An Efficient Approach to Heterocyclic Analogues of Xanthone: A Short Synthesis of All Possible Pyrido[5,6]pyrano[2,3-*c*]pyrazol-4(1*H*)-ones

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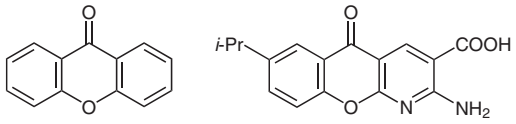
Dedicated to Prof. Wilhelm Fleischhacker with best personal wishes on the occasion of his 75th birthday

Abstract: An efficient and generally applicable synthesis of various [5,6]pyrano[2,3-*c*]pyrazol-4(1*H*)-ones by the reaction of either 1-substituted or 1,3-disubstituted 2-pyrazolin-5-ones with different *o*-halopyridinecarbonyl chlorides or with 3-chloroquinoline-2-carbonyl chloride, using calcium hydroxide in 1,4-dioxane, is described. In the course of the preparation of pyrazolo[4′,3′:5,6]pyrano[2,3-*c*]pyridin-4(1*H*)-ones, the intermediate 4-(3-chloroisonicotinoyl)-1*H*-pyrazol-5-ols did not cyclize spontaneously and thus were transformed into the corresponding tricycles by treatment with NaH in DMF. The N1-unsubstituted title compounds were obtained upon treatment of the corresponding 1-(4-methoxybenzyl) protected congeners with trifluoroacetic acid.

Key words: pyrazolones, acylations, nucleophilic aromatic substitutions, fused-ring systems, cyclizations

Naturally occurring xanthones (Figure 1), as well as synthetic derivatives thereof, exhibit a wide range of biological activities, making them attractive compounds both for synthetic and medicinal chemists.[1] As a result, aza-analogues of xanthones were studied in which one or both benzene rings of the parent dibenzo-γ-pyrone system had been replaced with N-heteroaromatic moieties leading, for example, to the anti-ulcer agent amlexanox (Figure 1).[2]



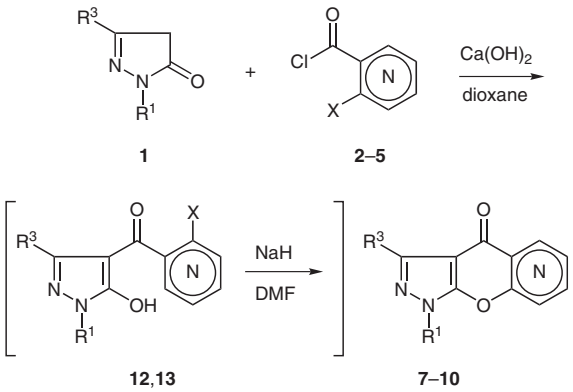
xanthone (dibenzo-γ-pyrone) **amlexanox** (Aphthasol™)

Figure 1

We were interested in a short, straightforward, and general synthetic route to xanthone derivatives containing both a pyridine and a pyrazol partial-structure. To date, only a few approaches for the construction of xanthone analogues bearing a pyrazole ring have been described in the literature.[3] Most of these involve multi-step sequences and are based on the reaction of 3-acyl-4-hydroxycoumarins with (substituted) hydrazine(s).

In contrast, we present here an easy and generally applicable method for the synthesis of condensed heterocyclic systems of type **7**–**11** in one (or two) step(s) starting from the corresponding pyrazolones **1** and *o*-haloarenecarbonyl chlorides **2**–**6** (Scheme 1). The wide range of tri- and tetracyclic systems that may be prepared according to this strategy is exemplified by the synthesis of representatives of all positional isomers of pyridino[X′,Y′:5,6]pyrano[2,3-*c*]pyrazol-4(1*H*)-ones (**7**–**10**), as well as with the synthesis of the related tetracycle **11** (Table 1). Compounds of type **7**, **8**, **9**, and **11** represent novel ring systems, whereas two derivatives of type **10** are already known.[3c] Moreover, the application of variously substituted pyrazolones and acid chlorides, which are either commercially available or easily accessible by known literature procedures, permits access to a large range of target compounds.

In most cases, reaction of pyrazolones **1** (tautomers of pyrazol-5-ols[4]) with acid chlorides **2** (Figure 2), following a general procedure,[5] ['Jensen' reaction: $Ca(OH)_2$, refluxing 1,4-dioxane] yielded the title compounds in good yields. However, during the synthesis of compounds **7c** and **9a**–**c**, no spontaneous cyclization into the target tricycle was observed. This can be readily explained by the fact that, in the intermediates **12c** and **13a**–**c** (Table 1), the leaving group X is situated in the 3-position of the pyridine, which is known to be least reactive towards nucleophilic displacement reactions. The acylation products, in these cases, were therefore isolated and subsequently transformed into the target compounds by treatment with sodium hydride in refluxing *N*,*N*-dimethylformamide (Scheme 1).



Scheme 1

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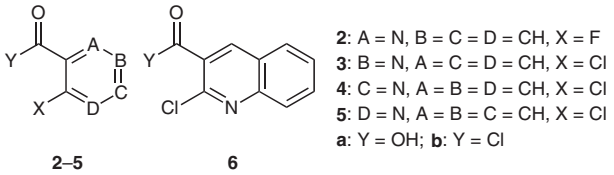


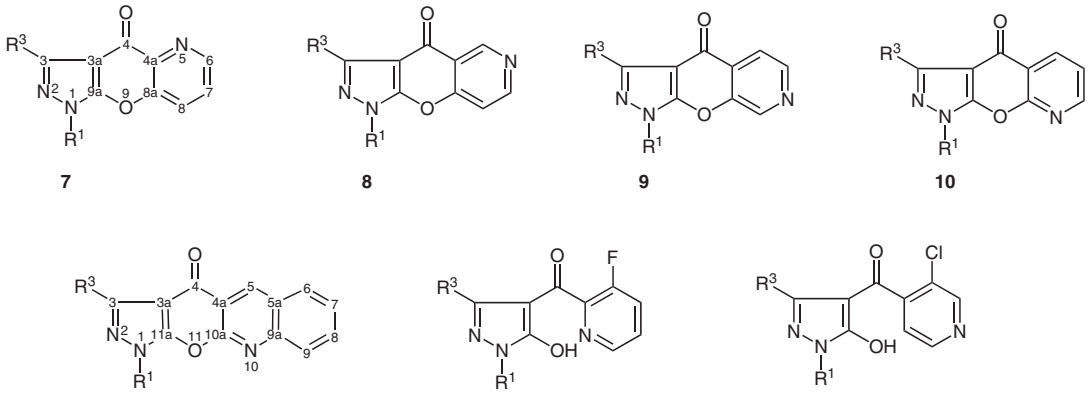
Figure 2

Scheme 2

Recently, we reported that the 4-methoxybenzyl (PMB) group was a suitable protecting group for use in the synthesis of N-unsubstituted 4-acylpyrazolones,[6] as well as for N-unsubstituted 6-phenylpyrano[2,3-*c*]pyrazol-4(1*H*)-ones.[7] The advantage of the PMB function lies in its stability during the primary pyrazolone ring synthesis, as well as in the acylation reaction under 'Jensen' conditions. Furthermore, it could be conveniently removed from the pyrazole core with trifluoroacetic acid. N-Unsubstituted ring systems of type **f** could be synthesized likewise (Scheme 2). The latter molecules are useful synthetic intermediates for the preparation of potential anticancer agents, currently under investigation in our research group.

Detailed NMR analyses for all the prepared compounds were undertaken and the data are summarized in Table 2 (^{1}H NMR), Table 3 (^{13}C NMR), Table 4 (^{13}C and ^{1}H spin coupling constants) and Table 5 (^{15}N NMR). Parent compounds **7f**, **8f**, **9f**, **10f** and **11f**, carrying no substituent at the pyrazole N1 atom, were found to be only slightly soluble even in DMSO-d_6. This fact together with the dynamic behavior of these compounds (prototropic tautomerism, as outlined for **8f** in Figure 3) seems to be responsible for the absence of the signals of the pyrazole N-atoms in the ^{15}N HMBC spectra. As demonstrated for model compound **8f** (Figure 3), the equilibrium between the 1*H*-form A and the 2*H*-form B is reflected by a marked

Table 1 Structures of Compounds **7**–**13**



Compound	R^1	R^3	Compound	R^1	R^3
7a	Ph	Me	**10c**	PMB[a]	H
7b	Ph	H	**10d**	Me	Me
7c	PMB[a]	H	**10e**	Bn	Me
8a	Ph	Me	**11a**	Ph	Me
8b	Ph	H	**11b**	Ph	H
8c	PMB[a]	H	**11c**	PMB[a]	H
9a	Ph	Me	**11d**	Me	Me
9b	Ph	H	**12c**	PMB[a]	H
9c	PMB[a]	H	**13a**	Ph	Me
10a	Ph	Me	**13b**	Ph	H
10b	Ph	H	**13c**	PMB[a]	H

[a] PMB = *p*-methoxybenzyl.

