5-Carbohydrazides and 5-carbonylazides of pyrazolo[3,4-*b*]pyridines as reactive intermediates in the synthesis of various heterocyclic derivatives

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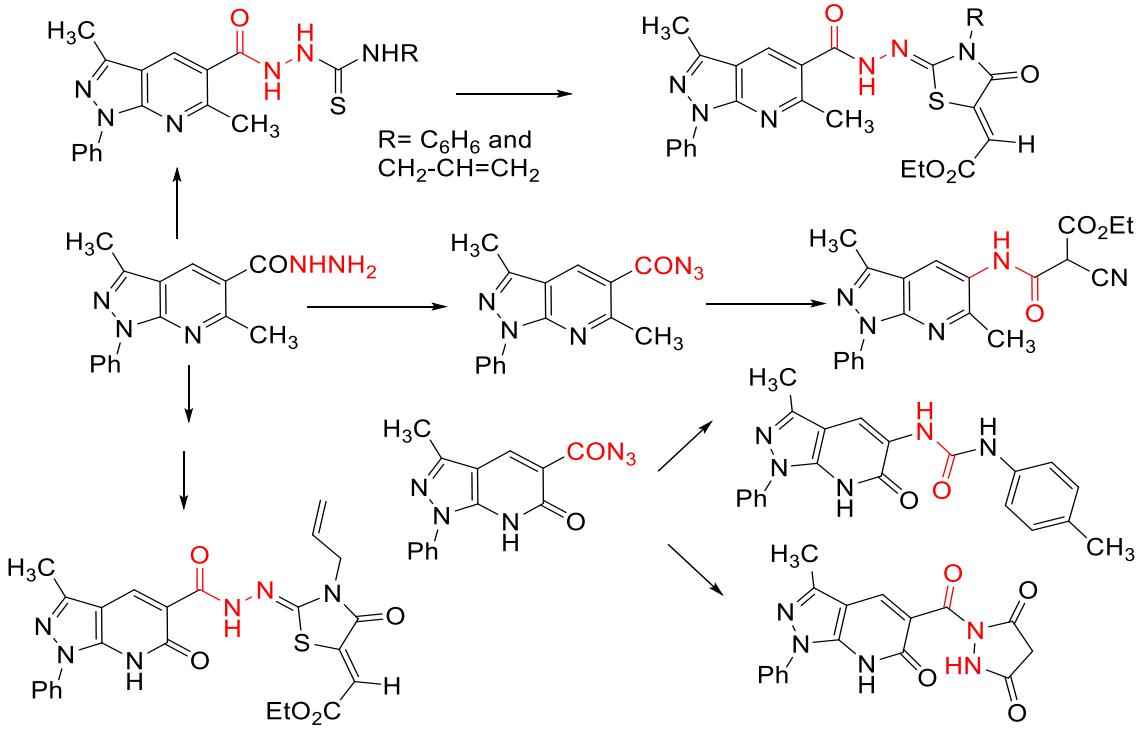
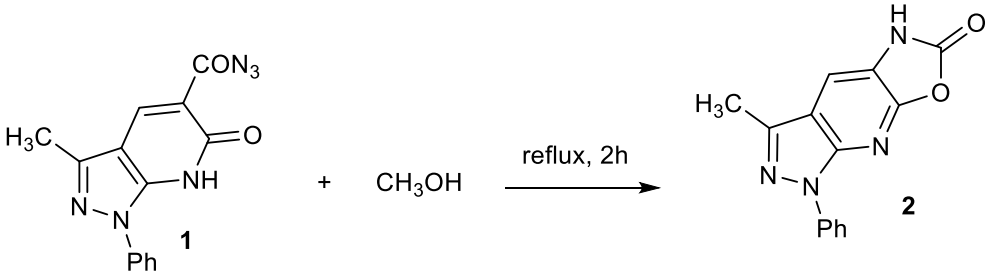


Abstract 5-Carbohydrazides and 5-carbonylazides of pyrazolo[3,4-*b*]pyridines are used to synthesize new heterocyclic derivatives. Some unexpected behaviors are observed in the reactions of the above two species. The structures of the obtained compounds are proved by spectroscopic studies together with elemental and X-ray structure analyses.

Keywords Pyrazolo[3,4-*b*]pyridine-5-carbohydrazides, pyrazolo[3,4-*b*]pyridine-5-carbonylazides, addition, active methylenes, acetylenedicarboxylate, thiazole, X-ray

Introduction

The pyrazolo[3,4-*b*]pyridine ring system has emerged as an important and pharmaceutically relevant scaffold in view of its occurrence as part of bioactive drugs and numerous biologically active compounds.[1] These compounds show a wide spectrum of biological diversity, such as antiviral,[2] anti-inflammatory,[3] anxiolytic,[4] hypoglycemic,[5] antitumor,[6] herbicidal,[7] antiherpetic, and antiallergic.[8] They also act as serotonin re-uptake inhibitors,[9] CCK agonists,[10] vasodilators,[11] potent cyclin dependent kinase 1 inhibitors,[12] HIV reverse transcriptase inhibitors,[13] CCR1 antagonists,[14] and protein kinase inhibitors.[15] Some pyrazolo[3,4-*b*]pyridine-embedded heterocycles are anxiolytic drugs[16] such as cartazolate, etazolate, and tracazolate. They are also present in the cardiovascular therapeutic agent, BAY 41-2272,[17] and in a GSK-3 inhibitor that is efficacious in the treatment of Alzheimer's disease.[18] In addition to their biological importance, their structural similarity to purine, an important constituent of DNA and RNA nucleosides,[18] is an added attraction that increases interest in the synthesis of pyrazolo[3,4-*b*]pyridines. Recently we found that heating 3-methyl-6-oxo-1-phenyl-6,7-dihydro-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonylazide (**1**) in MeOH resulted in a Curtius rearrangement to give 3-methyl-1-phenyl-1,5-dihydro-6*H*-oxazolo[5,4-*b*]pyrazolo[4,3-*e*]-pyridin-6-one (**2**) (Scheme 1).[19]



Scheme 1. Conversion of compound **1** *via* Curtius rearrangement into oxazolo[5,4-*b*]pyrazolo[4,3-*e*]pyridin-6-one **2**

A series of pyrazolopyridine derivatives was described by Geraldo et al.[20] as potential antithrombotic lead molecules due to their optimal inhibitory activity against platelet

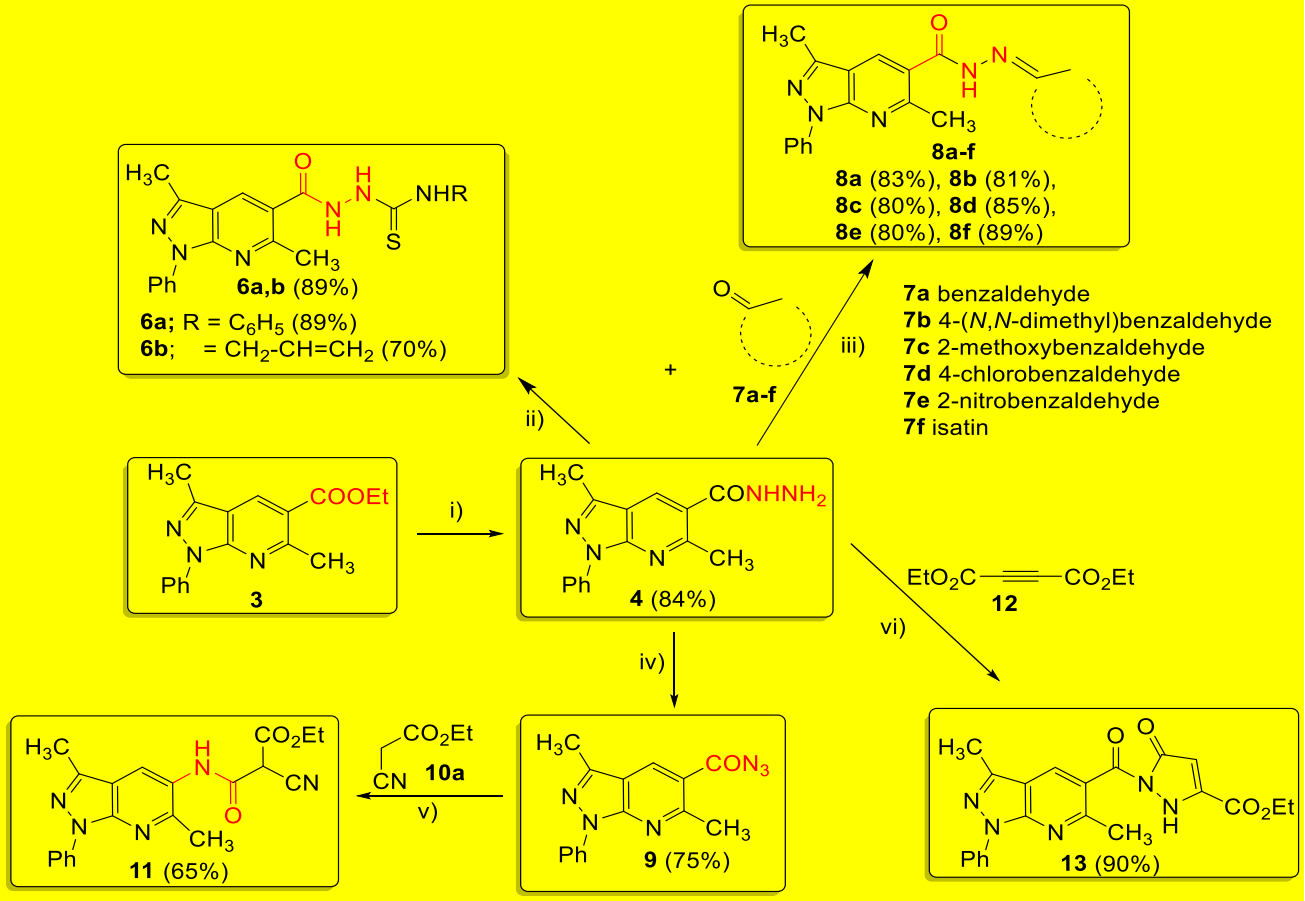
aggregation induced by collagen and arachidonic acid, both potent physiological stimuli for thrombus formation.[20]. In continuation of our work on pyrazolo[3,4-*b*]pyridines,[19,21-25] we aimed to synthesize various derivatives of these compounds including heterocyclic systems from reactions of 3,6-dimethyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbohydrazide (**4**) (see Scheme 2) and 3-methyl-6-oxo-1-phenyl-6,7-dihydro-1*H*-pyrazolo-[3,4-*b*]pyridine-5-carbohydrazide (**15**) (see Scheme 4) with various reagents *via* functional group manipulation. One of these reactions involved the Curtius rearrangement, which has been widely used in organic synthesis due to the utility of isocyanate intermediates.[26]

