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3-Formylchromones IV . The Rearrangement of 3-Formylchromone Enamines as a Simple, Facile Route to Novel Pyrazolo[3,4-b]pyridines and the Synthetic Utility of the Latter

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Abstract: One-pot and facile preparations of 6-(2-hydroxy-5-R-benzoyl)-4-methyl-2-R^1-pyrazolo[3,4-*b*]pyridines **4a-o** are described, using the reaction of 3-formyl chromones **1** with 5-amino-1-R^1-pyrazoles **2**. An enamine-intermediate 2-ethyloxy-6-R-3-(3-methyl-1-phenylpyrazol-5-ylaminomethylene)chroman-4-one **3** was isolated at lower temperatures. Acyloxy-derivatives **5** of compounds **4** were obtained by acylation with acid chlorides or acid anhydrides. Coumarins **6** substituted at the 3- and 4-positions were prepared from the pyrazolo[3,4-*b*]pyridines **4** by condensation reactions and hydrazones **7** were formed from their reaction with 2,4-dinitrophenyl hydrazine. Reactions under microwave irradiation proceeded significantly faster and with high yields.

Keywords: 4-Oxo-4*H*[1]benzopyrane, Coumarin, Pyrazole, Rearrangement, Enamine, Microwave irradiation

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Introduction

In our previous synthetic and theoretical studies [1,2] we reported on the reactions of 3-formyl chromones **1** with primary amine derivatives of benzothiazole and aromatic acids, respectively. These studies confirmed that the investigated amines undergo 1,2- or 1,4-additions to 3-formyl chromones **1**, forming a chroman-4-one enamine system as a main product. The relevant theoretical and kinetic studies of the reaction pathways of some 2- and 3-formylchromones with amine derivatives were published in the preceding papers [3-6] of this series. In general, 3-formylchromones **1** readily react with primary amines in an alcoholic medium yielding an enamine-adduct which rarely reacts further to give the corresponding Schiff base [7,10,11]. The important role of 3-formylchromones **1** as versatile synthons in heterocyclic chemistry as well as their pharmaceutical importance is well known [8,9,11]. These compounds also have interesting photochemical properties [7].

Our investigations of influence of microwave radiation – a widely used way to selectively excite primarily the polar components of reactants and solvent – on 3-formylchromone reactions were also reported elsewhere [12,13]. The main goal of this work was to examine the reaction of 1-substituted 5-aminopyrazoles **2** with 3-formylchromones **1** using classical and microwave heating, respectively.

Results and Discussion

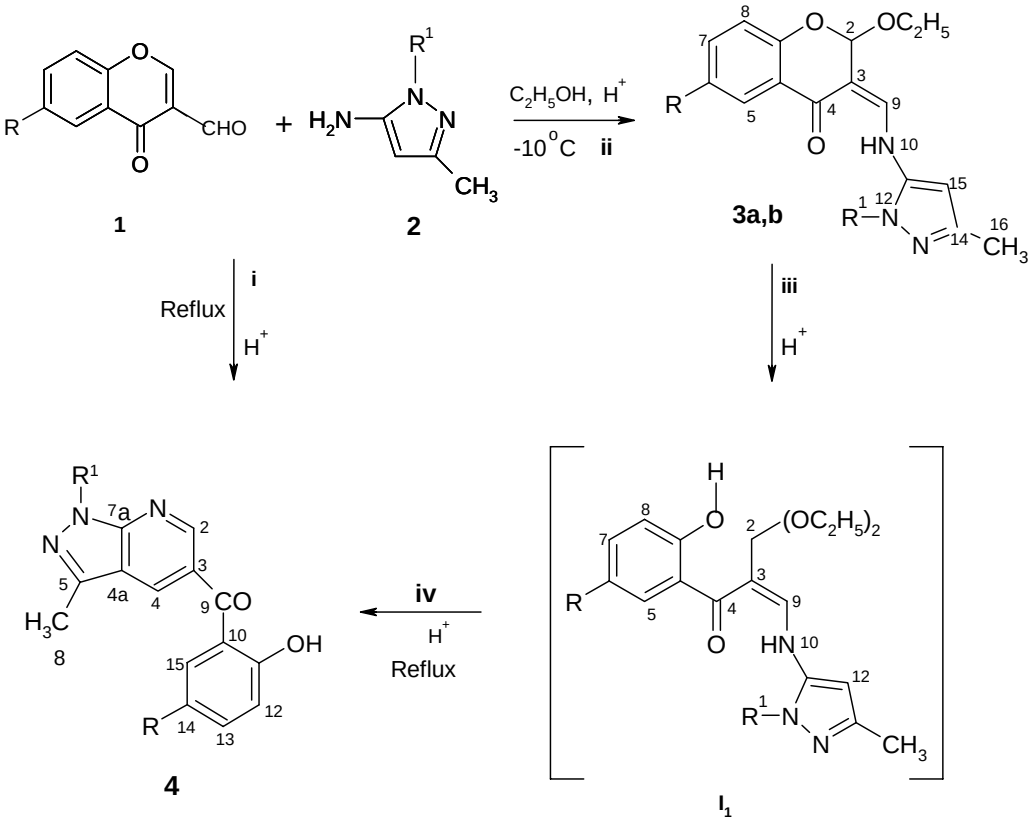
In this article we report on a very convenient and smooth, one-pot method for the preparation of substituted 3-(2-hydroxybenzoyl)pyrazolo[3,4-b]pyridines **4a-o.** Our results demonstrate a straight-forward entry to these pyrazolo[3,4-*b*]pyridine derivatives, which contain synthetically useful hydroxyl and carbonyl groups, and are formed via opening of the γ-pyrone ring and subsequent rearrangement of intermediate $\mathbf{I_1}$ with electrophilic substitution on the pyrazole ring. The 3-formylchromone starting compounds **1** are easily available from phenols according to Nohara [14,15].