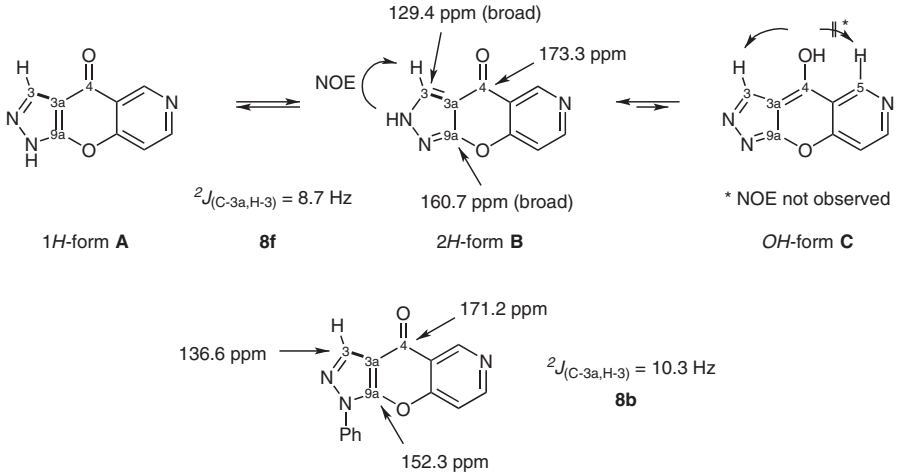


Figure 3

line broadening of the signals corresponding to C-3 and C-9a. Moreover, the reduction of the geminal $^2J_{C3a–H3}$ coupling constant[8] in **8f** (8.7 Hz) compared to that in the N-1-phenyl congener **8b** (^2J = 10.3 Hz) and the characteristic changes of the chemical shifts of C-3 (**8f**; 129.4 ppm, **8b**; 136.6 ppm) and C-9a (**8f**; 160.7 ppm, **8b**; 152.3 ppm) hint at a substantial contribution of the 2*H*-form B to the tautomeric composition. This was confirmed by a pronounced NOE on the signal due to H-3 upon irradiation at the NH-resonance, which is only consistent with isomer B, where the protons involved are close (Figure 3). It should be mentioned that similar phenomena were observed with 6-phenylpyrano[2,3-*c*]pyrazol-4(1*H*)-ones.[7] The involvement of a third possible tautomer C, could be excluded on the basis of the ^{13}C chemical shift of C-4 (δ = 173.3 ppm), which closely resembles those of the 'fixed' ketones **8a–c** (δ = 171.0–172.1 ppm). For the 'enolic' C-4 in tautomer C, a somewhat smaller chemical shift would be expected. Moreover, irradiation of the OH-transition frequency in species C, would be expected to lead to an NOE of both H-3 and H-5 signals. Consistent with the proposed structures, the latter enhancement was not observed (Figure 3).

In conclusion, we have developed a short, efficient, and generally applicable method for the synthesis of [5,6]pyrano[2,3-*c*]pyrazol-4(1*H*)-ones, containing a pyridine moiety, starting from the corresponding pyrazolones and *o*-halopyridinecarbonyl chlorides. Moreover, the compounds obtained were thoroughly characterized by means of NMR spectroscopy.

Table 2 ^{1}H NMR data of Compounds **7–11**

Compd	Solvent	R^3-H or H-3	H-5	H-6	H-7	H-8	H-9	H of R^1
7a	DMSO-d_6	2.56 (Me)	–	8.78[a]	7.83[a]	8.25[a]	–	7.45 (1 H, H′-4), 7.60 (2 H, H′-3,5), 7.91 (2 H, H′-2,6)
7b	DMSO-d_6	8.41 (H-3)	–	8.82[a]	7.88[a]	8.32[a]	–	7.49 (1 H, H′-4), 7.63 (2 H, H′-3,5), 7.95 (2 H, H′-2,6)
7c	DMSO-d_6	8.16 (H-3)	–	8.79[a]	7.85[a]	8.24[a]	–	3.71 (3 H, OMe), 5.42 (2 H, CH_2), 6.90 (2 H, H′-3,5), 7.31 (2 H, H′-2,6)
7f	DMSO-d_6	8.65 (H-3)	–	8.72[a]	7.81[a]	8.15[a]	–	13.86 (1 H, NH)
8a	DMSO-d_6	2.55 (Me)	9.27	–	8.88[b]	7.81[b]	–	7.49 (1 H, H′-4), 7.63 (2 H, H′-3,5), 7.91 (2 H, H′-2,6)
8b	DMSO-d_6	8.42 (H-3)	9.31	–	8.88[b]	7.81[b]	–	7.50 (1 H, H′-4), 7.64 (2 H, H′-3,5), 7.92 (2 H, H′-2,6)
8c	DMSO-d_6	8.19 (H-3)	9.29	–	8.88[b]	7.77[b]	–	3.71 (3 H, OMe), 5.43 (2 H, CH_2), 6.91 (2 H, H′-3,5), 7.31 (2 H, H′-2,6)
8f	DMSO-d_6	8.71 (H-3)	9.24	–	8.81[c]	7.69[c]	–	13.96 (1 H, NH)

Table 2 ^{1}H NMR data of Compounds **7–11** (continued)

Compd	Solvent	R^3-H or H-3	H-5	H-6	H-7	H-8	H-9	H of R^1
9a	$CDCl_3$	2.69 (Me)	8.14[d]	8.70[d]	–	9.01	–	7.42 (1 H, H′-4), 7.56 (2 H, H′-3,5), 7.85 (2 H, H′-2,6)
9b	$CDCl_3$	8.44 (H-3)	8.05[d]	8.71[d]	–	9.19	–	7.50 (1 H, H′-4), 7.64 (2 H, H′-3,5), 7.95 (2 H, H′-2,6)
9c	$CDCl_3$	8.10 (H-3)	8.13[d]	8.69[d]	–	9.01	–	3.78 (3 H, OMe), 5.41 (2 H, CH_2), 6.89 (2 H, H′-3,5), 7.32 (2 H, H′-2,6)
9f	DMSO-d_6	8.72 (H-3)	7.99[d]	8.62[d]	–	9.09	–	14.00 (1 H, NH)
10a	$CDCl_3$	2.67 (Me)	8.72[e]	7.49[e]	8.65[e]	–	–	7.37 (1 H, H′-4), 7.52 (2 H, H′-3,5), 7.92 (2 H, H′-2,6)
10b	$CDCl_3$	8.24 (H-3)	8.76[e]	7.52[e]	8.68[e]	–	–	7.41 (1 H, H′-4), 7.54 (2 H, H′-3,5), 7.96 (2 H, H′-2,6)
10c	$CDCl_3$	8.07 (H-3)	8.73[e]	7.49[e]	8.67[e]	–	–	3.76 (3 H, OMe), 5.42 (2 H, CH_2), 6.86 (2 H, H′-3,5), 7.36 (2 H, H′-2,6)
10d	$CDCl_3$	2.57 (Me)	8.70[e]	7.47[e]	8.62[e]	–	–	3.91 (3 H, Me)
10e	$CDCl_3$	2.44 (Me)	8.58[e]	7.62[e]	8.70[e]	–	–	5.43 (2 H, CH_2), 7.28–7.37 (5 H, Ph)
10f	DMSO-d_6	8.66 (H-3)	8.57[e]	7.55[e]	8.71[e]	–	–	13.92 (1 H, NH)
11a	DMSO-d_6[f]	2.59 (Me)	9.37	8.39	7.74	7.99	8.08	7.50 (1 H, H′-4), 7.67 (2 H, H′-3,5), 7.93 (2 H, H′-2,6)
11b	DMSO-d_6[f]	8.46 (H-3)	9.42	8.38	7.74	8.00	8.09	7.54 (1 H, H′-4), 7.70 (2 H, H′-3,5), 7.96 (2 H, H′-2,6)
11c	DMSO-d_6[f]	8.19 (H-3)	9.36	8.35	7.72	7.98	8.06	3.71 (3 H, OMe), 5.47 (2 H, CH_2), 6.93 (2 H, H′-3,5), 7.34 (2 H, H′-2,6)
11d	DMSO-d_6[f]	2.48 (Me)	9.33	8.37	7.73	7.99	8.05	3.88 (3 H, Me)
11f	DMSO-d_6[f]	8.67(H-3)	9.30	8.30	7.67	7.94	8.01	13.84 (1 H, NH)

[a] $^{3}J_{H6–H7}$ = 4.3 Hz, $^{3}J_{H7–H8}$ = 8.6 Hz, $^{4}J_{H6–H8}$ = 1.3 Hz.
[b] $^{3}J_{H7–H8}$ = 5.9 Hz.
[c] $^{3}J_{H7–H8}$ = 5.8 Hz.
[d] $^{3}J_{H5–H6}$ = 5.0 Hz.
[e] $^{3}J_{H6–H7}$ = 4.7 Hz, $^{3}J_{H5–H6}$ = 7.6 Hz, $^{4}J_{H5–H7}$ = 2.0 Hz.
[f] Only slightly soluble.