Results and Discussion

Previously, it was reported that 3,6-dimethyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbohydrazide (**4**) was synthesized by the reaction of pyrazolo[3,4-*b*]pyridine-5-carboxylate [19] with an excess amount of hydrazine hydrate for 5 hours (Scheme 2). In this context, we describe the reaction of compound **4** with various reagents such as phenyl isothiocyanate in order to synthesize a range of heterocyclic derivatives. In refluxing EtOH, the reaction between **4** and phenyl isothiocyanate (**5a**) afforded, after 8 hours, 2-(3,6-dimethyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonyl)-*N*-phenyl-hydrazine-1-carbothioamide (**6a**) in 89% yield (Scheme 2).

In the case of the reaction between **4** and allyl isothiocyanate (**5b**), the reaction proceeded after 10 hours in refluxing EtOH, to give compound **6b** in 70% yield (Scheme 2). The ^{1}H NMR spectrum of **6b** revealed three singlets due to NH protons at δ = 10.57, 8.50, and 8.12 related to to hydrazine-NH-thiourea, hydrazino-amide and NH-CH_2-, respectively. The allyl protons appeared as three multiplets at δ =4.21-4.26 (allyl CH_2N), 5.07-5.16 (allyl CH_2=) and 5.95-6.01 (allyl CH=). The ^{13}C NMR spectrum of **6b** also supported the assigned structure with the appearance of allyl carbon signals at δ = 44.2 (allyl CH_2N), 105.8 (allyl

CH_2=) and 129.3 (allyl CH=), respectively. Besides, the thioamide and carbonyl carbon signals appeared at δ = 178.0 and 164.4, respectively.



Scheme 2. Synthesis and reactions of various pyrazolo[3,4-*b*]pyridine-5-carbohydrazides **4.** *Reagents and conditions:* i) $NH_2NH_2{\cdot}H_2O$, reflux 5h; ii) PhNCS (**5a**) or CH_2=$CHCH_2NCS$ (**5b**), EtOH, reflux 8-10 h; iii) EtOH, piperidine, reflux 8-10 h; iv) $NaNO_2$/HCl, 0-5 ^oC; v) xylene/piperidine, reflux 12 h; vi) toluene, reflux 8 h.

On reacting **4** with various carbonyl compounds **7a-f** in EtOH and catalyzed by piperidine, the corresponding condensed products **8a-f** were obtained (Scheme 2). The distinctive carbons of compound **8b** are shown in Figure 1, whereas the spectroscopic data of compound **8b** is listed in Table 1. In the case of **8f**, the ^1H NMR spectrum showed five singlets at δ = 13.30, 11.20, 8.32, 2.80, and 2.50 related to hydrazine-NH, istatin-NH, pyridine-H-4, pyridine-CH_3, and pyrazole-CH_3, respectively. In ^{13}C NMR spectrum of **8f**, five distinctive carbon signals resonated at δ = 167.9, 165.9, 131.9, 23.9, and 12.2 due to isatin-C=O, hydrazine-CO, pyridine-H, pyridine-CH_3 and pyrazole-CH_3, respectively.

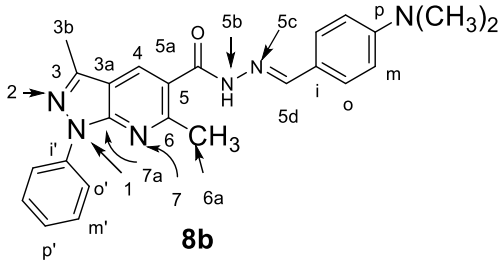


Figure 1. Distinctive carbons of compound (*E*)-**8b**

Table 1. NMR spectroscopic data of **8b**

^{1}H NMR (DMSO-d_6):	**COSY:**	**Assignment**
11.65 (s; 1H)		H-5b
8.50 (s; 1H)		H-4
8.31 (d, *J* = 7.9; 2H)	7.58, *7.33*	H-*o*
8.19 (s; 1H)		H-5d
7.58 ("t", *J* = 7.2; 2H)	8.31, 7.33	H-*m'*
7.56 (d, *J* = 8.6; 2H)	6.78	H-*o*
7.33 (t, *J* = 7.4; 1H)	*8.31*, 7.58	H-*p'*
6.78 (d, *J* = 8.8; 2H)	7.56	H-*m*
2.99 (s; 6H)		NMe_2
2.75 (s; 3H)		H-3b/6a
2.63 (s; 3H)		H-6a/3b

^{15}N NMR (DMSO-d_6):	**HSQC:**	**HMBC:**	**Assignment:**
308.3	2.63		N-7/2
269.1	2.75		N-2/7
177.2	11.65		N-5b
53.2	2.99		**N**Me_2

^{13}C NMR(DMSO-d_6):	**HSQC:**	**HMBC:**	**Assignment:**
163.6	11.65	C-5a	
157.1	8.50, 2.75	C-6(5)	
151.6	8.50, 2.63	C-3	
149.6	2.99	C-*p*	
148.5	8.19	11.65, 8.50, *8.34*	C-5d
143.4	8.50	C-7a	
139.1	8.31, 2.63	C-3a	
130.1	8.50		C-4
129.2	7.58, 7.56	8.31, 8.19	C-*o, m'*
125.5, 125.3, 7.3	8.31, 2.75		C-*p', i'*
121.3 or 121.2	6.78		C-*i*
119.8	8.31	8.31, 7.56, 7.33	C-*o'*
111.8	6.78	6.78, 2.99	C-*m*
39.5	2.99		NMe_2
23.6	2.75, 2.63		C-3b, 6a

Interestingly, the reaction of **4** with $NaNO_2$/HCl led to the formation of compound **9**[19] in 75% yield (Scheme 2). On subjecting compound **9** to reaction with ethyl 2-cyanoacetate

(**10a**) in xylene as the solvent and catalyzed by a few drops of piperidine, the new cyanoester **11** was obtained in 65% yield (Scheme 2). The elemental analysis and mass spectrum of compound **11** were in agreement with its molecular formula ($C_{20}H_{19}N_5O_3$). The ester protons of **11** appeared in the ^{1}H NMR spectrum as a triplet (3H) and a quartet (CH_2) at δ = 1.49 and 3.47, respectively. The carbonyl ester and amide carbons resonated at δ = 164.5 and 163.9, whereas the methyl carbon signals appeared at δ = 12.20, 18.9 and 22.4 for the methyl-ester, methyl-pyrazole and methyl-pyridine, respectively. The proton of the *tert*-carbon (CH) appeared at δ = 4.10 in the ^{1}H NMR spectrum, whereas the corresponding carbon signal appeared at δ = 46.8.

The mechanistic explanation is based upon extrusion of N_2 from **9** under heating to form intermediate **A** (Figure 2). Rearrangement of **A** *via* a Curtius pathway would form isocyanate **B**. Nucleophilic addition of the formed anion, from the deprotonation of **10a** by piperidine, to the carbonyl of the isocyanate would form compound **11** (Figure 2).