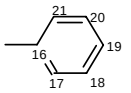
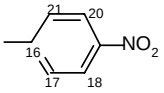
This synthesis of pyrazolo[3,4-*b*]pyridine derivatives **4a-o** was found to be very simple. Products were obtained by heating to reflux an equimolar mixture of 3-formylchromones **1** and 5-amino-pyrazole (**2**) in ethanol, using *p*-toluenesulfonic acid as catalyst (Scheme1). The duration of the reflux (2 to 4 hours) was found to be important for the purity of the final rearranged products. The progress of the reaction can readily be monitored visually. Products **4** are of a pale yellow to white color but the intermediates are bright yellow.

The reaction kinetics depend on the substituents R, R^1 and the solvent used. It was found that the methyl group (+I, +M effects) and similar substituents (H-) speeded up the formation of the final products. On the other hand, the compounds containing nitro groups on the chromone or pyrazole rings remained longer in the intermediate state (4 hours) before completing the reaction.

Ethanol was found to be more suitable for the synthesis of compounds **4** than other representative solvents like dioxane or toluene, as compared to these, ethanol facilitated faster reactions with higher yields and gave better product purities. This work as well as the previous kinetic studies [6] showed that alcohols are in general very good solvents for all reaction intermediates. This observation can be understood by noting that an alcohol, as a weak nucleophile, takes on a catalytic and stabilizing function after addition on to the chromanone ring and to the intermediates of this many-step-reaction, whereby forming complexes with lower energy.

Scheme 1.



R^1	compounds
	4a,4b,4c,4d,4e,4f
	4g,4h,4i,4j
CH_3	4k,4l,4m,4n,4o

In Scheme 1 a probable mechanism for the formation of compounds **4** is proposed. Our synthetic studies and kinetic measurements [6] showed that step **ii** – addition of aminopyrazole and alcohol to the aldehydes – is faster then the subsequent step **iv** which includes electrophilic attack of the opened chromanone system (intermediate $\mathbf{I_1}$) at the C-12 position of pyrazole ring and rearrangement. The shorter reaction time resulted in a final product with a certain amount of impurities. The ^{1}H-NMR-spectra and TLC showed that enamine-adducts or opened-intermediates $\mathbf{I_1}$ are the main impurities in the final products **4**. We observed that prolonging the duration of the reflux in ethanol provided the products **4** with higher purity. These products **4** are stable enough and further heating in ethanol does not change the composition of the reaction mixtures.

The role of the enamine-adduct **3a** as a reaction intermediate was confirmed by its isolation from the reaction mixtures at lower temperature (-10ºC). Nitro derivative **3b** show higher stability than the methyl analogue, and can still be isolated as the main product even after 20 minutes of reflux. Enamines, too, rearrange into the final products **4** after prolonged refluxing of the reaction mixtures**.**

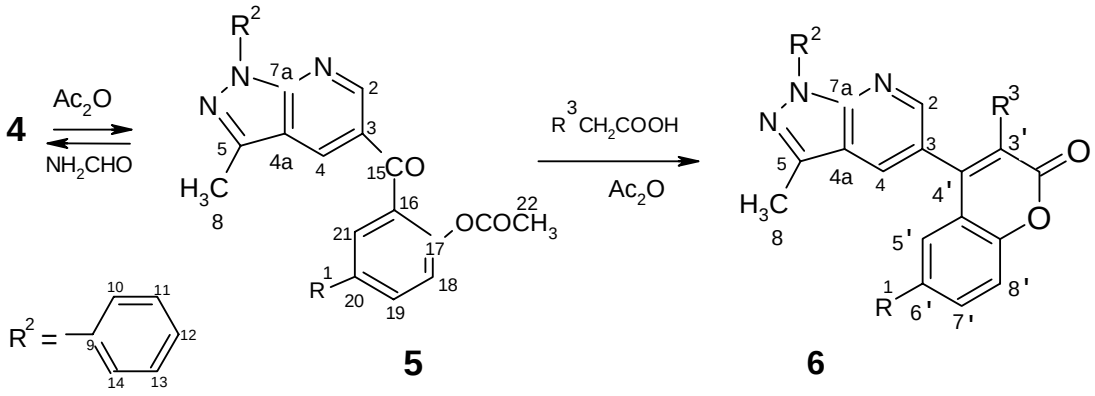
Synthesis under microwave irradiation proceeded significantly faster. The reaction time dropped down to 6 to 25 minutes under exposure to microwaves at 800 W and produced clean products **4** in high yields (90%). However, no isolation of intermediate **3** was possible in this case.

The structures of the rearranged compounds were proven by elemental analysis and by ^{1}H- and ^{13}C-NMR spectra. The assignment of the ^{1}H chemical shifts was deduced from the signal multiplicities and from the HH COSY spectra. The appropriate assignment of the ^{13}C chemical shifts was based on the HMQC spectra for the C-H carbons and for the quaternary carbons from the coupled ^{13}C spectrum (compound **4a**). All of the NMR spectra indicate that the products **4** contain the pyridine ring. This conclusion is based on the observation of typical pyridine-ring shift values of 8.96 (H-2) and of 8.46 (H-4) respectively, and of their coupling constant $J_{(2,4)}$=1.1 Hz (for compound **4a**). The presence of the doublet-doublet signal in the ^{13}C coupled spectrum at 151.5 δ (C-4a), with the coupling constants $^{3}J_{(C, H-2)}$ = 13.4 Hz and $^{3}J_{(C, H-4)}$ = 6.8 Hz confirms that the pyrazole ring is connected with the pyridine ring in the (3,4-b) position.

The detailed analysis of the ^{13}C-NMR data of compound **4a** (R = H), used as a reference compound, is presented in Table 1. The similar data for the compounds bearing other R substituents are available upon request from the corresponding author.