Table 3 ^{13}C NMR Chemical Shifts of Compounds **7–11** (Solvents as in Table 2)

Compd	C-3	C-3a	C-4	C-4a	C-5	C-5a	C-6	C-7	C-8	C-8a / 10a	C-9	C-9a	C-11a	C of R^1	C of R^3
7a	147.0	106.4	171.6	138.6	–	–	147.3	128.3	127.3	151.9	–	152.1	–	121.3 (H′-2,6), 127.6 (H′-4), 129.5 (H′-3,5), 136.4 (H′-1)	13.7 (Me)
7b	136.8	108.4	170.8	138.2	–	–	147.3	128.6	127.7	151.9	–	152.1	–	121.6 (H′-2,6), 128.0 (H′-4), 129.7 (H′-3,5), 136.4 (H′-1)	–
7c	135.4	106.9	170.6	138.3	–	–	147.2	128.3	127.1	151.7	–	152.2	–	50.2 (CH_2), 55.1 (OMe), 114.0 (H′-3,5), 127.3 (H′-1), 129.3 (H′-2,6), 159.0 (H′-4)	–
7f	129.4	107.2	172.7	137.6	–	–	146.2	128.5	127.2	153.0	–	160.2	–	–	–

Table 3 ^{13}C NMR Chemical Shifts of Compounds **7–11** (Solvents as in Table 2) (continued)

Compd	C-3	C-3a	C-4	C-4a	C-5	C-5a	C-6	C-7	C-8	C-8a / 10a	C-9	C-9a	C-11a	C of R^1	C of R^3
8a	147.0	105.4	172.1	118.4	149.0	–	–	154.1	113.2	159.7	–	152.4	–	121.6 (H′-2,6), 127.9 (H′-4), 129.7 (H′-3,5), 136.3 (H′-1)	13.8 (Me)
8b	136.6	107.3	171.2	118.1	149.1	–	–	154.1	113.1	159.5	–	152.3	–	121.9 (H′-2,6), 128.2 (H′-4), 129.6 (H′-3,5), 136.3 (H′-1)	–
8c	135.4	105.9	171.0	118.1	149.3	–	–	154.0	112.8	159.3	–	152.4	–	50.3 (CH_2), 55.06 (OMe), 114.1 (H′-3,5), 127.2 (H′-1), 129.4 (H′-2,6), 159.0 (H′-4)	–
8f	129.4[a]	106.3	173.3	117.9	149.2	–	–	153.9	113.1	160.8	–	160.7	–	–	–
9a	148.4	105.6	171.9	128.6	119.0	–	146.0	–	141.2	149.8	–	152.4	–	121.5 (H′-2,6), 127. 9 (H′-4), 129.5 (H′-3,5), 136.6 (H′-1)	14.1 (Me)
9b	136.7	106.8	170.8	127.6	118.3	–	145.7	–	141.7	149.5	–	152.4	–	121.7 (H′-2,6), 128.1 (H′-4), 129.7 (H′-3,5), 136.3 (H′-1)	–
9c	136.0	106.1	171.0	128.3	119.3	–	145.9	–	141.1	149.6	–	152.7	–	51.4 (CH_2), 55.3 (OMe), 114.4 (H′-3,5), 126.5 (H′-1), 129.5 (H′-2,6), 159.8 (H′-4)	–
9f	129.6	105.9	173.0	126.8	118.3	–	144.4	–	141.9	150.4	–	160.6	–	–	–
10a	148.1	105.0	172.8	118.4	137.6	–	122.1	152.3	–	158.9	–	152.6	–	121.3 (H′-2,6), 127.6 (H′-4), 129.5 (H′-3,5), 136.7 (H′-1)	14.0 (Me)
10b	136.7	106.7	172.0	118.0	137.8	–	122.3	152.6	–	158.8	–	152.5	–	121.5 (H′-2,6), 128.0 (H′-4), 129.5 (H′-3,5), 136.8 (H′-1)	–
10c	135.9	105.5	171.9	118.1	138.0	–	122.0	152.3	–	158.7	–	152.9	–	51.2 (CH_2), 55.2 (OMe), 114.3 (H′-3,5), 126.7 (H′-1), 129.6 (H′-2,6), 159.7 (H′-4)	–
10d	147.0	103.5	172.5	118.3	137.7	–	121.9	152.0	–	158.7	–	153.5	–	34.0 (Me)	13.9 (Me)
10e	145.7	103.0	172.1	117.8	137.1	–	122.4	152.5	–	158.4	–	153.1	–	50.4 (CH_2), 127.7 (H′-2,6), 127.9 (H′-4), 128.8 (H′-3,5), 135.7 (H′-1)	13.6 (Me)
10f	129.2 [a]	105.3	173.8	116.9	137.1	–	121.6	153.1	–	159.8	–	161.0 [a]	–	–	–
11a	147.2	103.9	172.6	117.5	139.4	126.2	129.8	126.9	133.4	156.0	127.3	147.2	153.2	121.7 (H′-2,6), 127.8 (H′-4), 129.6 (H′-3,5), 136.4 (H′-1)	13.7 (Me)

Table 3 ^{13}C NMR Chemical Shifts of Compounds **7–11** (Solvents as in Table 2) (continued)

Compd	C-3	C-3a	C-4	C-4a	C-5	C-5a	C-6	C-7	C-8	C-8a / 10a	C-9	C-9a	C-11a	C of R^1	C of R^3
11b	137.1	105.9	172.1	117.3	139.9	126.3	130.0	127.1	133.6	156.0	127.4	147.4	153.3	122.1 (H′-2,6), 128.3 (H′-4), 129.8 (H′-3,5), 136.5 (H′-1)	–
11c	135.7	104.5	171.7	117.2	139.8	126.1	129.8	126.9	133.3	155.8	127.3	147.2	153.3	50.3 (CH_2), 55.1 (OMe), 114.1 (H′-3,5), 127.4 (H′-1), 129.3 (H′-2,6), 159.0 (H′-4)	–
11d	[b]	[b]	[b]	[b]	139.5	[b]	129.8	126.8	133.2	[b]	127.3	[b]	[b]	33.8 (Me)	13.6 (Me)
11f	129.6[a]	104.9	173.8	117.0	139.6	125.6	129.8	126.3	133.2	157.1	127.2	147.7	160.9[a]	–	–

[a] Broad signal.
[b] Not found due to extremely low solubility.

Table 4 Selected ^{13}C–^{1}H Spin-Coupling Constants (Hz) of **7a–c**, **7f**, **8a–c**, **9a–c**, **10a–e**, **11f** (Solvents as in Table 2)

