138.2, 136.2, 135.7, 131.33, 131.30, 129.9, 129.7, 129.2, 127.7, 126.2, 123.0, 122.4, 113.9, 101.0, 62.3, 32.8, 14.5. HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{30}H_{23}{}^{79}BrN_3O_5$ 584.0816, found 584.0800 ; calcd for $C_{30}H_{23}{}^{81}BrN_3O_5$ 586.0801, found 586.0781.

Methyl 5-(3-acetyl-5-(4-*t*-butoxyphenyl)-4-oxo-7-phenyl-4*H*-pyrano[2,3-*b*]pyridin-2-ylamino)pyridine-2-carboxylate (6dc) was prepared from **4d** and methyl 5-aminopicolinate according to the general procedure, and was isolated by flash chromatography (DCM/MeOH 99:1). 28 mg (0.049 mmol, 49% yield), white solid (cyclohexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.95 (s, 1H), 9.08 (d, *J* = 2.4 Hz, 1H), 8.30 (d, *J* = 8.6 Hz, 1H), 8.20 (dd, *J* = 8.6, 2.6 Hz, 1H), 8.17 – 8.11 (m, 2H), 7.69 (s, 1H), 7.56 – 7.48 (m, 3H), 7.32 (dm, *J* = 8.6 Hz, 2H), 7.08 (dm, *J* = 8.6 Hz, 2H), 4.05 (s, 3H), 2.71 (s, 3H), 1.45 (s, 9H).

$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 201.1, 175.5, 165.2, 162.9, 158.5, 157.9, 156.3, 155.2, 144.4, 143.5, 136.5, 136.0, 133.5, 131.1, 129.6, 129.3, 129.2, 127.7, 126.2, 123.0, 122.7, 114.0, 101.2, 79.0, 53.2, 32.6, 29.1. HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{33}H_{30}N_3O_6$ 564.2129, found 564.2133.

Methyl 5-(3-acetyl-5-(4-morpholinophenyl)-4-oxo-7-phenyl-4*H*-pyrano[2,3-*b*]pyridin-2-ylamino)pyridine-2-carboxylate (6ec) was prepared from **4e** and methyl 5-aminopicolinate according to the general procedure, and was isolated by flash chromatography (DCM/MeOH 198:2 then 197:3). 21 mg (0.036 mmol, 36% yield), yellowish solid (cyclohexane). ^{1}H NMR (500 MHz, $CDCl_3$) δ 13.95 (s, 1H), 9.07 (d, *J* = 2.3 Hz, 1H), 8.30 (d, *J* = 8.6 Hz, 1H), 8.21 (dd, *J* = 8.6, 2.6 Hz, 1H), 8.16 – 8.10 (m, 2H), 7.68 (s, 1H), 7.55 – 7.50 (m, 3H), 7.37 (dm, *J* = 8.8 Hz, 2H), 6.98 (dm, *J* = 8.8 Hz, 2H), 4.05 (s, 3H), 3.93 – 3.85 (m, 4H), 3.33 – 3.25 (m, 4H), 2.72 (s, 3H). $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$) δ 201.1, 175.7, 165.2, 162.8, 158.4, 158.0, 155.2, 151.4, 144.3, 143.4, 136.5, 136.0, 131.0, 129.9, 129.7, 129.5, 129.2, 127.6, 126.3, 122.6, 114.4, 113.8, 101.2, 67.0, 53.2, 48.6, 32.8. HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{33}H_{29}N_4O_6$ 577.2082, found 577.2087.

ASSOCIATED CONTENT

Supporting Information. Copies of ^{1}H and ^{13}C NMR spectra of all new compounds described in the experimental section, copies of ^{1}H NMR spectra of **4-bromochalcone** and compound **2a**.

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