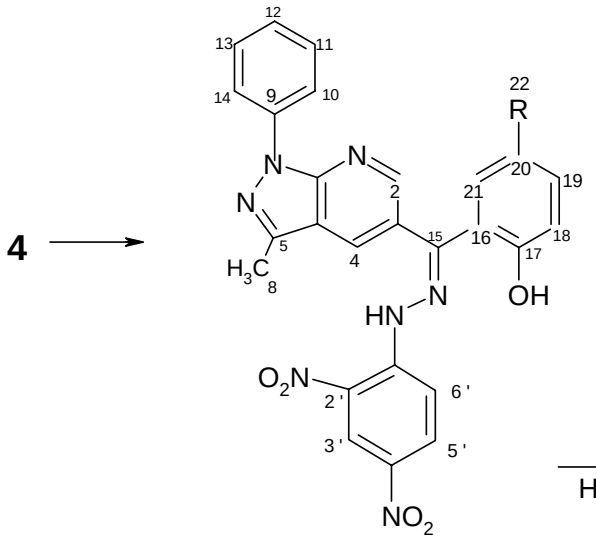
The pyrazolopyridine products **4** as bifunctional compounds were used for preparation of acyl- **5**, or coumarin derivatives **6.** Compounds **5** were prepared from the compound **4** by a standard acylation process. 3',4'-Substituted coumarins **6** were prepared by intramolecular ring formation of compounds **5** or by condensation reaction with methylene compounds by heating for 7 - 8 hours at 140-150°C (Scheme 2). A very simple deacylation process was realized by heating of compounds **5** at 110°C in formamide (Scheme 2).

Scheme 2.



The keto-groups of compounds **4** reacted with 2,4-dinitrophenylhydrazine at elevated temperature and formed hydrazones **7** (Scheme 3). Compounds **5**, **6** and **7** were identified by their microanalyses and by ^{1}H-NMR spectra.

Scheme 3



7

R	Compound
H, CH_3, F	7a, 7b, 7c

Conclusions

A simple, one pot and facile route for the preparation of 11-hydroxy-5-methyl-7-phenyl-3-(phenyloxo)pyrazolo[3,4-b]pyridine derivatives (**4a-4o**) from 4-oxo-4*H*[1]benzopyran-3-carboxaldehydes **1** by classical and microwave irradiation heating was described. Thus, the 3-formylchromones **1** react with 5-amino-*N*-phenylpyrazole (**2**) under reflux in ethanol and, after opening of the pyrone ring and an intramolecular electrophilic attack of the pyrazole ring, form a new pyrazolopyridine system **4.** An intermediate enamine-adduct **3** was isolated at lower temperature. Preparation of acyl derivatives **5**, 3,4-substituted coumarins **6,** and hydrazones **7** is also presented.

Acknowledgements

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Experimental

General

Melting points (uncorrected) of the synthesized compounds were determined on the Kofler block. The microanalyses (Carlo Erba Instrumentazione 1106) were in satisfactory agreement with the calculated values (the results for C, H, and N showed an agreement within ± 0.30%). The respective data are summarized in Tables 1-4. Microwave assisted reactions were carried out in a Lavis–1000 MultiQuant microwave oven. The apparatus was adapted for laboratory application with magnetic stirring and an external reflux condenser. ^{1}H-NMR spectra were measured at 300MHz, ^{13}C-NMR spectra at 75MHz on a Varian Gemini 2000 NMR spectrometer. The HHCOSY and HMQC analysis were performed using the manufacturer's software. Chemical shifts are given in δ-scale, coupling constants in Hz, TMS was used as an internal standard.

Synthesis of enamine adduct **3a**

A mixture of equimolar amounts of 6-methyl-3-formylchromone (20 mmol) and 5-amino-*N*-phenylpyrazole (20 mmol) in ethanol (30 mL) containing a catalytic amount of 4-toluenesulfonic acid (6 mg) gave a yellow solid intermediate **3a** after intensive stirring for 20 minutes at a temperature of – 15° C. The yellow solid was quickly removed from the solvent by filtration and then washed twice with cold ethanol. The purification of compound **3a** was performed by stirring in ethanol for 10 minutes at about 0 - 5º C , then the solvent was sucked away and the residue was dried in vacuum at room temperature.

Synthesis of enamine adduct **3b**

A mixture of equimolar amounts of 6-nitro-3-formylchromone (20 mmol) and 5-amino-*N*-phenyl-pyrazole (20 mmol) in ethanol (30 mL) with 4-toluenesulfonic acid (6 mg) resulted in a yellow solid intermediate **3b** after stirring for 20 minutes at 40-50° C. The product was removed by hot filtration, washed twice with ethanol and then dried under vacuum at room temperature.

Preparation of pyrazolo[3,4-b]pyridine derivatives **4a-4e,4g-4k** *(Classical conditions)*

A mixture of equimolar amounts of the appropriate 3-formylchromone derivatives (20 mmol) and 5-amino-*N*-(R^1)-pyrazole (20 mmol) in ethanol (30 mL) was stirring and heated at reflux with 4-toluenesulfonic acid (6 mg) for two hours. The pale-yellow crystalline products were isolated in about 85 % yields, and could be recrystallized from ethanol or toluene. NMR spectra of the prepared compounds **4** are given in Table 1 and Table 2.

Preparation of pyrazolo[3,4-b]pyridine derivatives **4f, 4l,4m,4n** *and* **4o** *(Classical conditions)*

A mixture of equimolar amounts of 6-nitro-3-formylchromone (20 mmol) and 5-amino-*N*-(R^1)-pyrazole (R^1 is 4-nitrophenyl) (20 mmol) in ethanol (30 mL) was heated with 4-toluenesulfonic acid (20 mg) for four hours. The yellow products were isolated at about 70 % yields, and were recrystallized from toluene or mixtures of ethanol-DMSO.

Microwave procedure for preparation of **4a-4o**

The mixture described in the previous section was irradiated at 800 W. For obtain an optimal yield of products **4** the irradiation times were varied between 6 and 25 minutes (nitro-derivatives required longer react times, from 18 - 25 minutes). The solid compounds were filtered off and recrystallized from ethanol or mixtures of ethanol-DMSO. The pure products were obtained in about 90 % yield.