Compd	*J* of C-3	*J* of C-3a	*J* of C-4	*J* of C-4a	*J* of C-5	*J* of C-6	*J* of C-7	*J* of C-8	*J* of C-8a	other couplings
7a	7.1 ($^2J_{3\text{-Me}}$)	2.7 ($^3J_{3\text{-Me}}$)	1.7 ($^4J_{H8}$)	3.6 ($^3J_{H8}$), 11.8 ($^3J_{H6}$), 1.3 ($^4J_{H7}$)	–	183.2 (^1J), 3.0 ($^2J_{H7}$), 7.7 ($^3J_{H8}$)	167.6 (^1J), 9.9 ($^2J_{H6}$)	169.2 (^1J), 1.4 ($^2J_{H7}$), 6.4 ($^3J_{H6}$)	3.7 ($^2J_{H8}$), 9.7 ($^3J_{H7}$), 1.8 ($^4J_{H6}$)	129.0 ($^1J_{C3\text{-Me}}$)
7b	195.2 (^1J)	10.3 ($^2J_{H3}$)	1.6 ($^4J_{H8}$)	[a]	–	183.4 (^1J), 3.0 ($^2J_{H7}$), 7.6 ($^3J_{H8}$)	168.1 (^1J), 9.8 ($^2J_{H6}$)	169.4 (^1J), 6.4 ($^3J_{H6}$)	3.6 ($^2J_{H8}$), 9.7 ($^3J_{H7}$), 1.7 ($^4J_{H6}$)	5.0 ($^3J_{C9a–H3}$)
7c	194.3 (^1J)	10.4 ($^2J_{H3}$)	1.6 ($^4J_{H8}$)	3.7 ($^3J_{H8}$), 11.9 ($^3J_{H6}$), 1.1 ($^4J_{H7}$)	–	183.1 (^1J), 3.0 ($^2J_{H7}$), 7.6 ($^3J_{H8}$)	167.7 (^1J), 9.8 ($^2J_{H6}$)	168.8 (^1J), 1.3 ($^2J_{H7}$), 6.5 ($^3J_{H6}$)	3.6 ($^2J_{H8}$), 9.7 ($^3J_{H7}$), 1.8 ($^4J_{H6}$)	142.0 ($^1J_{CH2}$), 144.3 ($^1J_{OMe}$), 2.5 ($^3J_{C9a–CH2}$), 5.0 ($^3J_{C9a–H3}$)
7f	195.2 (^1J)	8.4 ($^2J_{H3}$)	[a]	[a]	–	182.9 (^1J), 3.0 ($^2J_{H7}$), 7.7 ($^3J_{H8}$)	166.7 (^1J), 9.9 ($^2J_{H6}$)	167.4 (^1J), 1.7 ($^2J_{H7}$), 6.3 ($^3J_{H6}$)	[a]	–
8a	7.1 ($^2J_{3\text{-Me}}$)	2.7 ($^3J_{3\text{-Me}}$)	[a]	[a]	184.2 (^1J), 12.4 ($^3J_{H7}$)	–	183.4 (^1J), 1.2 ($^2J_{H8}$), 13.2 ($^3J_{H5}$)	171.0 (^1J)	[a]	129.1 ($^1J_{3\text{-Me}}$)
8b	195.6 (^1J)	10.3 ($^2J_{H3}$)	2.5 ($^3J_{H5}$), 1.4 ($^4J_{H8}$)	7.1 ($^2J_{H5}$), 3.8 ($^3J_{H8}$), 1.4 ($^4J_{H7}$)	184.5 (^1J), 12.3 ($^3J_{H7}$)	–	183.4 (^1J), 1.4 ($^2J_{H8}$), 13.3 ($^3J_{H5}$)	170.6 (^1J), 8.7 ($^2J_{H7}$), 1.5 ($^4J_{H5}$)	3.9 ($^2J_{H8}$), 7.7 ($^3J_{H5}$), 9.8 ($^3J_{H7}$)	5.0 ($^3J_{C9a–H3}$)
8c	194.8 (^1J)	10.6 ($^2J_{H3}$)	[a]	[a]	[a]	–	[a]	[a]	[a]	–
9a	7.2 ($^2J_{3\text{-Me}}$)	2.8 ($^3J_{3\text{-Me}}$)	4.0 ($^3J_{H5}$), 1.7 ($^4J_{H8}$)	3.7 ($^3J_{H8}$), 7.0 ($^3J_{H6}$)	168.9 (^1J), 9.7 ($^2J_{H6}$), 1.6 ($^4J_{H8}$)	183.2 (^1J), 2.9 ($^2J_{H5}$), 11.7 ($^3J_{H8}$)	–	185.1 (^1J), 11.4 ($^3J_{H6}$), 1.1 ($^4J_{H5}$)	3.2 ($^2J_{H8}$), 7.6 ($^3J_{H5}$), 1.9 ($^4J_{H6}$)	129.4 ($^1J_{3\text{-Me}}$)
9b	195.7 (^1J)	10.4 ($^2J_{H3}$)	4.0 ($^3J_{H5}$), 1.8 ($^4J_{H8}$)	<0.6 ($^2J_{H5}$), 3.8 ($^3J_{H8}$), 7.0 ($^3J_{H6}$)	168.6 (^1J), 9.6 ($^2J_{H6}$), 1.7 ($^4J_{H8}$)	183.7 (^1J), 2.6 ($^2J_{H5}$), 11.7 ($^3J_{H8}$)	–	186.8 (^1J), 11.4 ($^3J_{H6}$), 1.2 ($^4J_{H5}$)	3.3 ($^2J_{H8}$), 7.9 ($^3J_{H5}$), 1.9 ($^4J_{H6}$)	5.0 ($^3J_{C9a–H3}$)
9c	195.1 (^1J)	10.4 ($^2J_{H3}$)	4.0 ($^3J_{H5}$), 1.6 ($^4J_{H8}$)	3.8 ($^3J_{H8}$), 7.0 ($^3J_{H6}$)	168.7 (^1J), 9.7 ($^2J_{H6}$), 1.6 ($^4J_{H8}$)	183.1 (^1J), 2.9 ($^2J_{H5}$), 11.7 ($^3J_{H8}$)	–	184.9 (^1J), 11.3 ($^3J_{H6}$), 1.2 ($^4J_{H5}$)	3.4 ($^2J_{H8}$), 7.6 ($^3J_{H5}$), 1.8 ($^4J_{H6}$)	141.2 ($^1J_{CH2}$), 144.0 ($^1J_{OMe}$), 2.5 ($^3J_{C9a–CH2}$), 5.0 ($^3J_{C9a–H3}$)
10a	7.2 ($^2J_{3\text{-Me}}$)	2.8 ($^3J_{3\text{-Me}}$)	4.1 ($^3J_{H5}$)	7.0 ($^3J_{H6}$), 1.4 ($^4J_{H7}$)	168.0 (^1J), 1.7 ($^2J_{H6}$), 6.6 ($^3J_{H7}$)	167.8 (^1J), 1.0 ($^2J_{H5}$), 8.1 ($^2J_{H7}$)	182.6 (^1J), 4.2 ($^2J_{H6}$), 8.6 ($^3J_{H5}$)	–	8.5 ($^3J_{H5}$), 13.4 ($^3J_{H7}$), 1.4 ($^4J_{H6}$)	129.4 ($^1J_{3\text{-Me}}$)

Table 4 Selected ^{13}C–^{1}H Spin-Coupling Constants (Hz) of **7a–c**, **7f**, **8a–c**, **9a–c**, **10a–e**, **11f** (Solvents as in Table 2) (continued)

Compd	*J* of C-3	*J* of C-3a	*J* of C-4	*J* of C-4a	*J* of C-5	*J* of C-6	*J* of C-7	*J* of C-8	*J* of C-8a	other couplings
10b	195.2 (^{1}J)	10.3 ($^{2}J_{H3}$)	4.0 ($^{3}J_{H5}$)	7.0 ($^{3}J_{H6}$), 1.4 ($^{4}J_{H7}$)	168.3 (^{1}J), 1.7 ($^{2}J_{H6}$), 6.8 ($^{3}J_{H7}$)	168.0 (^{1}J), 1.0 ($^{2}J_{H5}$), 8.1 ($^{2}J_{H7}$)	182.9 (^{1}J), 4.2 ($^{2}J_{H6}$), 8.5 ($^{3}J_{H5}$)	–	8.5 ($^{3}J_{H5}$), 13.5 ($^{3}J_{H7}$), 1.4 ($^{4}J_{H6}$)	4.9 ($^{3}J_{C9a–H3}$)
10c	194.6 (^{1}J)	10.4 ($^{2}J_{H3}$)	4.0 ($^{3}J_{H5}$)	7.0 ($^{3}J_{H6}$), 1.4 ($^{4}J_{H7}$)	168.0 (^{1}J), 1.7 ($^{2}J_{H6}$), 6.7 ($^{3}J_{H7}$)	167.8 (^{1}J), 1.0 ($^{2}J_{H5}$), 8.1 ($^{2}J_{H7}$)	182.6 (^{1}J), 4.2 ($^{2}J_{H6}$), 8.6 ($^{3}J_{H5}$)	–	8.5 ($^{3}J_{H5}$), 13.5 ($^{3}J_{H7}$), 1.3 ($^{4}J_{H6}$)	141.1 ($^{1}J_{CH2}$), 143.9 ($^{1}J_{OMe}$), 2.5 ($^{3}J_{C9a–CH2}$), 5.0 ($^{3}J_{C9a–H3}$)
10d	7.1 ($^{2}J_{3\text{-Me}}$)	2.8 ($^{3}J_{3\text{-Me}}$)	4.0 ($^{3}J_{H5}$)	7.0 ($^{3}J_{H6}$), 1.4 ($^{4}J_{H7}$)	167.8 (^{1}J), 1.7 ($^{2}J_{H6}$), 6.6 ($^{3}J_{H7}$)	167.6 (^{1}J), 1.0 ($^{2}J_{H5}$), 8.1 ($^{2}J_{H7}$)	182.4 (^{1}J), 4.1 ($^{2}J_{H6}$), 8.6 ($^{3}J_{H5}$)	–	8.4 ($^{3}J_{H5}$), 13.4 ($^{3}J_{H7}$), 1.4 ($^{4}J_{H6}$)	129.4 ($^{1}J_{3\text{-Me}}$), 141.7 ($^{1}J_{1\text{-Me}}$), 2.3 ($^{3}J_{C9a–1\text{-Me}}$)
10e	7.1 ($^{2}J_{3\text{-Me}}$)	2.8 ($^{3}J_{3\text{-Me}}$)	4.0 ($^{3}J_{H5}$)	7.0 ($^{3}J_{H6}$), 1.4 ($^{4}J_{H7}$)	167.6 (^{1}J), 1.7 ($^{2}J_{H6}$), 6.6 ($^{3}J_{H7}$)	169.6 (^{1}J), 1.0 ($^{2}J_{H5}$), 8.1 ($^{2}J_{H7}$)	183.7 (^{1}J), 4.2 ($^{2}J_{H6}$), 8.4 ($^{3}J_{H5}$)	–	8.5 ($^{3}J_{H5}$), 13.5 ($^{3}J_{H7}$), 1.4 ($^{4}J_{H6}$)	128.7 ($^{1}J_{3\text{-Me}}$), 142.7 ($^{1}J_{CH2}$), 2.6 ($^{3}J_{C9a–CH2}$)
11f	[a]	8.6 ($^{2}J_{H3}$)	4.4 ($^{3}J_{H5}$)	[a]	166.9 (^{1}J), 4.5 ($^{3}J_{H6}$)	[a]	[a]	[a]	–	9.0 ($^{3}J_{C10a–H5}$)