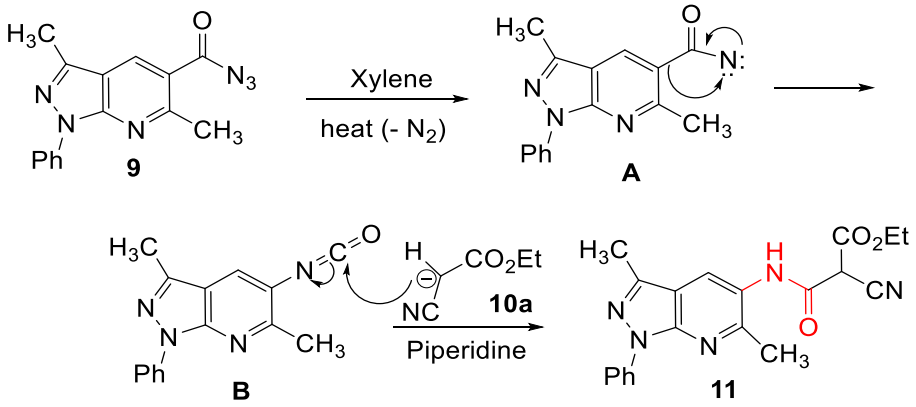
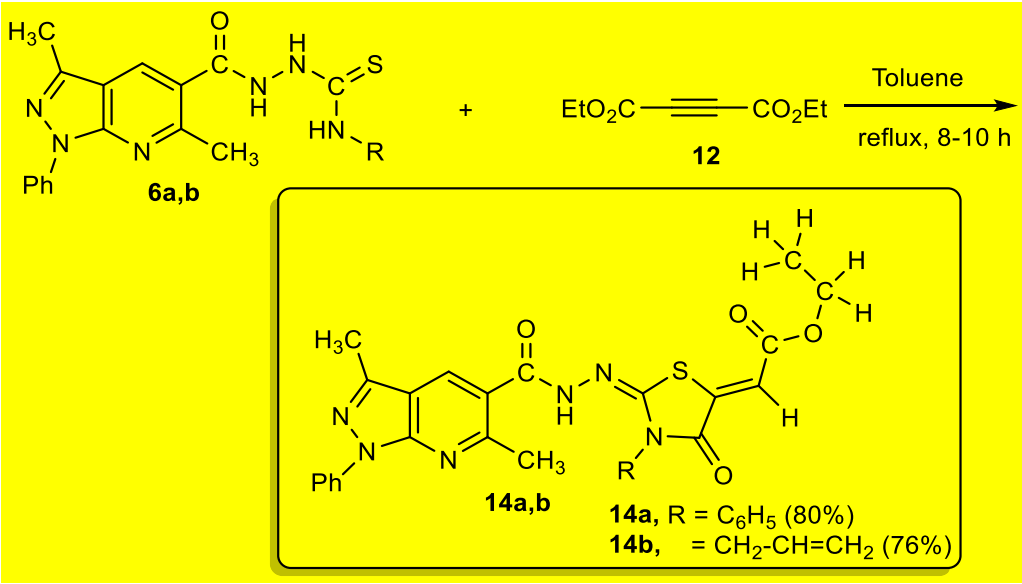


Figure 2. Mechanism for the formation of **11** from the reaction of **9** with **10a**

The reaction of **4** with diethyl acetylenedicarboxylate (**12**) in refluxing toluene gave the corresponding pyrazolone derivative **13** in 90% yield (Scheme 2). The ^{1}H NMR of **13** showed a signal at δ = 11.20 for the pyrazolone-NH proton. The peak at δ = 8.20 corresponded to the pyridine-H-4 proton. The pyrazolone structure was proved by the

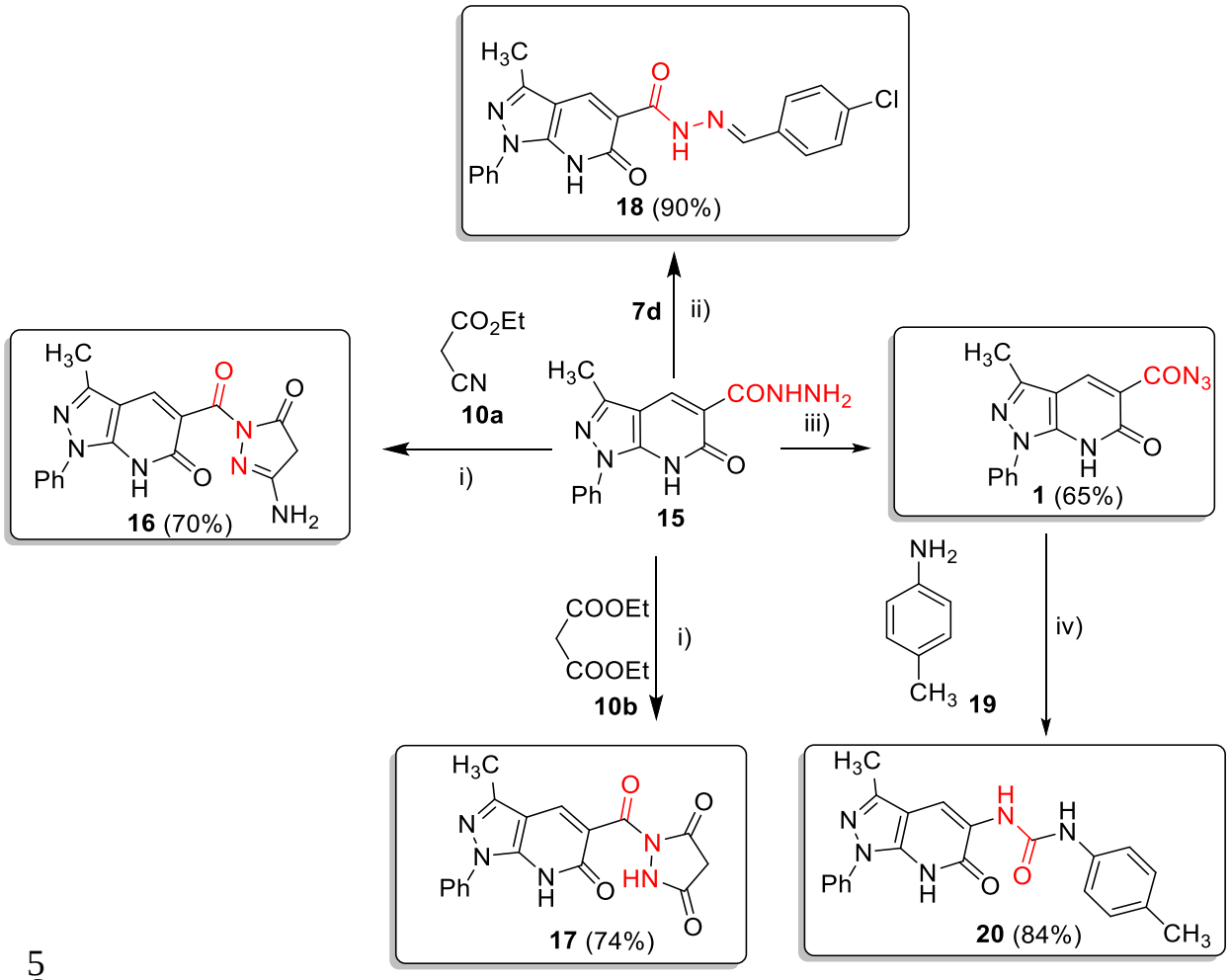
appearance of the pyrazolone-H resonating at δ = 6.82, whereas the ester protons resonated at δ = 1.30 as a triplet (*J* = 7.0 Hz) and at δ = 3.75 as a quartet (*J* = 7.0 Hz). The ester carbon signals appeared in the ^{13}C NMR spectrum at δ = 15.7 (CH_3) and 52.8 (CH_2). In addition, the pyrazolone-CH carbon appeared at δ = 124.6 and the carbonyl-pyrazolone resonated at δ = 163.3 (see the experimental Section).

Similarly, treatment of compounds **6a,b** with **12** afforded the thiazolone derivatives **14a,b** (Scheme 3). For products **14a** and **14b**, the ^{1}H NMR and ^{13}C NMR spectra were found to be in accordance with their proposed structures. For example, the ^{13}C NMR spectrum of **14a** showed three carbon signals at δ = 167.0, 165.9, and 163.0 for the carbonyl-carbons of the ester, thiazolone and carbohydrazine, respectively. Also, three carbon signals for three C=N carbons appeared at δ = 157.2, 152.6, 150.0 (see the experimental section). The ester carbons appeared at δ = 60.8 (CH_2) and δ = 11.6 (CH_3). In the case of **14b**, the ^{13}C NMR spectrum revealed the exocyclic thiazolone-CH at δ = 128.0, whereas the allyl carbons appeared at δ = 43.4 (allyl CH_2N), 103.8 (allyl CH_2=) and 132.1 (allyl CH=).



Scheme 3. Synthesis of 3,6-dimethyl-thiazolopyrazolo[3,4-*b*]pyridines **14a,b**

On reacting the second class of carbonylhydrazide derivative of pyrazolo[3,4-*b*]pyridone **15** [19] with active methylenes such as ethyl 2-cyanoacetate (**10a**) and/or diethyl malonate (**10b**) in AcOH acid and catalyzed by a few drops of conc H_2SO_4, the reaction produced compounds **16** and **17** (Scheme 4).



Scheme 4. Cyclo-condensation and rearrangement reactions of 2-oxo-pyrazolo[3,4-*b*]-pyridine-carbonylhydrazide **15.**
Reagents and conditions: i) AcOH/H_2SO_4, reflux, 10 h; ii) 4-Cl-C_6H_4-CHO, EtOH/piperidine./ reflux, 8 h; iii) $NaNO_2$/HCl, 0-5 ^oC; iv) xylene/piperidine./reflux, 6 h

The ^1H NMR spectrum of **16** showed the pyridone-NH, pyridone-CH-4 and NH_2 protons as three singlets at $\delta = 10.55$ (1H), 8.65 (1H), and 6.30 (2H), respectively. Besides, two other singlets appeared at $\delta = 2.70$, and 2.00 corresponding to pyrazole-CH_2-4 and pyrazole-CH_3 (see the experimental section). The ^{13}C NMR spectrum of **16** showed three distinctive

carbonyl carbon signals of the pyrazolone at δ = 166.8, the carbonylhydrazine at δ = 163.4 and the carbonyl-2-pyridine at δ = 162.3. Most indicative is the presence of the 4*H*-pyrazolone at δ = 2.70 in the ^{1}H NMR spectrum and at δ = 66.3 in the ^{13}C NMR spectrum. In the case of **17**, five singlets apparent in the ^{1}H NMR spectrum at δ = 10.98 (1H), 9.30 (1H), 8.65 (1H), 3.50 (3H) and 2.45 (3H) corresponding to the pyridone-NH, pyrazole-NH, pyridone-H-4, pyridone-CH_3 and pyrazole-CH_3, respectively. In the ^{13}C NMR spectrum, the carbonyl carbon signals resonated at δ = 166.8 (ester), 163.4, 162.3 (pyrazoledione) and 160.0 (pyridone-CH-4).