Preparation of compounds **5** *by acylation: procedure for* **5a,5b,5c** *(with acetic anhydride)*

Pyrazolo[3,4-*b*]pyridine derivatives **4** (2 mmol), anhydrous acetic anhydride (10 mL) and freshly melted sodium acetate (2 mmol) was stirred at 60 ^{o}C for 3 hours. Then the acetic anhydride was removed under vacuum and the residue was recrystallized from acetone or chloroform. The crystalline products were obtained in ca. 70 % yields.

Procedure for **5d,5e,5f** *(with acid chlorides)*

A mixture of equimolar amounts of pyrazolo[3,4-*b*]pyridine derivatives **4** (2 mmol) and KOH (2.4 mmol) in anhydrous acetone (20 mL) was heated under reflux for 1 hour. Subsequently it was vigorously stirred and cooled down to -5 ^{o}C while small amounts of a solution of acyl chloride (2.4 mmol) in anhydrous acetone (15 mL) were added. Upon completion of the addition the stirring was continued for another 2 hours at the room temperature. Acetone was removed under vacuum. The residue was treated with water, filtered off and recrystallized from ethanol or acetone in about 70 % yields.

Preparation of coumarin derivatives **6a, 6b**

Pyrazolo[3,4-*b*]pyridine derivatives **4** (2 mmol), anhydrous acetic anhydride (20 ml), fresh melted sodium acetate (2mmol) and phenylacetic acid or phenylthioacetic acid (2.4 mmol) was stirred and heated under reflux for 6 hours. Then the acetic anhydride was removed in vacuum and the residue was crystallized from toluene. The crystal products were obtained in 65 % yields.

Preparation of hydrazone derivatives 7

The mixture of equimolar amounts of pyrazolo[3,4-*b*]pyridine **(4)** (1 mmol) and 2,4-dinitrophenylhydrazine (1 mmol) in 10ml of acetic acid was heated and stirred for 15 minutes at 80 ^{o} C. The red crystal product was isolated after recrystallized from acetic acid in about 82 % yield.

Table 1: Physical data of the compounds **4**

No ------- **Yield**	**Compound name**		
	Formula / MW	**Melting point**	**Elemental analysis**
	3-(2-hydroxybenzoyl)-5-methyl-7-phenylpyrazolo[3,4-*b*]pyridine		
	$C_{20}H_{15}N_3O_2$ 329.4	120 –121 ºC	Calc.: 72.94 %C; 4.59 %H; 12.76 %N Found: 73.12 %C; 4.54 %H; 12.87 %N
4a ------- 89%	^{13}C-NMR ($CDCl_3$) δ(ppm), J(Hz): 12.73 q, J(C,H)=127.9(C-8); 116.57q, ^{3}J(C,H)=2.9(C-4a); 118.98dt, J(C,H)=162.3, ^{3}J(C,H)=7.3 (C-12); 119.23dd, J(C,H)=163.6, ^{3}J(C,H)=9.2(C-14); 119.59dt, ^{3} J(C,H)=4.7, ^{3}J(C,H)=7.6(C-10); 121.45dt, J(C,H)=161.6, ^{3}J(C,H)=7.5(C-17,21); 126.55dt, J(C,H)=162.9, ^{3}J(C,H)=7.6(C-19);		

Table 1. Cont.

	127.54d, ^{3}J(C,H-4)=8.0(C-5); 129.41dd, J(C,H)=161.5, ^{3}J(C,H) = 8.3(C-18,20); 131.87dd, J(C,H)=166.1, ^{3}J(C,H)=6.0(C-4); 133.27dd, J(C,H)=160.2, ^{3}J(C,H)=9.0(C-15); 136.85dd, J(C,H)=159.8, ^{3}J(C,H)=9.2(C-13); 139.24t, ^{3}J(C,H)=8.0(C16);144.50qd, ^{2}J(C,H)=7.1, ^{3}J(C,H)=2.5(C-16); 150.30dd, J(C,H)=183.3, ^{3}J(C,H)=5.5(C-2); 151.54dd, ^{3}J(C,H-2)=13.4, ^{3}J(C,H-4)=6.8(C-7a); 163.43dd, ^{3}J(C,H) 7.5,6.8 (C-11), 199.11t, ^{3}J(C,H) = 4.4(C-9).		
4b ------- 92%	3-(2-hydroxy-5-methylbenzoyl)-5-methyl-7-phenylpyrazolo[3,4-*b*]pyridine		
	$C_{21}H_{17}N_3O_2$ 343.4	142-144 ºC	Calc.: 73.38 %C; 4.99 %H; 12.23%N Found: 73.22 %C; 4.84 %H; 12.27 %N
4c ------- 87%	3-(2-hydroxy-5-fluorobenzoyl)-5-methyl-7-phenylpyrazolo[3,4-*b*]pyridine		
	$C_{20}H_{14}FN_3O_2$ 339.4	155-156 ºC	-----
4d ------- 87%	3-(2-hydroxy-5-bromobenzoyl)-5-methyl-7-phenylpyrazolo[3,4-*b*]pyridine		
	$C_{20}H_{14}BrN_3O_2$ 408.4	162-163º C	Calc.: 58.82 %C; 3.43 %H; 10.21%N Found: 58.62 %C; 3.21 %H; 10.01 %N
4e ------- 89%	3-(2-hydroxy-5-chlorobenzoyl)-5-methyl-7-phenylpyrazolo[3,4-*b*]pyridine		
	$C_{20}H_{14}ClN_3O_2$ 363.2	160-162 ºC	Calc.: 65.97 %C; 3.84 %H; 11.54%N; 9.74 %Cl Found: 66.22 %C; 3.88 %H;11.34%N; 9.70%Cl
4f ------- 70%	3-(2-hydroxy-5-nitrobenzoyl)-5-methyl-7-phenylpyrazolo[3,4-*b*]pyridine		
	$C_{20}H_{14}N_4O_4$ 374.4	207-208 ºC	Calc.: 77.36 %C; 4.52 %H; 18.07%N Found: 77.48 %C; 4.58 %H; 18.14%N
4g ------- 73%	3-(2-hydroxy-5-methylbenzoyl)-5-methyl-7-(4-nitrophenyl)pyrazolo[3,4-*b*] pyridine		
	$C_{21}H_{16}N_4O_4$ 388.4	224-226 ºC	Calc.: 64.94 % C; 4.15 % H; 14.43 % N Found: 64.78 % C; 4.03 % H; 14.37 % N
4h ------- 87%	3-(2-hydroxy-5-fluorobenzoyl)-5-methyl-7-4-(nitrophenyl)pyrazolo[3,4-*b*] pyridine		
	$C_{20}H_{13}FN_4O_4$ 392.4	222 -224 ºC	----------
4i ------- 82%	3-(2-hydroxy-5-bromobenzoyl)-5-methyl-7-(4-nitrophenyl)pyrazolo[3,4-*b*] pyridine		
	$C_{20}H_{13}BrN_4O_4$ 329.4	260-261 ºC	Calc.: 53.00 % C; 2.89 % H; 12.36 % N; 17.63 % Br Found: 53.19% C; 2.68 % H; 12.11% N;17.42 %Br
4j ------- 88%	3-(2-hydroxy-5-chlorobenzoyl)-5-methyl-7-4-(nitrophenyl)pyrazolo[3,4-*b*] pyridine		
	$C_{20}H_{13}ClN_4O_4$ 408.8	239-241 °C	Calc.: 58.76% C; 3.21% H; 13.71% N; 8.67%Cl Found: 58.67 %C; 3.11% H; 13.68% N; 8.58%Cl
4k ------- 87%	3-(2-hydroxy-5-methylbenzoyl)-5,7-dimethylpyrazolo[3,4-*b*]pyridine		
	$C_{16}H_{15}N_3O_2$ 281.3	176-177 °C	Calc.: 68.31 %C; 5.37 % H; 14.94 % N Found: 68.22 %C; 5.21 % H; 14.67 % N
4l ------- 87%	3-(2-hydroxy-5-fluorobenzoyl)-5,7-dimethylpyrazolo[3,4-*b*]pyridine		
	$C_{15}H_{12}FN_3O_2$ 285.3	160-161 ºC	----------