[a] Not unambiguously assigned or not found.

Table 5 ^{15}N NMR Chemical Shifts of Compounds **7–10** (Solvents as in Table 2)

Compd	N-1	N-2	Other N (position)	Compd	N-1	N-2	Other N (position)
7a	–192.6	–93.1	–63.8 (5)	**9c**	–190.6	–84.7	–52.6 (7)
7b	–186.2	–85.3	–66.6 (5)	**9f**	not found	not found	–48.5 (7)
7c	–190.1	–82.9	–62.9 (5)	**10a**	–191.6	–94.0	–101.7 (8)
8a	–191.8	–93.8	–74.5 (6)	**10b**	–185.7	–86.7	–101.6 (8)
8b	–185.2	–85.8	–73.6 (6)	**10c**	–190.2	–85.8	–102.4 (8)
8c	–189.7	–83.5	–73.9 (6)	**10d**	–210.2	–91.6	–102.9 (8)
9a	–191.8	–93.1	–52.9 (7)	**10e**	–197.3	–89.8	–99.6 (8)
9b	–185.4	–84.7	–48.6 (7)	**10f**	not found	not found	–98.9 (8)

Melting points were determined on a Reichert–Kofler hot-stage microscope and are uncorrected. Mass spectra were obtained on Shimadzu QP 1000 (EI, 70 eV) and Finnigan MAT 8230 instruments (EI, 70 eV, HRMS). IR spectra were recorded on a Perkin–Elmer FTIR 1605 spectrophotometer. Elemental analyses were performed at the Microanalytical Laboratory, University of Vienna. ^{1}H and ^{13}C NMR spectra were recorded on a Varian UnityPlus 300 spectrometer at 28 °C (299.95 MHz for ^{1}H, 75.43 MHz for ^{13}C) or on a Bruker Avance 500 spectrometer at 293 K (500.13 MHz for ^{1}H, 125.77 MHz for ^{13}C). The center of the solvent signal was used as an internal standard which was related to TMS with δ = 7.26 ppm (^{1}H in $CDCl_3$), δ = 2.49 ppm (^{1}H in DMSO-d_6), δ = 77.0 ppm (^{13}C in $CDCl_3$), and δ = 39.5 ppm (^{13}C in DMSO-d_6). ^{15}N NMR spectra were obtained on a Bruker Avance 500 instrument with a 'directly' detecting broadband observe probe and were referenced against external nitromethane (coaxial capillary). Full and unambiguous assignment for all NMR signals was achieved by combined application of standard NMR techniques[9a] such as fully ^{1}H-coupled ^{13}C NMR (gated decoupling), APT, 1D-TOCSY, NOE-difference, NOESY, HMQC, gs-HSQC, gs-HMBC, and selective long-range INEPT in both 1D and 2D modes.[9b] The starting materials were commercially available and/or prepared in accordance to literature procedures: **1b**,[10] **1c**,[6] **1e**,[11] **3a**,[12] **6a**.[13] Yields of products were not optimized.

o-Halopyridinecarbonyl Chlorides 2–6; General Procedure

A suspension of the corresponding *o*-halopyridinecarboxylic acid in toluene (10 mL per mmol acid), DMF (1 drop) and $SOCl_2$ (10 equiv) was refluxed for 3 h. The solvent and excess $SOCl_2$ were removed under reduced pressure, additional toluene (5 mL per mmol acid) was added, and the solvent was removed under reduced pressure. The remaining acid chlorides were used immediately, without further purification, in the next step.

3-Fluoropyridine-2-carboxylic Acid (2a) and 3-Fluoropyridine-2-carbonyl Chloride (2b)

Avoiding the tedious procedure described previously,[14] commercially available lithium 3-fluoropicolinate (1.47 g, 10 mmol, 90% technical grade) was recrystallized from the minimum amount of EtOH–H_2O (9:1), which had been acidified with drops of concd HCl to give **2a**.

Yield: 1.14 g (81%); colorless needles; mp 151–155 °C (Lit.[15] 152–155 °C).

^{1}H NMR (300 MHz, DMSO-d_6): δ = 7.67 (m, $^3J_{H5–H6}$ = 4.5 Hz, $^3J_{H5–H4}$ = 8.5 Hz, $^4J_{H5–F}$ = 4.2 Hz, 1 H, H-5), 7.86 (ddd, $^3J_{H4–H5}$ = 8.5 Hz, $^3J_{H4–F}$ = 10.7 Hz, $^4J_{H4–H6}$ = 1.3 Hz, 1 H, H-4), 8.50 (ddd, $^3J_{H6–H5}$ = 4.5 Hz, $^4J_{H6–H4}$ = 1.3 Hz, $^5J_{H6–F}$ = 1.8 Hz, 1 H, H-6), 11.81 (br s, 1 H, OH).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 125.6 (C-4, ^1J = 169.6 Hz, $^2J_{C4–F}$ = 19.6 Hz, $^3J_{C4–H6}$ = 6.9 Hz), 128.6 (C-5, ^1J = 168.9 Hz, $^2J_{C5–H4}$ = 1.5 Hz, $^2J_{C5–H6}$ = 9.6 Hz, $^3J_{C5–F}$ = 5.1 Hz), 137.8 (C-2, $^2J_{C2–F}$ = 10.4 Hz, $^3J_{C2–H4}$ = 3.9 Hz, $^3J_{C2–H6}$ = 12.0 Hz, $^4J_{C2–H5}$ = 1.5 Hz), 145.3 (C-6, ^1J = 183.5 Hz, $^2J_{C6–H5}$ = 2.9 Hz, $^3J_{C6–H4}$ = 7.5 Hz, $^4J_{C6–F}$ = 5.1 Hz), 158.2 (C-3, $^1J_{C3–F}$ = 265.9 Hz, $^2J_{C3–H4}$ = 4.5 Hz, $^3J_{C3–H5}$ = 9.7 Hz, $^4J_{C3–H6}$ = 1.9 Hz), 164.2 (CO, $^3J_{CO–F}$ = 5.5 Hz, $^4J_{CO–H4}$ = 1.8 Hz).

MS: *m*/*z* (%) = 141 (1) [M$^+$], 124 (7), 97 (100), 96 (44), 76 (36), 70 (55).

Applying the general procedure for the preparation of acid chlorides yielded **2b** as colorless needles.

Mp 42–44 °C.

3-Chloroquinoline-2-carbonyl Chloride (6b)

Applying the general procedure for the preparation of acid chlorides gave **6b** as colorless needles.

Mp 99–101 °C (Lit.[16] 98–100 °C).

IR (KBr): 1756 (C=O) cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.70 (ddd, $^3J_{H6–H7}$ = 7.0 Hz, $^3J_{H6–H5}$ = 7.0 Hz, $^4J_{H6–H8}$ = 1.1 Hz, 1 H, H-6), 7.93 (ddd, $^3J_{H7–H6}$ = 7.0 Hz, $^3J_{H7–H8}$ = 7.0 Hz, $^4J_{H7–H5}$ = 1.4 Hz, 1 H, H-7), 8.00 (m, 1 H, H-5), 8.07 (m, 1 H, H-8), 9.00 (s, 1 H, H-4).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 125.5 (C-4a), 126.6 (C-3), 128.5* (C-8), 128.6* (C-6), 129.1 (C-5), 134.3 (C-7), 145.0 (C-4), 146.2 (C-2), 148.7 (C-8a), 164.1 (CO). * Not unequivocally assigned.