Reaction of equimolar amounts of the carbohydrazide **15** and *p*-chlorobenzaldehyde (**7d**) in refluxing EtOH, gave yellow crystals of compound **18** in 90% yield. The structure of **18** was proved by NMR spectroscopy. Five singlets appeared at δ = 12.00 (NH-pyridone), 9.00 (carbonylhydrazine), 8.60 (azomethine), 8.15 (pyridinone-H-4) and 2.50 (CH_3), respectively, in the ^{1}H NMR spectrum. The ^{13}C NMR spectrum of **18** revealed the two carbonyl carbon signals at δ = 165.3 and 163.6. The two azomethine carbon signals appeared at δ = 156.9 and 147.6. The *E* form of compound **18** was proved *via* X-ray structure analysis (Figure 3).

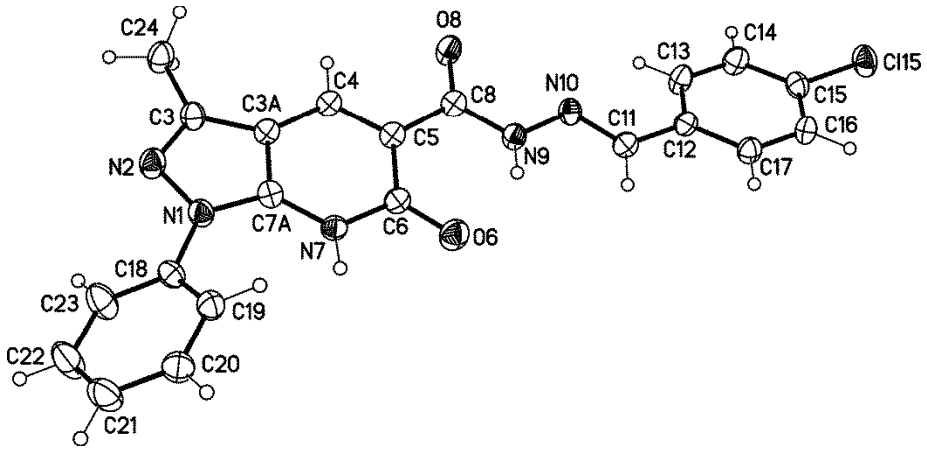
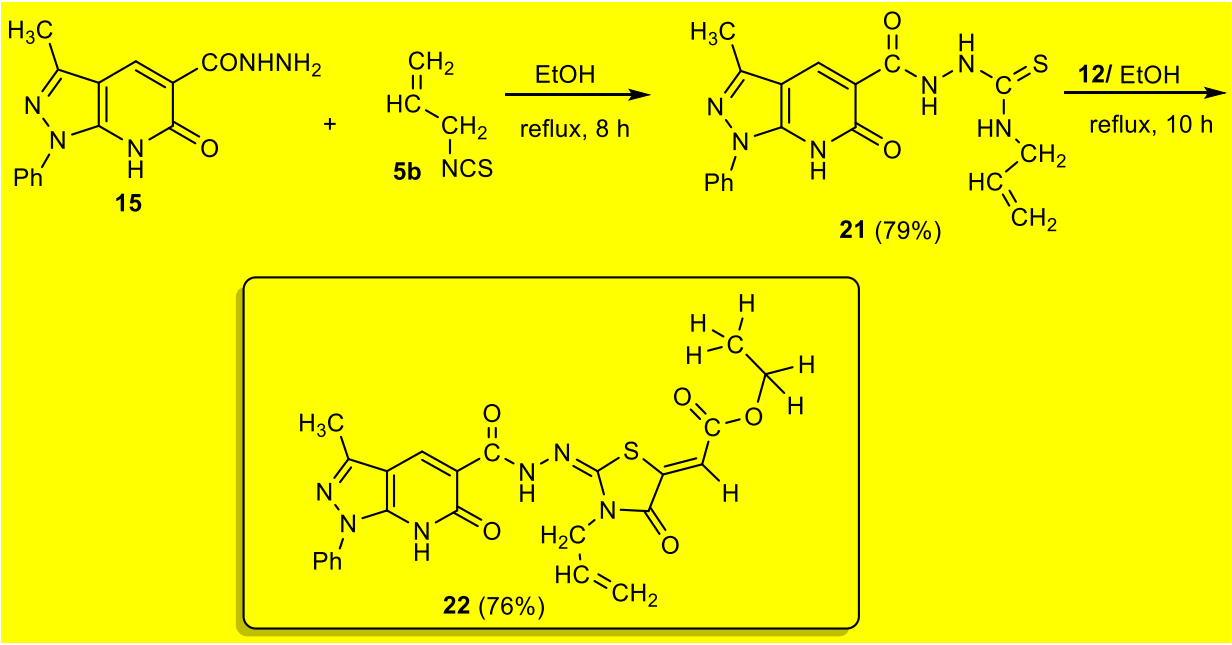


Figure 3. Molecular structure of one of the independent molecules of **18**. (*E*)-*N*'-(4-Chlorobenzylidene)-3-methyl-6-oxo-1-phenyl-3a,6,7,7a-tetrahydro-1*H*-pyrazolo [3,4-*b*]pyridine-5-carbohydrazide (displacement parameters are drawn at the 50% probability level)

Treatment of **15**[19] with $NaNO_2$/HCl at 0-5 °C led to the formation of **1**[19] (Scheme 4). Treatment of **1** with *p*-toluidine (**19**) occurred with thermolysis and extrusion of N_2, accompanied by rearrangement to give urea derivative **20** in 84% yield (Scheme 4). The structure of **20** was confirmed by the presence of six singlets resonating in the ^{1}H NMR spectrum at $\delta = 10.70$ (1H, NH), 9.85 (1H, NH), 8.55 (1H, pyridone-H), 8.25 (1H, NH), 3.35 (3H, CH_3) and 2.35 (3H, CH_3).

For further investigation of the reaction of the carbohydrazine group in compound **15**, we reacted it with allyl isothiocyanate (**5b**) in refluxing EtOH and *N*-allyl-2-(3-methyl-6-oxo-1-phenyl-6,7-dihydro-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonyl)hydrazine-1-carbothioamide (**21**) was obtained in 79% yield (Scheme 5). The ^{1}H NMR spectrum of **21** revealed the four NH protons at $\delta = 11.20$, 9.90, 9.20, and 7.50 (see the experimental section). Three multiplets were also observed at $\delta = 4.26$-4.31, 5.12-5.18, and 5.90-6.94 related to the (allyl CH_2N), (allyl CH_2=) and allyl-CH_2 moieties, respectively. The allyl carbons resonated in the ^{13}C NMR spectrum at $\delta = 46.5$, 106.4 and 134.0. Moreover, the carbothioamide-C, pyridone-C and carbonyl-hydrazine-C resonated at $\delta =$ 178.2, 166.2 and 163.4, respectively. Subsequently, reaction of **21** with **12** in EtOH afforded the corresponding pyrazolo[3,4-*b*]pyridine thiazole derivative **22** in 76% yield (Scheme 5). The ^{1}H NMR spectrum revealed the NH protons at $\delta = 11.15$ and 9.25 assignable to the pyridone-NH and amide-NH, whereas the other NH protons had disappeared indicating that they were involved in the cyclization process. The ester carbon signals appeared at $\delta = 168.7$, 57.0, and 13.5 for the carbonyl-ester, CH_2-ester and CH_3-ester, respectively. Besides, the exocyclic vinyl thiazolidine and the two C=N carbons appeared at $\delta = 135.6$, 154.6 and 153.3, respectively. The structure of compound **22** was finally confirmed by X-ray structure analysis (Figure 4).



Scheme 5. Synthesis of 3-methyl-thiazolopyrazolo[3,4-*b*]pyridin-6-one **22**

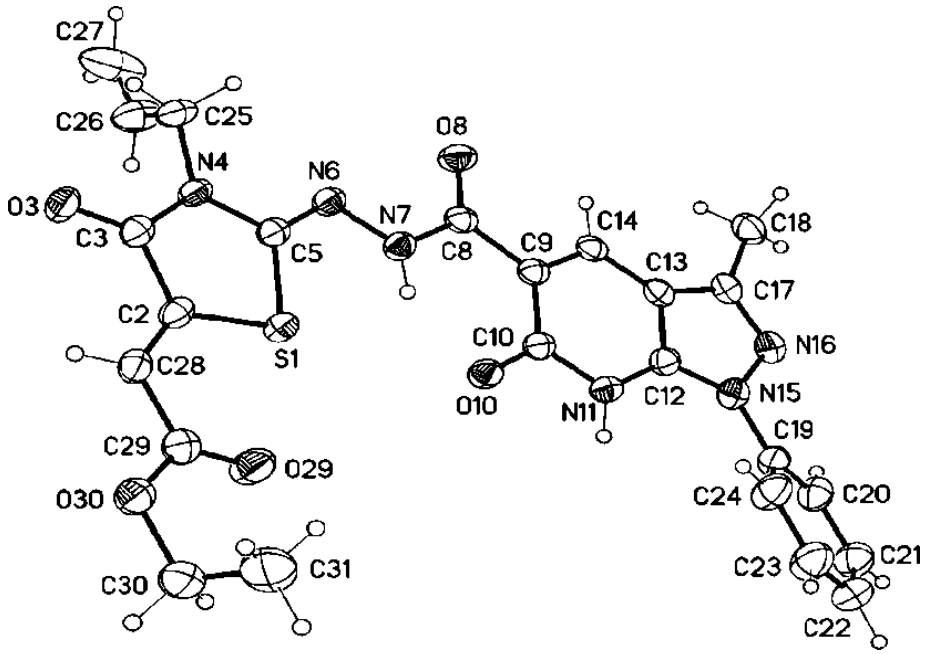


Figure 4. Molecular structure of one of the independent molecules of **22**. Ethyl (*Z*)-2-((*Z*)-3-allyl-2-(2-(3-methyl-6-oxo-1-phenyl-6,7-dihydro-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonyl)-hydrazineylidene)-4-oxothiazolidin-5-ylidene)acetate (displacement parameters are drawn at the 50% probability level)

Conclusion

In conclusion, we have described the utility of carbohydrazides of pyrazolo[3,4-*b*]pyridine as versatile precursors to synthesize various new heterocyclic derivatives, which might be important in different biological and pharmaceutical contexts.