Table 1. Cont.

4m	3-(2-hydroxy-5-bromobenzoyl)-5,7-dimethylpyrazolo[3,4-*b*]pyridine		
------- 89%	$C_{15}H_{12}BrN_3O_2$ 346.2	150-151 °C	Calc.: 52.04 %C; 3.49 %H; 12.14 % N; 23.08 % Br Found : 52.19 %C; 3.32 %H; 12.11 % N; 23.17 % Br
4n	3-(2-hydroxy-5-chlorobenzoyl)-5,7-dimethylpyrazolo[3,4-*b*]pyridine		
------- 87%	$C_{15}H_{12}ClN_3O_2$ 301.7	170-171 °C	Calc.: 59.71 % C; 4.01% H; 13.93 % N; 11.75 %Cl Found: 59.58 % C; 4.16% H; 14.11 % N; 11.42 %Cl
4o	3-(2-hydroxy-5-nitrobenzoyl)-5,7-dimethylpyrazolo[3,4-*b*] pyridine		
------- 86%	$C_{15}H_{12}N_4O_4$ 312.3	213-215 °C	Calc.: 57.69 % C; 3.87 %H; 17.94 % N Found : 57.53 % C; 3.68 %H; 18.11 % N

Table 2: ^{1}H-NMR spectral data of pyrazolo[3,4-b]pyridines **4**

No	R	R[1]/8	OH	2	4	12	13	15	17(21) (2H)	18(20) (2H)	19
4a	**H-14** 7.63dd, J= 8.0 J= 1.4	2.71s	11.86s	8.96d, J=2.1	8.46d, J = 2.1	7.13dd, J = 8.2, J = 1.1	7.57td J= 8.2, J = 1.4	7.63dd, J = 8.0 J= 1.4	8.26dd J= 7.5 J=1.1	7.55t J= 7.5	7.34t J= 7.5 J= 1.1
4b	CH_3	2.28s 2.64s	11.06s	8.94d J=1.9	8.47d J=1.9	7.04d J=7.7	7.38dd J=7.8 J=0.8	7.39t J=3.1 J=2.6	8.26dd,2H J=7.6 J=1.1	7.55t,2H J=7.6 J=1.1	7.34t J=7.6 J=1.1
4c	F	2.72s	11.57s	8.95d J=1.9	8.45d J=1.9	7.10dd $J_{11,12}$=10.2 $J_{11,F}$ = 4.4	7.2-7.4 m 3H* 13,15,19	*	8.25dd,2H J=8.0 J=1.1	7.55t,2H J=8.0 J=1.1	*
4d	Br	2.73s	11.75s	8.94d J=1.9	8.46d J=1.9	7.05d J=8.8	7.64dd J=8.8 J=2.5	7.38t J=7.7	8.25dd,2H J=7.7 J=1.1	7.56t,2H J=7.7 J=1.1	7.38t J=7.7 J=1.1
4e	Cl	2.73s	11.74s	8.95d J=2.1	8.47d J=2.1	7.10d J=9.0	7.51dd J=9.0 J=2.5	7.60d J=2.5	8.25dd,2H J=7.7 J=1.1	7.56t,2H J=7.7 J=1.1	7.35t J=8.0 J=1.1
4f	NO_2	2.73s	12.60s	8.99d J=2.0	8.49d J=2.0	7.23d J=9.0	8.46dd J=9.0 J=2.6	8.65d J=2.6	8.25dd,2H J=7.6 J=1.1	7.56t,2H J=7.5 J=1.1	7.55t J=7.5 J=1.1
4g	CH_3	2.28s 2.68s	10.21s	8.95d J=1.9	8.71d J=1.9	6.92d J=8.2	7.29dd J=8.2 J=2.2	7.33d J=2.2	8.48dd,2H J=9.4 J=1.9	8.67dd,2H J=9.4 J=1.9	---
4h	F	2.67s	10.08s	8.97d J=2.2	8.69d J=2.2	7.05dd J=8.8 J=4.4	7.2-7.3m 2H	H-13,15	8.41dd,2H J=9.3 J=1.1	8.62dd,2H J=9.3 J=1.9	---
4i	Br	2.67s	10.37s	8.95d J=1.9	8.68d J=1.9	7.00d J=8.6	7.53dd J=8.6 J=2.6	7.33d J=2.2	8.41dd,2H J=9.2 J=2.0	8.60dd,2H J=9.2 J=2.0	---

Table 2: Cont.