^{15}N NMR (50 MHz, $CDCl_3$): δ = –77.7.

Compounds 7–13; General Procedure

Under anhyd conditions, to a suspension of pyrazolone **1** (1 equiv) and $Ca(OH)_2$ (2 equiv) in anhyd 1,4-dioxane (2 mL per mmol of **1**) a soln/suspension of the corresponding *o*-halopyridinecarbonyl chloride **2–6** (1 equiv) in anhyd 1,4-dioxane (2 mL per mmol) was added. The reaction mixture was heated at reflux for 3 h under stirring. After cooling to r.t., the mixture was treated with 2 M HCl (4 mL per mmol), stirred for 15 min, and poured into H_2O (10 mL per mmol). After 30 min, solid products were filtered off, washed with H_2O, and recrystallized. The oily compound **13c** was isolated by extraction with CH_2Cl_2 then used without further purification in the next reaction step.

Cyclization of 4-Aroylpyrazol-5-ols 12c and 13a–c; General Procedure

Under anhyd conditions, the 4-aroylpyrazol-5-ol (1 equiv) was dissolved in anhyd DMF (3 mL per mmol) and added to a suspension of NaH (60% in mineral oil; 1 equiv) in anhyd DMF (3 mL per mmol). The reaction mixture was heated at reflux overnight and then the solvent was removed under reduced pressure. H_2O (3–5 mL per mmol) was added to the residue and stirring was continued for further 1 h. The precipitate formed was filtered off, washed with H_2O and petroleum ether and recrystallized.

NMR data are presented in Tables 2–5.

3-Methyl-1-phenylpyrazolo[4′,3′:5,6]pyrano[3,2-*b*]pyridin-4(1*H*)-one (7a)

Yield: 68%; colorless needles; mp 215–218 °C (aq EtOH).

IR (KBr): 1670 (C=O) cm^{-1}.

MS: *m*/*z* (%) = 277 (100) [M$^+$].

Anal. Calcd for $C_{16}H_{11}N_3O_2 \cdot 0.1\ H_2O$: C, 68.86; H, 4.05; N, 15.06. Found: C, 68.78; H, 4.12; N, 14.88.

1-Phenylpyrazolo[4′,3′:5,6]pyrano[3,2-*b*]pyridin-4(1*H*)-one (7b)

Yield: 44%; yellowish powder; mp 157.5–160.5 °C.

IR (KBr): 1680 (C=O) cm^{-1}.

MS: *m*/*z* (%) = 263 (100) [M$^+$], 77 (49).

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_{15}H_9N_3O_2$: 263.0694; found: 263.0702.

1-(4-Methoxybenzyl)pyrazolo[4′,3′:5,6]pyrano[3,2-*b*]pyridin-4(1*H*)-one (7c)

Yield: 55%; orange crystals; mp 174–176.5 °C (aq EtOH).

IR (KBr): 1673 (C=O) cm^{-1}.

MS: *m*/*z* (%) = 307 (16) [M$^+$], 121 (100).

Anal. Calcd for $C_{17}H_{13}N_3O_3 \cdot 0.1\ H_2O$: C, 66.06; H, 4.30; N, 13.59. Found: C, 65.76; H, 4.22; N, 13.36.

3-Methyl-1-phenylpyrazolo[4′,3′:5,6]pyrano[3,2-*c*]pyridin-4(1*H*)-one (8a)

Yield: 32%; yellowish needles; mp 190–194 °C (aq EtOH).

IR (KBr): 1666 (C=O) cm^{-1}.

MS: *m*/*z* (%) = 277 (100) [M$^+$], 276 (72), 91 (16).

Anal. Calcd for $C_{16}H_{11}N_3O_2$: C, 69.31; H, 4.00; N, 15.15. Found: C, 69.04; H, 3.73; N, 15.03.

1-Phenylpyrazolo[4′,3′:5,6]pyrano[3,2-*c*]pyridin-4(1*H*)-one (8b)

Yield: 56%; beige crystals; mp 198–202 °C (aq EtOH).

IR (KBr): 1663 cm^{-1} (C=O).

MS: *m*/*z* (%) = 263 (100) [M$^+$], 142 (21), 122 (63), 77 (50), 51 (25).

Anal. Calcd for $C_{15}H_9N_3O_2$: C, 68.44; H, 3.45; N, 15.96. Found: C, 68.24; H, 3.36; N, 16.00.

1-(4-Methoxybenzyl)pyrazolo[4′,3′:5,6]pyrano[3,2-*c*]pyridin-4(1*H*)-one (8c) and 2-(4-Methoxybenzyl)pyrazolo[4′,3′:5,6]pyrano[3,2-*c*]pyridin-4(2*H*)-one (8ci)

The NMR spectra showed a ~1:1 mixture of the 1-PMB (**8c**) and the 2-PMB isomer (**8ci**) to be present. As the synthetic target was the N-unsubstituted compound **8f**, which was expected to be accessible from both isomers by removal of the N-protecting group, no separation of **8c** and **8ci** was attempted. However, complete NMR data for the individual isomers were unambiguously extracted from the mixture.

Overall yield of **8c/8ci**: 20%; beige crystals; mp 172–180 °C (aq EtOH).

^{1}H NMR of **8ci** (300 MHz, DMSO-d_6): δ = 3.72 (s, 3 H, OMe), 5.37 (s, 2 H, CH_2), 6.92 (m, 2 H, Ph-3,5), 7.33 (m, 2 H, Ph-2,6), 7.63 (d, $^3J_{H8–H7}$ = 5.7 Hz, 1 H, H-8), 8.79 (s, 1 H, H-3), 8.79 (d, $^3J_{H7–H8}$ = 5.7 Hz, 1 H, H-7), 9.21 (s, 1 H, H-5).

^{13}C NMR of **8ci** (75 MHz, DMSO-d_6): δ = 55.08 (OMe), 55.7 (CH_2), 106.7 (C-3a, $^2J_{C3a–H3}$ = 8.6 Hz), 112.9 (C-8), 114.0 (Ph-3,5), 117.8 (C-4a), 127.5 (Ph-1), 129.7 (Ph-2,6), 130.0 (C-3), 149.1 (C-5), 154.0 (C-7), 159.2 (Ph-4), 160.2 (C-9a), 160.4 (C-8a), 172.6 (C-4).

^{15}N NMR of **8ci** (50 MHz, DMSO-d_6): δ = –168.4 (N-2), –110.4 (N-1), –77.1 (N-6).

MS: *m*/*z* (%) = 307 (16) [M$^+$], 121 (100).

HRMS (EI): *m/z* $[M]^+$ calcd for $C_{17}H_{13}N_3O_2$: 307.0957; found: 307.0952.

3-Methyl-1-phenylpyrazolo[4′,3′:5,6]pyrano[2,3-*c*]pyridin-4(1*H*)-one (9a)
Yield: 71%; mp 179–180 °C (aq EtOH).

IR (KBr): 1671 (C=O) cm^{-1}.

MS: *m/z* (%) = 277 (100) $[M^+]$, 77 (23).

Anal. Calcd for $C_{16}H_{11}N_3O_2$: C, 69.31; H, 4.00; N, 15.15. Found: C, 69.00; H, 3.98; N, 15.08.

1-Phenylpyrazolo[4′,3′:5,6]pyrano[2,3-*c*]pyridin-4(1*H*)-one (9b)
Yield: 51%; mp 186–188 °C (aq EtOH).

IR (KBr): 1684 (C=O) cm^{-1}.

MS: *m/z* (%) = 263 (100) $[M^+]$, 142 (37), 122 (36), 77 (56).

Anal. Calcd for $C_{15}H_9N_3O_2$: C, 68.44; H, 3.45; N, 15.96. Found: C, 68.23; H, 3.51; N, 15.7.

1-(4-Methoxybenzyl)pyrazolo[4′,3′:5,6]pyrano[2,3-*c*]pyridin-4(1*H*)-one (9c)
Yield: 62%; mp 176–178 °C (aq EtOH).

IR (KBr): 1682 (C=O) cm^{-1}.

MS: *m/z* (%) = 307 (18) $[M^+]$, 121 (100).

Anal. Calcd for $C_{17}H_{13}N_3O_3$: C, 66.64; H, 4.26; N, 13.67. Found: C, 66.68; H, 4.24; N, 13.37.