Experimental

General

Melting points were determined using an APP Digital ST 15 melting point apparatus and are uncorrected. TLC analyses were performed using analytical Merck 9385 silica aluminum sheets (Kieselgel 60) with PF_{254} indicator. The IR spectra were recorded as KBr disks on a Shimadzu-408 infrared spectrophotometer, at the Faculty of Science, Minia University. The NMR spectra were measured using a Bruker AV-400 spectrometer at the Karlsruhe Institut für Technologie (KIT), Institute of Organic Chemistry, Karlsruhe, Germany. Chemical shifts are expressed as δ (ppm) with tetramethylsilane as an internal reference. The samples were dissolved in DMSO-d_6, s = singlet, d = doublet, dd = doublet of doublets and t = triplet. Mass spectra were recorded on a Varian MAT 312 instrument in EI mode (70 eV), at the Karlsruhe Institut für Technologie (KIT), Institute of Organic Chemistry, Karlsruhe, Germany. Elemental analyses were obtained out using a Varian Elementary device at the National Research Center, Giza, Egypt.

Starting materials

Compounds **1, 3, 4**, **9**, **12** and **15** were prepared according to literature procedures [19].

Crystal Structure Determinations of 18 and 22

The single-crystal X-ray diffraction studies were carried out on a Bruker D8 Venture diffractometer with a PhotonII CPAD detector at 123(2) K using Cu-Kα radiation (λ = 1.54178 Å). Dual space methods [SHELXT][27] were used for structure solution and refinement was carried out using SHELXL-2014 (full-matrix least-squares on F^2).[28] Hydrogen atoms were refined using a riding model (H(N, O) free). Semi-empirical absorption corrections were applied. In **18**, refinement with the listed atoms shows residual electron density due to two heavily disordered EtOH solvent molecules in the unit cell,

which could not be refined with a split atom model. Therefore, the option "SQUEEZE" of the program package PLATON[29] was used to create a hkl file taking into account the residual electron density in the void areas (see cif-file for details).

18: Yellow crystals, $C_{21}H_{16}ClN_5O_2 \cdot 2\ H_2O) \cdot ½\ C_2H_6O$, M_r = 464.90, crystal size 0.24 × 0.04 × 0.02 mm, triclinic, space group *P-1* (No. 2), a = 7.7981(2) Å, b = 17.1490(5) Å, c = 18.6509(5) Å, α = 62.718(2)°, β = 82.813(2)°, γ = 89.055(2)°, V = 2196.95(11) Å^3, Z = 4, ρ = 1.406 Mg/m^{-3}, μ(Cu-K$_\alpha$) = 1.906 mm^{-1}, F(000) = 972, $2\theta_{max}$ = 145.2°, 30237 reflections, of which 8623 were independent (R_{int} = 0.057), 597 parameters, 16 restraints, R_1 = 0.048 (for 6556 I > 2σ(I)), wR_2 = 0.123 (all data), S = 1.03, largest diff. peak / hole = 0.832 / -0.302 e Å^{-3}.

22: Yellow crystals, $C_{24}H_{22}N_6O_5S \cdot 2\ H_2O$, M_r = 542.57, crystal size 0.20 × 0.06 × 0.03 mm, monoclinic, space group *P2$_1$/n* (No. 14), a = 9.9686(4) Å, b = 22.6653(10) Å, c = 22.4652(10) Å, β = 97.078(2)°, V = 5037.1(4) Å^3, Z = 8, ρ = 1.431 Mg/m^{-3}, μ(Cu-K$_\alpha$) = 1.638 mm^{-1}, F(000) = 2272, $2\theta_{max}$ = 144.2°, 55336 reflections, of which 9920 were independent (R_{int} = 0.042), 723 parameters, 16 restraints, R_1 = 0.067 (for 8138 I > 2σ(I)), wR_2 = 0.180 (all data), S = 1.10, largest diff. peak / hole = 0.674 / -0.352 e Å^{-3}.

CCDC 1905952 (**18**) and CCDC 1905953 (**22**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Preparation of compounds 6a,b.

A mixture of compound **4** (0.50 g, 1.77 mmol) and **5a** (0.24 g, 1.77 mmol) or **5b** (0.18 g, 1.77 mmol) was heated under reflux for 8-10 h in EtOH. The solution was cooled, poured onto ice cold water and the obtained products **6a,b** were filtered off, washed with water, dried and were recrystallized from the stated solvents

2-[(3,6-Dimethyl-*1*-phenyl-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl)carbonyl]-*N*-phenylhydrazine-carbothioamide (6a).

White fine crystals (dioxane–water; 4:1), 0.66 g (89%); M.p. 240-241 ºC; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.50 (s, 1H, NHPh), 9.80 (s, 1H, NH-C=S), 8.50 (s, 1H, NHCO), 8.30 (s, 1H, pyridine-H), 7.70-7.00 (m, 10H, Ph-H), 3.20 (s, 3H, CH_3-6), 2.40 (s, 3H, CH_3-3); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 180.0 (C=S), 165.9 (C=O), 159.3, 154.6 (C=N), 150.0, 149.7, 144.2 (Ar-C), 139.0 (pyridine-CH), 138.2, 137.6 (Ar-C), 128.2, 128.0, 127.6, 127.0 (Ar-2CH), 120.0, 114.6 (Ar-CH), 24.0, 14.2 (CH_3). IR (KBr): ν = 3447 (NH), 3137 (NH), 3020-3010 (Ar-CH), 2918 (Aliph-CH), 1679 cm^{-1} (CO); MS (70 eV, %): *m/z* = 417 (M+1) (15), 250 (80), 109 (59), 97 (100), 95 (75). Anal. Calcd. $C_{22}H_{20}N_6OS$ (416.50): C, 63.44; H, 4.84; N, 20.18. Found: C, 63.20; H, 4.60; N, 20.00

2-[(3,6-Dimethyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl)carbonyl]-*N*-(prop-2-en-1-yl)hydrazinecarbothioamide (6b).

White fine crystals (EtOH), 0.47 g (70%); Mp 204 ºC; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.57 (s, 1H, NHPh), 8.50 (s, 1H, NHCO), 8.12 (s, 1H, $NHCH_2$), 8.05 (s, 1H, pyridine-H), 7.66-7.40 (m, 5H, Ph-H), 5.95-6.01 (m, 1H, allyl CH=), 5.07-5.16 (m, 2H, allyl CH_2=), 4.21-4.26 (m, 2H, Allyl CH_2N), 3.25 (s, 3H, pyridine-CH_3), 2.50 (s, 3H, pyrazole-CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 178.0 (C=S), 164.4 (C=O), 160.8, 156.4 (C=N), 153.0, 151.6, 146.0, 134.8, 134.0 (Ar-C), 131.6 (pyridine-CH), 129.3 (allyl-CH=), 126.0, 125.5 (Ar-2CH), 119.8 (Ar-CH), 105.8 (allyl-CH_2=), 44.2 (Allyl-CH_2), 24.6, 15.0 (CH_3). IR (KBr): ν = 3376 (NH), 3176 (NH), 3070 (Ar-CH), 2921 (Aliph-CH), 1683 cm^{-1} (CO). Anal. Calcd. for $C_{19}H_{20}N_6OS$ (380.47): C, 59.98; H, 5.30; N, 22.09. Found: C, 59.80; H, 5.05; N, 21.90.

Preparation of condensed products 8a-f

A mixture of compound **4** (0.50 g, 1.8 mmol) and carbonyl compounds **7a-f** (1.8 mmol) was heated under reflux in EtOH (20 mL) and a few drops of piperidine for 8-10 h. The reaction mixture was poured-onto ice cold water (200 mL) and the products **8a-f** were filtered off, washed with water and recrystallized from the stated solvents.

(*E*)-*N*'-Benzylidene-3,6-dimethyl-*1*-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbohydrazide (8a)

Buff needles [dioxane-water (2:1)], 0.54 g (83%); Mp: 244-246 ^{o}C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.00 (s, 1H, NH), 8.70 (s, 1H, pyridine), 8.43 (s, 1H, CH=N), 7.70-7.35 (m, 10H, Ar-H), 2.55 (s, 3H, CH_3), 2.45 (s, 3H, CH_3). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 165.9 (C=O), 164.1, 161.3 (C=N), 154.1 (CH=N), 149.7, 148.5, 147.2 (Ar-C), 138.8 (pyridine-CH), 136.1, 135.4 (Ar-2C), 129.9, 128.4, 127.2, 125.5 (Ar-2CH), 120.2, 118.7 (Ar-CH), 17.9 (CH_3), 14.1 (CH_3). IR (KBr): ν = 3206 (NH), 3045 (Ar-CH), 2922 (Aliph-CH), 1680 (CO) cm^{-1}; MS (70 eV, %): *m/z* = 369 (M^+, 35), 295 (28), 250 (100). Anal. Calcd for $C_{22}H_{19}N_5O$ (369.42): C, 71.53; H, 5.18; N, 18.96. Found: C, 71.70; H, 5.40; N, 18.73

(*E*)-*N*'-(4-(Dimethylamino)benzylidene)-3,6-dimethyl-*1*-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbohydrazide (8b)

Yellow crystals (EtOH), 0.59 g (81%); M.p 310-312 ^{o}C; NMR: (DMSO-d_6): see Table 1. IR (KBr): ν = 3169 (NH), 2916 (Aliph-CH), 1656 (CO) cm^{-1}; MS (70 eV, %): *m/z* = 412 (M^+, 88), 250 (28), 154 (100). Anal. Calcd. for $C_{24}H_{24}N_6O$ (412.49): C, 69.88; H, 5.86; N, 20.37. Found: C, 69.70; H, 5.65; N, 20.40

(*E*)-*N*'-(2-Methoxybenzylidene)-3,6-dimethyl-*1*-phenyl-1*H*-pyrazolo-[3,4-*b*]pyridine-5-carbohydrazide (8c).