4j	Cl	2.68s	10.37s	8.96d J=1.9	8.69d J=1.9	7.05d J=8.5	7.47dd J=8.5 J=2.7	7.45d J=2.7	8.43dd,2H J=9.3 J=2.2	8.62dd,2H J=9.3 J=2.2	---
No	**R**	**R[1]**	**8**	**OH**	**2**	**4**	**12**	**13**	**15**		
4k	CH_3	2.28s 2.64s	4.15s	11.67 s	8.87d J=1.9	8.40d J=1.9	7.04t J=9.1 J=4.4	7.34-7.39 m, (2H) 13, 15	*		
4l	F	2.63s	4.15s	11.56s	8.87d J=2.0	8.39d J=2.0	7.11dd J=8.9 J=4.6	7.31td J=8.9 J=3.1 J=2.6	7.29t J=3.1 J=2.6		
4m	Br	2.63s	4.15s	11.74s	8.86d J=1.9	8.38d J=1.9	7.04d J=8.8	7.63dd J=8.8 J=2.4	7.69d J=2.4		
4n	Cl	2.65s	4.16s	11.74s	8.87d J=2.0	8.39d J=2.0	7.09d J=8.9	7.51dd J=8.9 J=2.5	7.56d J=2.4		
4o	NO_2	2.62s	4.17s	12.50s	8.91d J=2.0	8.42d J=2.0	7.22d J=8.9	7.44dd J=8.9 J=2.7	8.61d J=2.7		

* multiplet

Table 3: ^{13}C-NMR: δ(ppm), J (Hz)($CDCl_3$)

N_o	**R**	**N-CH_3**	**C 14(CH_3)**	**8(CH_3)**	**2**	**3**	**4**	**4a**
4b	CH_3		20.73	12.72	150.23	127.76	130.92	116.72
4c	F			12.76	150.14	127.02	131.86	116.63
4d	Br			12.76	150.11	126.92	132.01	116.73
4e	Cl			12.76	150.11	126.91	131.96	116.57
4m	Br	33.73		12.52	149.75	125.86	132.21	114.41
N_o	**R**	**5**	**7a**	**9**	**10**	**11**	**12**	**13**
4b	CH_3	144.48	151.5	199.04	119.31	161.37	118.74	137.93
4c	F	144.61	151.6	198.19d $^4J_{C,F}$=2,5	119.11d $J_{C,F}$=6.3	159.59	120.38d $^3J_{C,F}$=7,4	124.45d $^2J_{C,F}$=23.8
4d	Br	144.61	151.6	198.08	120.87	161.30	121.01	139.52
4e	Cl	144.61	151.6	198.14	120.2	161.84	120.62	136.72
4m	Br	142.93	151.9	198.28	120.89	162.18	120.56	139.02
N_o	**R**	**14**	**15**	**16**	**17,21**	**18,20**	**19**	
4b	CH_3	128.45	132.88	139.25	121.48	129.41	126.54	
4c	F	155.02d $^1J_{C,F}$=246.5	117.98d $^2J_{C,F}$=23.8	139.11	121.54	129.45	126.68	
4d	Br	110.89	135.07	139.21	121.58	129.46	126.72	
4e	Cl	124.07	132.07	139.24	121.54	129.44	126.69	
4m	Br	110.51	135.13	-------	--------	--------	-------	