3-Methyl-1-phenylpyrazolo[4′,3′:5,6]pyrano[2,3-*b*]pyridin-4(1*H*)-one (10a)
Yield: 88%; almost colorless needles; mp 223–224 °C (aq EtOH; Lit.[3c] 224–224.5 °C).

IR (KBr): 1667 (C=O) cm^{-1}.

MS: *m/z* (%) = 277 (100) $[M^+]$, 276 (64), 77 (68).

Anal. Calcd for $C_{16}H_{11}N_3O_2$: C, 69.31; H, 4.00; N, 15.15. Found: C, 69.26; H, 4.14; N, 15.15.

1-Phenylpyrazolo[4′,3′:5,6]pyrano[2,3-*b*]pyridin-4(1*H*)-one (10b)
Yield: 77%; slightly yellowish needles; mp 195–197 °C (aq EtOH).

IR (KBr): 1678 (C=O) cm^{-1}.

MS: *m/z* (%) = 264 (22) $[M + H]^+$, 263 (100) $[M^+]$, 122 (17).

Anal. Calcd for $C_{15}H_{19}N_3O_2$: C, 68.44; H, 3.45; N, 15.96. Found: C, 68.49; H, 3.69; N, 15.87.

1-(4-Methoxybenzyl)pyrazolo[4′,3′:5,6]pyrano[2,3-*b*]pyridin-4(1*H*)-one (10c)
Yield: 47%; colorless needles; mp 149–151 °C (aq EtOH).

IR (KBr): 1674 (C=O) cm^{-1}.

MS: *m/z* (%) = 307 (19) $[M^+]$, 121 (100).

Anal. Calcd for $C_{17}H_{13}N_3O_3$: C, 66.44; H, 4.26; N, 13.67. Found: C, 66.36; H, 4.26; N, 13.57.

1,3-Dimethylpyrazolo[4′,3′:5,6]pyrano[2,3-*b*]pyridin-4(1*H*)-one (10d)
Yield: 46%; colorless crystals; mp 209–210 °C (aq EtOH; Lit.[3c] 217–218.5 °C).

IR (KBr): 1676 (C=O) cm^{-1}.

MS: *m/z* (%) = 215 (100) $[M^+]$, 214 (29), 200 (20).

Anal. Calcd for $C_{11}H_9N_3O_2$: C, 61.39; H, 4.22; N, 19.53. Found: C, 61.37; H, 3.92; N, 19.61.

1-Benzyl-3-methylpyrazolo[4′,3′:5,6]pyrano[2,3-*b*]pyridin-4(1*H*)-one (10e)
Yield: 40%; colorless crystals; mp 158–161 °C (aq EtOH).

IR (KBr): 1675 (C=O) cm^{-1}.

MS: *m/z* (%) = 291 (28) $[M^+]$, 200 (11), 91 (100), 65 (30).

Anal. Calcd for $C_{17}H_{13}N_3O_2$: C, 70.09; H, 4.50; N, 14.42. Found: C, 69.89; H, 4.71; N, 14.43.

3-Methyl-1-phenylpyrazolo[4′,3′:5,6]pyrano[2,3-*b*]quinolin-4(1*H*)-one (11a)
Yield: 81%; colorless crystals; mp 223–224 °C (propan-1-ol).

IR (KBr): 1669 (C=O) cm^{-1}.

MS: *m/z* (%) = 328 (22) $[M + H]^+$, 327 (100) $[M^+]$, 326 (46), 207 (63), 190 (36), 127 (27), 77 (40).

Anal. Calcd for $C_{20}H_{13}N_3O_2$: C, 73.38; H, 4.00; N, 12.84. Found: C, 73.32; H, 4.02; N, 12.73.

1-Phenylpyrazolo[4′,3′:5,6]pyrano[2,3-*b*]quinolin-4(1*H*)-one (11b)
Yield: 68%; colorless crystals; mp 269–270 °C (toluene).

IR (KBr): 1681 (C=O) cm^{-1}.

MS: *m/z* (%) = 314 (24) $[M + H]^+$, 313 (100) $[M^+]$, 172 (47), 77 (33), 44 (81).

Anal. Calcd for $C_{19}H_{11}N_3O_2$: C, 72.84; H, 3.54; N, 13.41. Found: C, 72.58; H, 3.63; N, 13.22.

1-(4-Methoxybenzyl)pyrazolo[4′,3′:5,6]pyrano[2,3-*b*]quinolin-4(1*H*)-one (11c)
Yield: 41%; yellowish needles; mp 233–236 °C (toluene).

IR (KBr): 1673 (C=O) cm^{-1}.

MS: *m/z* (%) = 357 (26) $[M^+]$, 121 (100).

Anal. Calcd for $C_{21}H_{15}N_3O_3$: C, 70.58; H, 4.23; N, 11.76. Found: C, 70.58; H, 4.23; N, 11.46.

1,3-Dimethylpyrazolo[4′,3′:5,6]pyrano[2,3-*b*]quinolin-4(1*H*)-one (11d)
Yield: 79%; colorless crystals; mp 220 °C (EtOH–DMF).

IR (KBr): 1674 (C=O) cm^{-1}.

MS: *m/z* (%) = 265 (32) $[M^+]$, 209 (38), 207 (100), 190 (53), 162 (32), 101 (28).

Anal. Calcd for $C_{15}H_{11}N_3O_2$: C, 67.92; H, 4.18; N, 15.84. Found: C, 67.66; H, 3.96; N, 15.81.

(3-Fluoropyridin-2-yl)-[5-hydroxy-1-(4-methoxybenzyl)-1*H*-pyrazol-4-yl]methanone (12c)
Yield: 55%; yellow crystals; mp 132–135 °C (aq EtOH).

IR (KBr): 1637 (C=O) cm^{-1}.

It was observed that **12c** slowly cyclized into **7c** during the NMR recordings in DMSO-d_6 solution.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.71 (s, 3 H, OMe), 5.05 (s, 2 H, CH_2), 6.88 (m, 2 H, Ph-3,5), 7.19 (m, 2 H, Ph-2,6), 7.75 (s, 1 H, H-3), 7.83 (m, 1 H, pyridine H-5), 8.24 (ddd, $^3J_{H4–H5}$ = 8.6 Hz, $^3J_{H4–F}$ = 11.1 Hz, $^4J_{H4–H6}$ = 1.2 Hz, 1 H, pyridine H-4), 8.64 (ddd, $^3J_{H6–H5}$ = 4.7 Hz, $^4J_{H6–H4}$ = $^5J_{H6–F}$) = 1.2 Hz, 1 H, pyridine H-6), 10.50 (br s, 1 H, OH).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 49.1 (CH_2), 55.0 (^1J = 144.3 Hz, OMe), 104.8 ($^2J_{C4–H3}$ = 9.1 Hz, C-4), 113.9 (Ph-3,5), 127.8

($^2J_{C4–F}$ = 19.5 Hz, pyridine C-4), 128.5 (Ph-1), 128.9 (Ph-2,6), 129.0 ($^3J_{C5–F}$ = 6.2 Hz, pyridine C-5), 140.8 (^1J = 190.1 Hz, C-3), 141.8 ($^2J_{C2–F}$ = 7.4 Hz, pyridine C-2), 143.7 ($^4J_{C6–F}$ = 5.2 Hz, pyridine C-6), 154.5 (C-5), 158.2 ($^1J_{C3–F}$ = 267.8 Hz, pyridine C-3), 158.7 (Ph-4), 190.8 ($^3J_{CO–F}$ = 4.4 Hz, CO).

MS: *m*/*z* (%) = 327 (16) [M$^+$], 121 (100).

Anal. Calcd for $C_{17}H_{14}FN_3O_3$: C, 62.38; H, 4.31; N, 12.84. Found: C, 62.27; H, 4.37; N, 12.65.

(3-Chloropyridin-4-yl)-(5-hydroxy-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)methanone (13a)
Yield: 40%; mp 168–172 °C (aq EtOH).

IR (KBr): 1660 (C=O) cm^{-1}.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 2.36 (s, 3 H, Me), 5.03 (br s, 1 H, OH), 7.26 (m, 1 H, Ph-4), 7.41 (d, $^3J_{H5–H6}$ = 5.0 Hz, 1 H, pyridine H-5), 7.43 (m, 2 H, Ph-3,5), 7.61 (m, 2 H, Ph-2,6), 8.59 (d, $^3J_{H6–H5}$ = 5.0 Hz, 1 H, pyridine H-6), 8.70 (s, 1 H, pyridine H-2).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 14.1 (Me), 103.4 (C-4), 120.8 (Ph-2,6), 122.3 (pyridine C-5), 126.0 (Ph-4), 127.1 (pyridine C-3), 129.1 (Ph-3,5), 136.3 (Ph-1), 147.8 (pyridine C-6), 148.2 (pyridine C-4), 148.5 (pyridine C-2), 150.6 (C-3), 159.4 (C-5), 184.6 (CO).