Yellow crystals (EtOH), 0.57 g (80%); Mp: 230-232ºC; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.60 (s, 1H, NH), 8.90 (s, 1H, Ar-CH-b), 8.65 (s, 1H, pyridine-H), 8.30 (s, 1H, CH=N), 7.50-6.75 (m, 8H, Ph-H), 3.40 (s, 3H, OCH_3), 2.70 (s, 3H, CH_3), 2.40 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 165.9 (C=O), 159.3 (C=N), 154.8 (Ar-C), 151.6 (C=N), 144.6 (Ar-C), 142.4 (CH=N), 140.7, 139.2, 138.8, 138.2 (Ar-C), 138.0 (pyridine-CH), 132.8, 131.6, 129.0 (Ar-2CH), 126.8, 126.4, 116.5 (Ar-CH), 56.0 (OCH_3), 22.1, 14.1 (CH_3). IR (KBr): ν = 3176 (NH) 2995 (Aliph-CH), 1647 (CO). Anal. Calcd for $C_{23}H_{21}N_5O_2$ (399.45): C, 69.16; H, 5.30; N, 17.53. Found: C, 69.30; H, 5.52; N, 17.35

(*E*)-*N'*-(4-Chlorobenzylidene)-3,6-dimethyl-*1*-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbohydrazide (8d).

Buff crystals [(dioxane- EtOH (3:1)], 0.60 g (85%); Mp: 280-282 ºC; ^{1}H NMR: (400 MHz, DMSO-d_6): δ = 12.10 (s, 1H, NH), 8.60 (s, 1H, pyridine), 8.12 (s, 1H, CH=N), 7.80-7.22 (m, 9H, Ph-H), 2.80 (s, 3H, CH_3), 2.52 (s, 3H, CH_3), ^{13}C NMR (100 MHz, DMSO-d_6): δ = 164.2 (C=O), 157.2, 152.4 (C=N), 147.6 (CH=N), 143.3, 142.4, 138.4, 137.4, 136.4 (Ar-C), 132.4 (pyridine-CH), 131.6, 128.4, 127.6, 126.5 (Ar-2CH), 120.7 (Ar-CH), 116.7 (Ar-C), 17.9, 15.2 (CH_3). IR (KBr): ν = 3224 (NH), 3044 (Ar-CH), 2920 (Aliph-CH), 1644 (CO) cm^{-1} Anal. Calcd for $C_{22}H_{18}ClN_5O$ (403.86): C, 65.43; H, 4.49, N, 17.34. Found: C, 65.20; H, 4.60; N, 17.20

(*E*)-*N'*-(2-Nitrobenzylidene)-3,6-dimethyl-*1*-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbohydrazide (8e).

Buff crystals (EtOH), 0.58 g (80%); Mp: 220-222 ºC; ^{1}H NMR (400 MHz, DMSO-d_6): δ =12.10 (s, 1H, NH), 8.90 (s, 1H, pyridine-H), 8.75 (s, 1H, CH=N), 7.80-7.20 (m 9H, Ph-H), 2.75 (s, 3H, CH_3), 2.20 (s, 3H, CH_3); ^{3}C NMR (100 MHz, DMSO-d_6): δ = 164.3 (C=O), 157.3, 149.7 (C=N), 148.2 (CH=N), 143.5, 139.1, 138.4 (Ar-C), 133.8 (pyridine-CH),

132.4, 130.6 (Ar-C), 128.7 (Ar-2CH), 125.6, 124.4 (Ar-CH), 123.2 (Ar-C), 122.7, 115.6 (Ar-2CH), 23.8, 12.2 (CH_3). IR (KBr): ν = 3185 (NH), 3030 (Ar-CH), 2916 (Aliph-CH), 1645 (CO). MS (70 eV, %): *m/z* = 414 (M^+, 93), 250 (43), 136 (65). Anal. Calcd for $C_{22}H_{18}N_6O_3$ (414.42): C, 63.76; H, 4.38; N, 20.28. Found: C, 63.70; H, 4.42; N, 20.53.

(*E*)-3,6-dimethyl-*N'*-(2-oxoindolin-3-ylidene)-*1*-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbohydrazide (8f).

Orange crystals (CH_3CN), 0.64 g (89%); M.p: 280-282 °C; ^{1}H NMR: (400 MHz, DMSO-d_6): δ = 13.30 (s, 1H, NH), 11.20 (s, 1H, NH isatin), 8.32 (s, 1H, pyridine), 7.60-6.95 (m, 9H, Ar-H), 2.80 (s, 3H, CH_3), 2.50 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 167.9, 165.9 (C=O), 162.6, 158.4, 149.8, (C=N), 143.7, 142.5, (Ar-C), 141.0 (Ar-2CH), 138.9, 133.0, 132.4 (Ar-C), 131.9 (pyridine-CH), 127.6, 125.6, 124.4 (Ar-2CH), 116.2 (Ar-CH), 111.2 (Ar- C), 23.9, 12.2 (CH_3). IR (KBr): ν = 3251 (NH), 3050 (Ar-CH), 2917 (Aliph-CH), 1700-1684 (CO) cm^{-1}; MS (70 eV, %): *m/z* = 410 (M^+, 46), 250 (77), 154 (100). Anal. Calcd. for $C_{23}H_{18}N_6O_2$ (410.43): C, 67.31; H, 4.42; N, 20.48. Found: C, 67.50; H, 4.52; N, 20.25

Reaction of 9 with ethyl cyanoacetate (10a)

A mixture of compound **9** (0.50 g, 1.7 mmol) and ethyl cyanoacetate **10a** (0.19 g, 1.7 mmol) in xylene containing piperidine (0.3 mL), was heated under reflux for 12 h. The solution was cooled, poured onto petroleum ether (100 mL) and the product **11** was filtered off, washed with petroleum ether, and dried.

Ethyl 2-(3,6-dimethyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridin-5-ylcarbamoyl)-2-cyanoacetate (11)

White fine crystals (DMF-H_2O; 2:1), 0.40 g (65%); Mp 320-322 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.58 (s, 1H, NH), 8.29 (s, 1H, pyridine-H), 7.53-7.49 (m 5H, Ph-H), 4.10 (s,

1H, CH), 3.47 (q, 2H, *J* = 7.0 Hz, CH_2), 2.67 (s, 3H, CH_3), 2.55 (s, 3H, *J* = 7.0, CH_3), 1.49 (t, 3H, *J* = 7.0 Hz, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 164.5 (CO-ester), 163.9 (CO-amide), 152.4, 150.0 (C=N), 142.8, 139.9, 136.5 (Ar-C), 134.4 (pyridine-CH), 127.9 (Ar-C), 124.4, 123.5 (Ar-2CH), 115.2 (Ar-CH), 112.4 (CN), 62.0 (CH_2-ester), 46.8 (CH), 22.4, 18.9, 12.20 (CH_3). IR (KBr): ν = 3265 cm^{-1} (NH) 2920 (Aliph-CH), 1696 cm^{-1} (CO-ester). MS (70 eV, %): *m/z* = 376 (M-1, 19), 307 (16), 154 (100). Anal. Calcd for $C_{20}H_{19}N_5O_3$ (377.40): C, 63.65; H, 5.07; N, 18.56. Found: C, 63.40; H, 5.25; N, 18.20

Reaction of 4 with diethyl acetylenedicarboxylate (12)

A mixture of **4** (2.81 g, 10 mmol) with **12** (1.7 g, 10 mmol) in toluene was heated under reflux for 8 h. The solution was cooled, poured onto petroleum ether (60/80) (100 mL) and the product **13** was then filtered off, washed with petroleum ether and dried.

Ethyl 1-(3,6-dimethyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonyl)-5-oxo-2,5-dihydro-1*H*-pyrazole-3-carboxylate (13)

Fine buff crystals of **13** (EtOH), 0.64 g (90%); Mp 340-342 °C; ^1H NMR (400 MHz, DMSO-d_6): δ = 11.20 (s, 1H, pyrazole-NH), 8.20 (s, 1H, pyridine-H), 7.90-7.87 (m 2H, Ph-H), 7.25-7.22 (m, 3H, Ph-H), 6.82 (s, 1H, pyrazolone-H), 3.75 (q, 2H, *J* = 7.0 Hz, CH_2), 2.97 (s, 3H, CH_3), 2.25 (s, 3H, CH_3), 1.30 (t, 3H, *J* = 7.0 Hz, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 164.7 (CO-ester), 163.3 (CO-N-pyrazolone), 162.4 (pyrazolone-C-3), 154.4, 151.0 (C=N), 141.2, 140.5, 138.8, 138.2, 136.5 (Ar-C), 134.4 (pyridine-CH), 128.4, 126.7 (Ar-2CH), 124.6 (pyrazolone-CH), 118.0 (Ar-CH), 52.8 (CH_2-ester), 23.4, 18.9, 15.70 (CH_3). IR (KBr): ν = 3121 cm^{-1} (NH), 3029 (Ar-CH), 2976 (Aliph-CH), 1732, 1690-1680 cm^{-1} (CO- ester). Anal. Calcd for $C_{21}H_{19}N_5O_4$ (405.41): C, 62.22; H, 4.72; N, 17.27. Found: C, 62.00; H, 4.55; N, 17.07.