Table 4: Physical and ^{1}H-NMR data for compounds **3,5,6,7**

No	**Compound name**		
-------	**Formula / MW**	**Melting point**	**Elemental analysis**
Yield	**NMR data ($CDCl_3$ unless otherwise indicated) [δ(ppm) , J (Hz)]**		
3a ------- 72%	2-Ethyloxy-6-methyl-3-(3-methyl-1-phenylpyrazol-5-ylaminomethylene)chroman-4-one		
	$C_{23}H_{23}N_3O_3$ 383.5	164 – 166 °C	Calc.: 70.93%C; 5.95%H; 10.79%N Found: 70.90%C; 6.01%H; 10.59%N
	^{1}H-NMR: 1.24 (t, 3H, CH_3); 2.17 (s, 3H, CH_3 on C-14), 2.49 (s, 3H, CH_3 -6); 3.71 (q, 2H, CH_2); 6.25 (s, 1H, H-2); 7.37- 7.42 (m, 3H, H-18,19,20); 7.52 (dd, 2H, ^{3}J =8.4, ^{4}J =2, H-17,21); 7.56 (d, 1H, ^{3}J =8.4, H-8); 7.65 (dd, 1H, ^{3}J =8.4, ^{4}J =2, H-7); 7.67 (d, 1H, ^{4}J =2, H-5); 8.08 (s, 1H, H-9); 8.67 (s, 1H, H-10); 8.99 (d, 1H, ^{4}J =2, H-15); 9.02 (d, 1H, ^{4}J =2.4, NH).		
3b ------- 61%	2-Ethyloxy-6-nitro-3-(3-methyl-1-phenylpyrazol-5-ylaminomethylene)chroman-4-one		
	$C_{22}H_{20}N_4O_5$ 420.4	187 – 189 °C	Calc.: 62.85%C; 4.75%H; 13.33%N Found: 61.40%C; 4.63%H; 13.19%N
	^{1}H-NMR: 1.25 (t, 3H, CH_3); 2.70 (s, 3H, CH_3 on C-14); 3.91 (q, 2H, CH_2); 6.37 (s, 1H, H-2); 7.35 (t, 1H, ^{3}J =7.4, H-19); 7.52-758 (m, 2H, H-18,20); 8.24 (m, 2H, H-17,21); 8.35 (d, 1H , ^{3}J =7.7, H-8); 8.42 (dd, 1H, ^{3}J =7.7, ^{4}J =2.7, H-7); 8.48 (d, 1H, ^{3}J = 2.4, H-9); 8.64 (d,1H, ^{4}J =2.7, H-5); 8.98 (d,1H,^{4}J =2.0, H-15); 9.02 (d, 1H, ^{4}J =2.4, NH)		
5a ------- 68%	3-(2-acetyloxybenzoyl)-5-methyl-7-phenylpyrazolo[3,4-*b*]pyridine		
	$C_{22}H_{17}N_3O_3$ 371.2	109-111 °C	Calc.: 71.12 %C; 4.58 %H, 11.31%N Found: 71.26 %C; 4.50 %H, 11.28%N
	^{1}H-NMR: 2.03 (s, 3H, CH_3CO); 2.68 (s, 3H, CH_3-8); 7.30 (dd, 1H, ^{3}J=7.3, ^{4}J=2.1, H-13); 7.32-7.39 (m, 3H, H-11,18,20); 7.49-7.56 (m, 2H,H-10,12), 7.55 (t,1H, ^{3}J=7.6, H-14); 8.26 (dd, 2H, ^{3}J=7.7, ^{4}J= 2.1, H-19,21); 8.48 (d, 1H, ^{4}J=1.2,H-4); 9.05 (d, 1H, ^{4}J=1.2, H-2)		
5b ------- 61%	3-(2-acetyloxy-5-methylbenzoyl)-5-methyl-7-phenylpyrazolo[3,4-*b*]pyridine		
	$C_{23}H_{19}N_3O_3$ 385.2	125-127 ° C	Calc.: 71.65 %C; 4.93 %H, 10.90%N Found: 71.44 %C; 5.09 %H, 10.81%N
	^{1}H-NMR: 1.99 (s, 3H, CH_3CO); 2.40 (s, 3H, CH_3 on C-20); 2.67 (s, 3H, CH_3-8); 7.11 (d, 1H, ^{3}J=8.3, H-18); 7.30 (dd, 1H, ^{3}J=7.3, ^{4}J=2.1, H-19); 7.35 (d, 1H, ^{4}J=2.2, H-21); 7.39 (m, 1H, H-14); 7.55 (t, 2H, ^{3}J=7.6, H-10,12); 8.23 (dd, 2H, ^{3}J=7.6, ^{4}J=1.1, H-11,13); 8.49 (d, 1H, ^{4}J(2,4)=1.2, H-4); 9.04 (d, 1H, ^{4}J=1.2, H-2).		
5c ------ 58%	3-(2-ethyloxycarbonyloxy-5-methylbenzoyl)-5-methyl-7-phenylpyrazolo[3,4-*b*]-pyridine		
	$C_{24}H_{21}N_3O_4$ 415.4	154-156 ° C	Calc.: 69.39 %C; 5.09 %H; 10.11%N Found: 69.48 %C; 5.00 %H; 10.02%N
	^{1}H-NMR:1.07 (t,3H, ^{3}J=7,3,CH_3); 2.55 (s,3H,CH_3); 2.66 (s, 3H, CH_3-8); 4.09 (q,2H, ^{3}J=7,3, CH_2); 7.23 (t, 1H, ^{3}J=8.3, H-18); 7.37 (d, 1H, ^{3}J=8.3, H-12); 8.09 (tt, 2H, ^{3}J=7.6, H-11,13); 8.24 (dd, 2H, ^{3}J=8.8, ^{4}J=1.1, H-17,21); 8.49 (d, 1H, ^{4}J=1.3, H-4); 9.04 (d, 1H, ^{4}J=1.3Hz, H-2).		
5d ------- 63%	3-[2-(3-methylphenyloxyacetyloxy-5-methyl)benzoyl]-5-methyl-7-phenylpyrazolo[3,4-*b*]-pyridine		
	$C_{30}H_{25}N_3O_4$ 491.3	118-120 ° C	Calc.: 73.27%C; 5.09 %H, 8.55%N Found: 73.24%C; 5.19 %H, 8.41%N

Table 4: Cont.