^{15}N NMR (50 MHz, DMSO-d_6): δ = –199.8 (N-1), –66.5 (pyridine N-1); N-2 was not found.

MS: *m*/*z* (%) = 315 (17) [M + 2]$^+$, 313 (50) [M$^+$], 278 (100), 201 (14).

Anal. Calcd for $C_{16}H_{12}ClN_3O_2·H_2O$: C, 57.93; H, 4.25; N, 12.67. Found: C, 58.13; H, 4.25; N, 12.67.

(3-Chloropyridin-4-yl)(5-hydroxy-1-phenyl-1*H*-pyrazol-4-yl)methanone (13b)
Yield: 72%; mp 162–163 °C (aq EtOH).

IR (KBr): 1645 (C=O) cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 7.33 (m, 1 H, Ph-4), 7.55 (d, $^3J_{H5–H6}$ = 4.9 Hz, 1 H, pyridine H-5), 7.48 (m, 2 H, Ph-3,5), 7.50 (br s, 1 H, OH), 7.68 (s, 1 H, H-3), 7.70 (m, 2 H, Ph-2,6), 8.65 (d, $^3J_{H6–H5}$ = 4.9 Hz, 1 H, pyridine H-6), 8.77 (s, 1 H, pyridine H-2).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 105.0 ($^2J_{C4–H3}$ = 9.4 Hz, C-4), 121.9 (Ph-2,6), 122.5 (^1J = 168.4 Hz, $^2J_{C5–H6}$ = 9.6 Hz, $^4J_{C5–H2}$ = 1.3 Hz, pyridine C-5), 126.7 (Ph-4), 127.0 ($^2J_{C3–H2}$ = 4.6 Hz, $^3J_{C3–H5}$ = 6.6 Hz, $^4J_{C3–H6}$ = 2.1 Hz, pyridine C-3), 129.0 (Ph-3,5), 137.3 (Ph-1), 141.4 (^1J = 189.5 Hz, C-3), 146.4 ($^2J_{C4–H5}$ = 0.6 Hz, $^3J_{C4–H2}$ = 4.4 Hz, $^3J_{C4–H6}$ = 6.7 Hz, pyridine C-4), 148.0 (^1J = 183.5 Hz, $^2J_{C6–H5}$ = 2.5 Hz, $^3J_{C6–H2}$ = 11.0 Hz, pyridine C-6), 149.2 (^1J = 187.8 Hz, $^3J_{C2–H6}$ = 11.5 Hz, pyridine C-2), 156.3 ($^3J_{C5–H3}$ = 4.9 Hz, C-5), 183.6 ($^3J_{CO–H5}$ = 4.0 Hz, CO).

^{15}N NMR (50 MHz, DMSO-d_6): δ = –182.0 (N-1), –63.0 (pyridine N-1); N-2 was not found.

MS: *m*/*z* (%) = 301 (14) [M + 2]$^+$, 299 (38) [M$^+$], 264 (100), 140 (12).

Anal. Calcd for $C_{15}H_{10}ClN_3O_2·0.15\ H_2O$: C, 59.57; H, 3.43; N, 13.89. Found: C, 59.59; H, 3.37; N, 13.83.

(3-Chloropyridin-4-yl)-[5-hydroxy-1-(4-methoxybenzyl)-1*H*-pyrazol-4-yl]methanone (13c)
Yield: 83%; yellowish oil.

IR (KBr): 1652 (C=O) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.79 (s, 3 H, OMe), 5.12 (s, 2 H, CH_2), 6.88 (m, 2 H, Ph-3,5), 7.31 (m, 2 H, Ph-2,6), 7.33 (d, $^3J_{H5–H6}$ = 5.0 Hz, 1 H, pyridine H-5), 7.35 (s, 1 H, H-3), 7.83 (br s, 1 H, OH), 8.63 (br d, $^3J_{H6–H5}$ = 5.0 Hz, 1 H, pyridine H-6), 8.74 (br s, 1 H, pyridine H-2).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 50.0 (^1J = 140.8 Hz, $^3J_{CH2–H2,6}$ = 4.6 Hz, CH_2), 55.3 (^1J = 143.9 Hz, OMe), 103.5 ($^2J_{C4–H3}$ = 10.7 Hz, C-4), 114.2 (Ph-3,5), 122.2 (pyridine C-5), 127.0 ($^2J_{C1–CH2}$ = 4.6 Hz, $^3J_{C1–H3,5}$ = 7.6 Hz, Ph-1), 128.0 (pyridine C-3), 129.7 (Ph-2,6), 139.2 (^1J = 190.7 Hz, C-3), 143.5 ($^3J_{C4–H2}$ = 4.7 Hz, $^3J_{C4–H6}$ = 6.7 Hz, pyridine C-4), 148.0 (^1J = 183.3 Hz, $^2J_{C6–H5}$ = 2.3 Hz, $^3J_{C6–H2}$ = 11.3 Hz, pyridine C-6), 150.8 (^1J = 187.9 Hz, $^3J_{C2–H6}$ = 11.5 Hz, pyridine C-2), 157.9 ($^3J_{C5–CH2}$ = 2.6 Hz, $^3J_{C5–H3}$ = 4.6 Hz, C-5), 159.6 (Ph-4), 187.3 (CO).

^{15}N NMR (50 MHz, $CDCl_3$): δ = –187.4 (N-1), –95.9 (N-2); pyridine N-1 was not found.

MS: *m*/*z* (%) = 345 (3) [M + 2]$^+$, 343 (8) [M$^+$], 121 (100).

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_{17}H_{14}N_3O_3{}^{35}Cl$: 343.0724; found: 343.0731.

Compounds 7f, 8f, 9f, 10f, and 11f; General Procedure
Under anhyd conditions, a solution of the PMB-substituted congener of type **c** and TFA (3–5 mL per mmol) was stirred overnight at 70 °C. After removal of excess TFA under reduced pressure, the residue was dried over solid KOH for 1 h. Then ice-cold Et_2O–acetone (2:1, 3–5 mL per mmol) was added and the resulting suspension was filtered and the solid was washed with cold Et_2O to give the unsubstituted parent compounds of type **f**.

NMR data are presented in Tables 2–5.

Pyrazolo[4′,3′:5,6]pyrano[3,2-*b*]pyridin-4(1*H*)-one (7f)
Yield: 89%; beige powder; mp 290–295 °C.

IR (KBr): 3434, 3098, 2902, 1679, 1659 (C=O) cm^{-1}.

MS: *m*/*z* (%) = 187 (100) [M$^+$].

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_9H_5N_3O_2$: 187.0382; found: 187.0378.

Pyrazolo[4′,3′:5,6]pyrano[3,2-*c*]pyridin-4(1*H*)-one (8f)
Yield: 62%; off-white powder; mp 335 °C (EtOH–DMF).

IR (KBr): 3111, 2812, 2652, 1683, 1674 (C=O) cm^{-1}.

MS: *m*/*z* (%) = 187 (100) [M$^+$], 135 (25), 110 (25).

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_9H_5N_3O_2$: 187.0382; found: 187.0378.

Pyrazolo[4′,3′:5,6]pyrano[2,3-*c*]pyridin-4(1*H*)-one (9f)
Yield: 64%; beige powder; mp 323–327 °C (EtOH–DMF).

IR (KBr): 3093, 2788, 2667, 1672 (C=O) cm^{-1}.

MS: *m*/*z* (%) = 187 (100) [M$^+$].

Anal. Calcd for $C_9H_5N_3O_2$: C, 57.76; H, 2.69; N, 22.45. Found: C, 57.88; H, 2.70; N, 22.34.

Pyrazolo[4′,3′:5,6]pyrano[2,3-*b*]pyridin-4(1*H*)-one (10f)
Yield: 10%; grayish powder; mp 308–315 °C (EtOH–DMF).

IR (KBr): 3424, 3157, 2926, 1681, 1650 (C=O) cm^{-1}.

MS: *m*/*z* (%) = 187 (100) [M$^+$].

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_9H_5N_3O_2$: 187.0382; found: 187.0385.

Pyrazolo[4′,3′:5,6]pyrano[2,3-*b*]quinolin-4(1*H*)-one (11f)
Yield: 11%; off-white powder; mp 315–321 °C (EtOH–DMF).

IR (KBr): 3460, 3102, 2915, 1682, 1675 (C=O) cm^{-1}.

MS: *m*/*z* (%) = 237 (100) [M$^+$], 153 (13).

Anal. Calcd for $C_{13}H_7N_3O_2·0.18\ H_2O$: C, 64.93; H, 3.09; N, 17.48. Found: C, 65.32; H, 3.24; N, 17.09.

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