Reaction of 6a,b with 12; Synthesis of compounds 14a,b

A mixture of **6a** or **6b** (10 mmol) with **12** (1.7 g, 10 mmol) in toluene (100 mL) was heated under reflux for 8-10 h. The solution was cooled, and the solid products **14a,b** were filtered off, washed with water, dried and recrystallized from the stated solvents.

Ethyl 2-(2-(3,6-dimethyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonyl)hydrazono)-4-oxo-3-phenylthiazolidine-5-ylidene)acetate (14a).

Yellow crystals (dioxane); 0.51 (80%), Mp 284-286 ^{o}C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.20 (s, 1H, pyrazole-NH), 8.50 (s, 1H, pyridine-H), 8.23-8.20 (m, 2H, Ph-H), 7.60-7.45 (m 8H, Ph-H), 6.80 (s, 1H, exovinyl-H), 3.75 (q, 2H, *J* = 7.0 Hz, CH_2), 2.65 (s, 3H, pyridinone-CH_3), 2.25 (s, 3H, pyrazole-CH_3), 1.30 (t, 3H, *J* = 7.0 Hz, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 167.0 (CO-ester), 165.9 (thiazolone-C), 163.0 (hydrazine-CO), 157.2, 152.6, 150.0 (C=N), 142.0, 141.5, 139.8, 138.2, 136.5 (Ar-C), 134.4 (pyridine-CH), 133.0 (exovinyl-C=) 129.4, 128.2, 127.6, 126.7 (Ar-2CH), 124.6 (pyrazolone-CH), 112.6, 111.6 (Ar-CH), 60.8 (CH_2-ester), 23.4, 18.9, 11.6 (CH_3). IR (KBr): ν = 3229 (NH), 3051 (Ar-CH), 2916 (Aliph-CH), 1726, 1680 cm^{-1} (CO-ester). Anal. Calcd for $C_{28}H_{24}N_6O_4S$ (540.59): C, 62.21; H, 4.47; N, 15.55. Found: C, 62.00; H, 4.23; N, 15.31

Ethyl 2-(3-allyl)-2-(3,6-dimethyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonyl)hydrazono)-4-oxothiazolidine-5-ylidene)acetate (14b).

Yellow crystals (EtOH), 0.50 (76%), Mp 226-228 ^{o}C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.50 (s, 1H, pyrazole-NH), 8.65 (s, 1H, pyridine-H), 8.20-8.15 (m, 2H, Ph-H), 7.50-7.46 (m 3H, Ph-H), 6.83 (s, 1H, exovinyl-H), 5.96-5.94 (m, 1H, Allyl-CH=), 5.09-5.07 (m, 2H, Allyl-CH_2=), 4.18 (q, 2H, *J* = 7.0 Hz, CH_2-ester), 3.20-3.18 (m, 2H, Allyl-CH_2), 2.75 (s, 3H, pyridinone-CH_3), 2.30 (s, 3H, pyrazole-CH_3), 1.30 (t, 3H, *J* = 7.0 Hz, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 167.2 (CO-ester), 165.4 (thiazolone-C), 163.0 (hydrazine-CO), 155.0, 152.1, 150.4 (C=N), 141.3, 139.4, 138.6, 138.2 (Ar-C), 134.4 (pyridine-CH), 132.1

(Allyl-CH=), 128.0 (exovinyl-C=), 124.5, 123.2 (Ar-2CH), 124.8 (pyrazolone-CH), 113.6 (Ar-CH), 103.8 (Allyl-CH_2=), 60.8 (CH_2-ester), 43.4 (Allyl-CH_2), 23.4, 16.9, 13.6 (CH_3). IR (KBr): ν = 3243 cm^{-1} (NH), 3060 (Ar-CH), 2981 (Aliph-CH), 1719 cm^{-1} (CO- ester). Anal. Calcd for $C_{25}H_{24}N_6O_4S$ (504.56): C, 59.51; H, 4.79; N, 16.66. Found: C, 59.30; H, 4.55; N, 16.42

Preparation of compound 16 or 17

A mixture of the carbohydrazide **15** (0.50 g, 1.8 mmol) and **10a** (0.2 g, 1.8 mmol) or **10b** (0.28 g, 1.8 mmol) was heated under reflux for 10-12 h in acetic acid (20 mL) and a few drops of sulfuric acid. The solution was cooled and poured onto ice-cold water (100 mL). The products **16** or **17** were filtered off, washed with water, dried, and crystallized from the stated solvents.

5-(3-Amino-5-oxo-4,5-dihydro-1*H*-pyrazole-1-carbonyl)-3-methyl-1-phenyl-1,7-dihydro-6*H*-pyrazolo[3,4-*b*]pyridine-6-one (16).

Yellow crystals (dioxane: EtOH: H_2O; 3:1:1), 0.43 g (70%); Mp 270- 272 ^oC; ^1H NMR (400 MHz, DMSO-d_6): δ = 10.55 (s, 1H, pyridone-NH), 8.65 (s, 1H, pyridone-CH-4), 7.95-7.35 (m 5H, Ph-H), 6.30 (s, 2H, NH_2), 2.70 (s, 2H, CH_2), 2.00 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 166.8, 163.4, 162.3 (C=O), 154.6, 148.9 (C=N), 145.2 (Ar-C), 142.8, 137.8 (Ar-C), 136.2 (pyridone-CH), 130.1 (Ar-C), 129.0, 126.1 (Ar-2CH), 121.7 (Ar-CH), 66.3 (CH_2), 14.6 (CH_3). IR (KBr): ν = 3307 cm^{-1} (NH_2), 3020 (Ar-CH), 2917 cm^{-1} (Aliph-CH), 2226 cm^{-1} (CN), 1708 (CO), 1660 cm^{-1} (CO-pyridone). Anal. Calcd. for $C_{17}H_{14}N_6O_3$ (350. 34): C, 58.28; H, 4.03; N, 23.99. Found: C, 58.46; H, 4.35; N, 23.65

1-(3-Methyl-6-oxo-1-phenyl-6,7-dihydro-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonyl)pyrazolidine-3,5-dione (17).

Grey crystals (EtOH), 0.46 g (74%); Mp 310-312 ^{o}C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.98 (s, 1H, pyridone-NH), 9.30 (s, 1H, pyrazole-NH), 8.65 (s, 1H, pyridone-H), 8.00-7.25 (m 5H, Ph-H), 3.50 (s, 2H, CH_2), 2.45 (s, 3H, CH_3). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 166.8, 163.4, 162.3, 160.0 (C=O), 145.2 (C=N), 143.4, 142.0, 138.9 (Ar-C), 134.2 (pyridone-CH), 129.1 (Ar-C), 126.0, 124.5 (Ar-2CH), 121.0 (Ar-CH), 64.3 (CH_2-ester), 14.6 (CH_3). IR (KBr): ν = 3146 cm^{-1} (NH), 3043 cm^{-1} (Ar-CH), 2922 cm^{-1} (Aliph.-CH), 1702-1660 cm^{-1} (CO). Anal. Calcd. for $C_{17}H_{13}N_5O_4$ (351. 32): C, 58.12; H, 3.73; N, 19.93. Found: C, 58.26; H, 3.55; N, 19.65.

Reaction of 15 with *p*-chlorobenzaldehyde (7d)

Amixture of the carbohydrazide **15** (0.50 g, 1.8 mmol) and 4-chlorobenzaldehyde **7d** (0.25 g, 1.8 mmol) was heated under gentle reflux for 10 h in EtOH and a few drops of piperidine. The solution was cooled, poured onto ice cold water (100 mL), and the product **18** was filtered off, washed with water (100 mL) and dried.

(14*E*)-*N*'-(4-Chlorobenzylidene)-6,7-dihydro-3-methyl-6-oxo-*1*-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbohydrazide (18).

Yellow crystals (EtOH), 0.64 g (90%), Mp 224-226 ^{o}C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.00 (s, 1H, NH), 9.00 (s, 1H, NH), 8.60 (s,1H, CH=N), 8.15 (s,1H, pyridone-H), 7.70-7.15 (m, 9H, Ph-H), 2.50 (s, 3H, CH_3). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 165.3, 163.6 (C=O), 156.9 (C=N), 147.6 (CH=N), 140.0, 139.6, 138.7 (Ar-C), 133.4 (pyridone-CH), 134.2, 133.6, 132.3 (Ar-C), 128.4, 128.0, 124.7, 123.2 (Ar-2CH), 122.0 (Ar-CH), 18.4 (CH_3). IR (KBr): ν = 3438 (NH), 3048 (Ar-CH), 2917 (Aliph-CH), 1710-1660 (CO) cm^{-1}. Anal. Calcd. for $C_{21}H_{16}ClN_5O_2$ (405.84): C, 62.15; H, 3.97; N, 17.26. Found: C, 62.36; H, 3.75; N, 17.45.

Reaction of 1 with *p*-toluidine (19)

A mixture of compound **1** (0.50 g, 1.7 mmol) and *p*-toluidine **19** (0.18 g, 1.8 mmol) was heated under reflux for 6 h in xylene (30 mL) and iperidine (0.2 mL). The solution was cooled, poured onto petroleum ether (60/80 ^{o}C) (100 mL) and the product **20** was filtered off and dried.

Dihydro-3-methyl-6-oxo-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl)-3-*p*-tolylurea (20).