	^{1}H-NMR: 2.41 (s, 3H, CH_3); 2.25 (s, 3H, CH_3); 2.64 (s, 3H, CH_3-8); 4.62 (s, 2H, CH_2); 6.73 (d, 1H, ^{4}J=2.1, H_{PhO}); 7.06-7.13 (m, 3H, H_{PhO}); 7.3-7.4 (m, 3H, H-12,18,19); 7.45 (dd, 2H, ^{3}J=7.3, ^{4}J=2.1, H-11,13); 8.23 (dd, 2H, ^{3}J=7.3, ^{4}J=2.1, H-10,14); 8.47 (d, 1H, ^{4}J=1.1, H-4); 9.04 (d, 1H, ^{4}J=1.1, H-2).		
6a ------- 68%	3-(6'methyl-3'-phenylcoumarin-4'-yl)-5-methyl-7-phenylpyrazolo[3,4-*b*]pyridine		
	$C_{29}H_{21}N_3O_2$ 443.3	222-224 °C	Calc.: 78.50 %C; 4.73 %H, 9.47%N Found: 78.26 %C; 4.69 %H, 9.28%N
	^{1}H-NMR: 2.29 (s, 3H, CH_3); 2.59 (s, 3H, CH_3-8); 6.95 (s, 1H, H-5'); 7.1-7.2 (m, 5H, Ph on 3'); 7.29 (t, 1H, ^{3}J=7.3, ^{4}J=1.9, H-12); 7.38 (dd, 2H, ^{3}J=7.3, J=1.9, H-11,13); 7.51 (d, 1H, ^{3}J=7.4, H-8'); 7.54 (dd, ^{3}J=7.4, ^{4}J=1.9, H-7'); 7.78 (d, 1H, ^{4}J=1.2, H-4); 8.23 (dd, 2H, ^{3}J=7.6, ^{4}J=2.0, H-10,14); 8.39 (d, 1H, ^{4}J=1.2, H-2).		
6b ------- 61%	3-[(6'methyl-3'-phenylthio)coumarin-4'-yl]-5-methyl-7-phenylpyrazolo[3,4-*b*]pyridine		
	$C_{29}H_{21}N_3O_2S$ 475.2	319-323 ° C	Calc.: 67.12 %C; 4.52 %H, 11.18%N Found: 66.98 %C; 4.35 %H, 11.28%N
	^{1}H-NMR (DMSO-d_6): 2.25 (s, 3H, CH_3); 2.62 (s, 3H, CH_3-8); 6.97 (s, 1H, H-5'); 7.1-7.2 (s, 5H, Ph on 3'); 7.33 (t, 1H, ^{3}J=7.5, ^{4}J=1.9, H-12); 7.48 (d,1H, ^{3}J=8.1, H-8'); 7.52-7.55 (m, 2H, H-11,13); 7.56 (dd, 1H, ^{3}J=8.3, ^{4}J=1.9, H-7'); 8.26 (dd, 2H, ^{3}J=8.6, ^{4}J=2.0, H-10,14); 8.39 (d, 1H, ^{4}J=1.2, H-4); 8.64 (d, 1H, ^{4}J=1.2, H-2).		
7a ------- 63%	3-(2-hydroxybenzoyl)-5-methyl-7-phenylpyrazolo[3,4-*b*]pyridine-15-(2',4'-dinitrophenyl)hydrazone		
	$C_{26}H_{19}N_7O_5$ 509.5	280-281 °C	Calc.: 61.23 %C; 3.73 %H, 19.24%N Found: 61.45 %C; 3.40 %H, 19.02%N
	^{1}H-NMR: 2.72 (s, 3H, CH_3); 6.82-6.86 (m, 2H, H-19,21); 7.13 (dd, 1H, ^{3}J=8.3Hz, ^{4}J=2 Hz, H-18); 7.32-7.43 (m, 2H, H-12,20); 7.56 (t, 2H, ^{3}J=7.9Hz, ^{4}J=2Hz, H-11,13); 8.17 (d, 1H, ^{4}J=1.6Hz, H-4); 8.27 (d, 1H, ^{3}J=8.9Hz, H-6'); 8.28 (dd, 2H, ^{3}J=7.9Hz, ^{4}J=1.9Hz, H-10,14); 8.45 (dd, 1H, ^{3}J=9 Hz, ^{4}J=2Hz, H-5'); 8.59 (d, 1H, ^{4}J=1.6Hz, H-2); 9.09 (d, 1H, ^{4}J=2Hz, H-3'); 11.26 (s, NH); 11.37 (s, OH).		
7b ------- 68%	3-(2-hydroxy-5-methylbenzoyl)-5-methyl-7-phenylpyrazolo[3,4-*b*]pyridine-15-(2', 4'-dinitrophenyl)hydrazone		
	$C_{27}H_{21}N_7O_5$ 523.5	290-292 °C	Calc.: 61.89 %C; 4.01 %H, 18.72%N Found: 61.78 %C; 4.11 %H, 18.53%N
	^{1}H-NMR: 2.26 (s, 3H, CH_3); 2.75 (s, 3H, CH_3-8); 6.58 (s, 1 H, H-21); 7.05 (d, 1H, ^{3}J=8.5Hz, H-18); 7.17 (dd, 1H, ^{3}J=8.6Hz, ^{4}J=2.4Hz, H-19); 7.34 (t, 1H, ^{3}J=7.6Hz, ^{4}J=1.1Hz, H-12); 7.55 (dd, 2H, ^{3}J=8.5Hz, ^{4}J=2Hz, H-11,13); 7.75 (dd, 1H,^{3}J=8.4Hz, ^{4}J=2.5Hz, H-6'); 8.32 (dd, 2H, ^{3}J=8.1Hz, ^{4}J=2Hz, H-10,14); 8.44 (dd, 1H, ^{3}J=9.1Hz, ^{4}J=2.6Hz, H-5'); 8.15 (d, 1H, ^{4}J=2.8Hz, H-4); 8.57 (d, 1H, ^{4}J=2.0, H-2); 9.07 (d, 1H, ^{4}J=2.6 H-3'); 11.13 (s, NH); 11.20 (s, OH).		
7c ------- 70%	3-(2-hydroxy-5-fluorobenzoyl)-5-methyl-7-phenylpyrazolo[3,4-*b*]pyridine-15-(2', 4'-dinitrophenyl)hydrazone		
	$C_{26}H_{18}FN_7O_5$ 528.4	291-292 °C	----------

Table 4: Cont.

	^{1}H-NMR: 2.66 (s, 3H, CH_3); 6.94 (dd, 1H, ^{3}J=8.8Hz, ^{4}J=2.4Hz, H-19); 7.12 (d, 1H, ^{3}J=8.8Hz, H-18); 7.51 (t, 1H, ^{3}J=8.8Hz, ^{4}J=2Hz, H-12); 7.56 (d, 1 H, ^{4}J=2.4Hz, H-21); 8.14 (d, 1H, ^{4}J=1.9Hz, H-4); 8.16 (dd, 2H, ^{3}J=8.8Hz, ^{4}J=2 Hz, H-11,13); 8.39 (dd, 1H, ^{3}J=9.1Hz, ^{4}J=2.6 Hz, H-5'); 8.43 (dd, 2H, ^{3}J=8.1Hz, ^{4}J=2Hz, H-10,14); 9.07 (d, 1H, ^{4}J=1.9Hz, H-2); 9.09 (d, 1H, ^{4}J=2.6 Hz, H-3'); 11.06 (s, NH); 11.27 (s, OH).

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