Fine buff crystals EtOH-H_2O (2:1), 0.63g (84%); Mp 245-247 ^{o}C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.70 (s, 1H, NH), 9.85 (s, 1H, NH), 8.55 (s, 1H, pyridone-H), 8.25 (s, 1H, NH), 7.95-6.95 (m 9H, Ph-H), 3.35 (s, 3H, CH_3), 2.35 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 167.3, 163.0 (C=O), 157.4 (C=N), 145.2, 144.4 , 139.2, 138.6, 137.4 (Ar-C), 135.1 (pyridone-CH), 134.1 (Ar-C), 131.7, 129.4, 123.2, 122.8 (Ar-2CH), 121.8 (Ar-CH), 24.2, 12.5 (CH_3). IR (KBr): ν = 3428, 3176 (NH), 3061 (Ar-CH), 2918 (Aliph-CH), 1710-1660 cm^{-1} (CO). Anal. Calcd for $C_{21}H_{19}N_5O_2$ (373.41): C, 67.55; H, 5.13; N, 18.76. Found: C, 67.46; H, 5.05; N, 18.65.

Reaction of 15 with 5b

A mixture of compound **15** (2.83 g, 10 mmol) and **5b** (1.7 g, 10 mmol) was heated under reflux for 8 h in EtOH (20 mL). The solution was cooled, poured onto water and the product **21** was filtered off and dried.

2-[(3-Methyl-6-oxo-1-phenyl-6,7-dihydro-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl)-carbonyl]-*N*-(prop-2-en-1-yl)-hydrazinecarbothioamide (21).

Fine white crystals (EtOH); 0.53 g (79%); Mp 236-238 ^{o}C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.20 (s, 1H, NH), 9.90 (s, 1H, NH), 9.20 (s, 1H, NH), 8.45 (s, 1H, pyridone-H), 7.50 (s, 1H, NH), 7.34-7.32 (m 2H, Ph-H), 7.20-7.15 (m, 3H, Ph-H), 5.94-5.90 (m, 1H, Allyl-CH=), 5.18-5.12 (m, 2H, Allyl-CH_2=), 4.31-4.26 (m, 2H, Allyl-CH_2), 2.35 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 178.2 (C=S), 166.2, 163.4 (C=O), 154.6 (C=N),

153.5, 143.0, 142.4, 140.0 (Ar-C), 134.0 (pyridone-CH), 134.0 (Allyl-CH=), 124.4, 123.6 (Ar-2CH), 114.6 (Ar-CH), 106.4 (Allyl-CH_2=), 46.5 (Allyl-CH_2), 13.5 (CH_3). IR (KBr): ν = 3428, 3215 (NH), 3071 (Ar-CH), 2918 (Aliph-CH), 1677-1660 cm^{-1} (CO). Anal. Calcd. for $C_{18}H_{18}N_6O_2S$ (382.44): C, 56.53; H, 4.74; N, 21.97. Found: C, 56.30; H, 4.48; N, 21.79.

Reaction of 21 with 12

A mixture of compound **21** (3.82 g, 10 mmol) and **12** (1.7 g, 10 mmol) was heated under reflux for 10 h in EtOH (100 mL). The solution was cooled, poured onto water and the formed product **22** was filtered off and dried.

Ethyl 2-(3-allyl-2-(2-(3-methyl-6-oxo-1-phenyl-6,7-dihydro-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonyl)hydrazono)-4-oxothiazolidin-5-ylidene)acetate (22).

Yellow crystals (EtOH); 0.50 g (76%); Mp 255-257 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.15 (s, 1H, pyridone-NH), 9.25 (s, 1H, NH), 8.32 (s, 1H, pyridone-H), 7.55-7.33 (m 5H, Ph-H), 6.80 (s, 1H, vinyl-H), 6.10-6.05 (m, 1H, Allyl-CH=), 5.62-5.58 (m, 2H, Allyl-CH_2=), 4.67-4.64 (m, 2H, Allyl-CH_2), 3.90 (s, 2H, J = 7.0 Hz, CH_2-ester), 2.35 (s, 3H, pyrazole-CH_3), 1.50 (t, 3H, J = 7.0 Hz, ester-CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 168.7, 167.3, 164.8, 164.0 (CO), 154.6, 153.3 (C=N), 149.2, 147.6, 142.2, 141.0 (Ar-C), 135.6 (vinyl-CH=), 134.0 (Ar-C), 133.6 (vinyl-C=), 133.1 (pyridone-CH), 125.2, 124.8 (Ar-2CH), 121.8 (Ar-CH), 104.0 (Allyl-CH_2=), 57.0 (CH_2-ester), 49.6 (Allyl-CH_2), 18.9 (pyrazole-CH_3), 13.5 (CH_3-ester). IR (KBr): ν = 3397 (NH), 3060 (Ar-CH), 2917 (Aliph-CH), 1712 cm^{-1} (CO-ester). Anal. Calcd for $C_{24}H_{22}N_6O_5S$ (506.53): C, 56.91; H, 4.38; N, 16.59. Found: C, 56.74; H, 4.17; N, 16.33.

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References

1. Yu G, Mason H, Wu X, Wang J, Chong S, Dorough G, Henwood A, Pongrac R, Seliger L, He B, Normandin D, Adam L and Krupinski J. *J Med Chem* 2001; 44: 1025.
2. Tucker T J, Sisko J T, Tynebor R M, Williams T M, Felock P, Flynn J A, Lai M T, Liang Y, McGaughey G, Liu M, Miller M, Moyer G, Munshi V, Perlow-Poehnelt R, Prasad S, Reid J C, Sanchez R, Torrent M, Vacca, J P, Wan B L and Yan Y. *J Med Chem* 2008; 51: 6503.
3. Ochiai H, Ishida A, Ohtani T, Kusumi K, Kishikawa K, Yamamoto S, Takeda H, Obata T, Makai H and Toda M. *Bioorg Med Chem* 2004; 12: 4089.
4. Bare T M, McLaren C D, Campbell J B, Firor J W, Resch J F, Walters C P, Salama A I, Meiners B A and Patel J B. *J Med Chem* 1989; 32: 2561.
5. Xing Y, Zuo J, Krogstad P and Jung M E. *J Med Chem* 2018; 61: 1688.
6. Chu I and Lynch B M. *J Med Chem* 1975; 18: 161.
7. Feurer A, Luithle J, Wirtz S, Koenig G, Stasch J, Stahl E, Schreiber R, Wunder F and Lang D. WO 2004009589, 2004.
8. Gudmundsson, Johns B A, Wang Z, Turner E M, Allen S H, Freeman G A, Jr. Boyd F L, Sexton C J, Selleseth D W, Monirib E R, Creech K I. *Bioorg Med Chem* 2005; 13: 5346.
9. Shutske G M and Roehr J E. *J Heterocycl Chem* 1997; 34: 789.
10. Henke B R, Aquino C J, Birkemo L S, Croom G N, Ervin J E, Grizzle M K, Hirst G C, James M K, Johnson M F, Queen K L, Sherrill G R, Sugg E E, Suh E M, Szewczyk J W, Unwalla R J, Yingling J and Willson T M. *J Med Chem* 1997; 40: 2706.
11. Straub A, Benet-Buckholtz J, Frode R, Kern A, Kohlsdorfer C, Schmitt P, Schwarz T, Siefert H-M and Stasch J-P. *Bioorg Med Chem* 2002; 10: 1711.
12. Huang S, Lin R, Yu Y, Lu Y, Connolly P J, Chiu G, Li S, Emanuel S L and Middleton

S A. *Bioorg Med Chem Lett*. 2007; 17: 1243.

13. Saggar S A, Sisko J T, Tucker T J, Tynebor R M, Su D S, Anthony N J. US Patent 2007021442, 2007.

14. Zhang P, Pennell A M K, Wright J J K, Chen W, Leleti M R, Li Y, Li L and Xu Y, WO 2007002293, 2007.

15. Chiu G, Li S, Connolly P J, Middleton S A, Emanuel S L, Huang S, Lin R, and Xu Y. WO 2006130673, 2006.

16. Patel J B, Malick J B, Salama A I and Goldberg M E. *Pharmacol Biochem Behav* 1985; 23: 675.

17. Boerrigter G and Burnett J C. Cardiovasc. *Drug Rev* 2007; 25: 30.

18. Sanghvi Y S, Larson S B, Willis R C, Robins R K and Revankar G R. *J Med Chem* 1989; 32: 945.

19. Aly A A, El-Emary T I, Mourad A E, Alyan Z K, Bräse S and Nieger M. *J Heterocycl Chem* 2019; 56: 1369.

20. Geraldo R B, Bello M L, Dias L R S, Vera M A F, Nagashima T, Abreu P A, Santos M B, Albuquerque M G, Cabral L M, Freitas A C C, Kalil M V, Rodrigues C R and Castro H C. *Thromb* 2010; 17: 730.

21. El-Emary T I. *J Chin. Chem. Soc* 2007; 54: 507.

22. Hussein A M and El-Emary T I. *J Chem. Res* 1998; 20.

23. El-Emary T I. *J Chin Chem Soc* 1999; 46: 585.

24. El-Emary T I and El-Mohsen S A A. *Molecules* 2012; 7: 14464.

25. El-Emary T I, Hussein A M and El-Kashef H S. *Pharmazie* 2000; 55:358.

26. Leuser H, Perrone S, Liron F, Kneisel F F and Knochel P. *Angew Chem Int Ed*. 2005; 44: 4627.

27. Sheldrick G M. *Acta Crystallogr.* 2015; A71: 3.

28. Sheldrick GM. *Crystallogr* 2015; C71: 3.

29. Spek A I. *Acta Crystallogr* 2009; D65:148.