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Convenient method for synthesis of various fused heterocycles via utility of 4-acetyl-5-methyl-1-phenyl-pyrazole as precursor

Sobhi MOHAMED GOMHA, Ahmad SAMI SHAWALI, Abdou OSMAN ABDELHAMID*
Department of Chemistry, Faculty of Science, University of Cairo, Giza, Egypt

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Abstract: A new, less expensive, solvent-free procedure was developed for the synthesis of some new derivatives of various fused heterocyclic ring systems, namely azolopyridazine, azolotriazine, azinotriazine, thienopyridine, and pyrazolopyridine. The structures of the products prepared were established by their spectral data and elemental analyses. Eight compounds were evaluated for their in vitro antimicrobial activity. Some of the tested compounds exhibited moderate to significant antibacterial and antifungal activities.

Key words: Azolopyridazine, azolotriazine, azinotriazine, thienopyridine, pyrazolopyridine, antimicrobial activities

1. Introduction

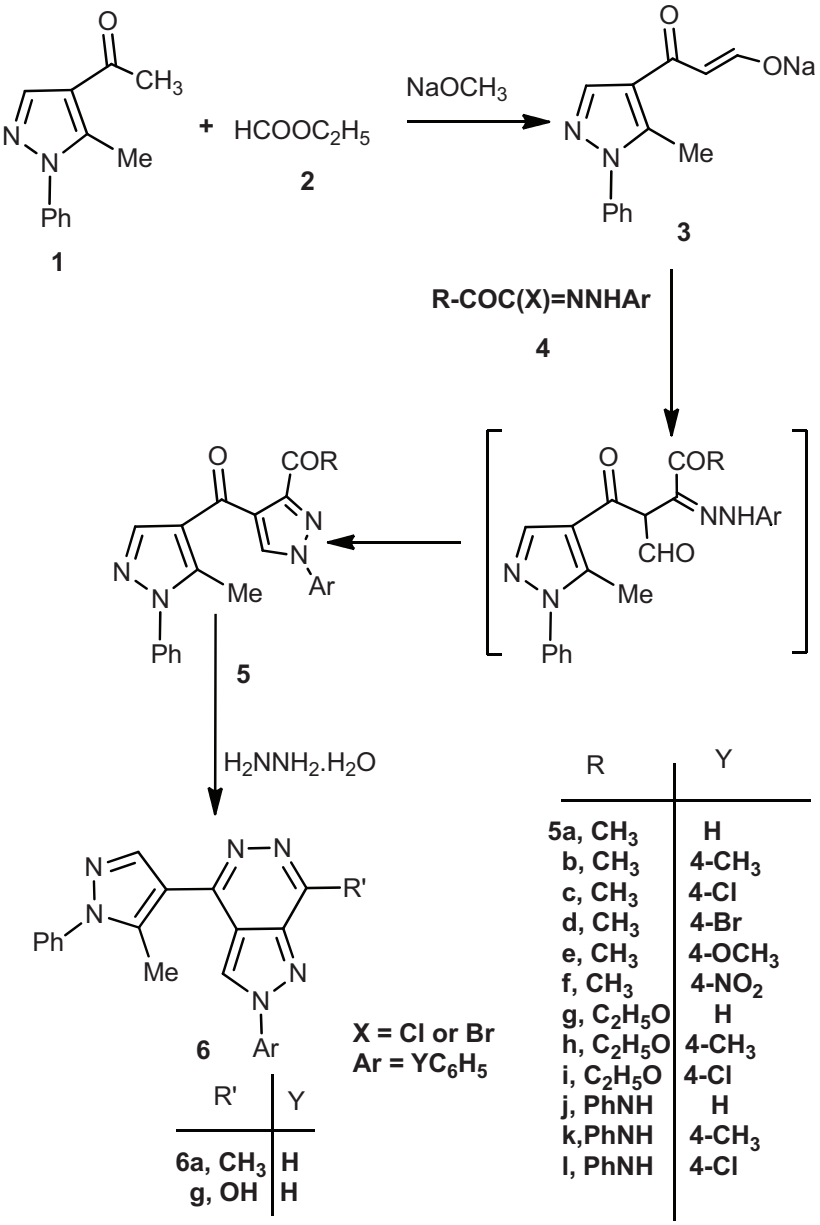
A literature survey revealed that many fused heterocyclic systems exhibit diverse biological activities. For example, some pyrazolo[3,4-*d*]pyridazines were reported to show good antimicrobial, anti-inflammatory, and analgesic activities[1] as well as antibacterial and antifungal activities.[2] Moreover, pyrazolo[5,1-*c*][1,2,4]triazines were reported to exhibit remarkable cytotoxic activity against colon, breast, and lung carcinoma cells,[3] while some other derivatives were reported to have selective cytotoxicity in hypoxic and normoxic conditions.[4] Furthermore, some thieno[2,3-*b*]pyridines exhibit inhibitory activity against c-Src[5] and eEF2-K.[6] Pyrazolo[3,4-*b*]pyridines were reported to act as potent A_1 adenosine antagonists.[7] In the light of these findings and in continuation of our interest in the synthesis of various heterocycles via the utility of hydrazonoyl halides as useful precursors,[8–10] we wish to report herein a new synthetic strategy for synthesis of pyrazolo[3,4-*d*]pyridazine and isoxazolo[3,4-*d*]pyridazine derivatives of expected biological interest. The previously reported method for synthesis of the former ring system depends on the conversion of the title compounds into the corresponding enaminones via their reaction with DMF-DMA, which is an expensive reagent. Instead of this method, we report herein the use of a much less expensive reagent, namely ethyl formate/sodium methoxide, to convert the title compound into the corresponding sodium salt of the enol tautomer of 3-(5-methyl-1-phenyl-1*H*-pyrazol-4-yl)-3-oxopropanaldehyde **3** (Scheme 1). The latter salt proved to be a very useful precursor for solvent-free synthesis of the target compounds as indicated below.

2. Results and discussion

Treatment of 4-acetyl-5-methyl-1-phenylpyrazole[11] **1** with ethyl formate in sodium methoxide afforded the sodium 3-(5-methyl-1-phenyl-1*H*-pyrazol-4-yl)-3-oxoprop-1-en-1-olate[12] **3** (Scheme 1). In this investigation,

*Correspondence: abdelhamid45@gmail.com

grinding of the latter sodium salt **3** with each of the hydrazonoyl halides **4** in the presence of sodium carbonate gave, in each case, one isolable product as evidenced by TLC analysis of the crude product. The isolated products proved, on the basis of their spectra (IR, MS, and ^{1}H- and ^{13}C-NMR) and elemental analyses (see Experimental), to have structure **5** (Scheme 1).



Scheme 1. Synthesis of pyrazolo[3,4-*d*]pyridazines.

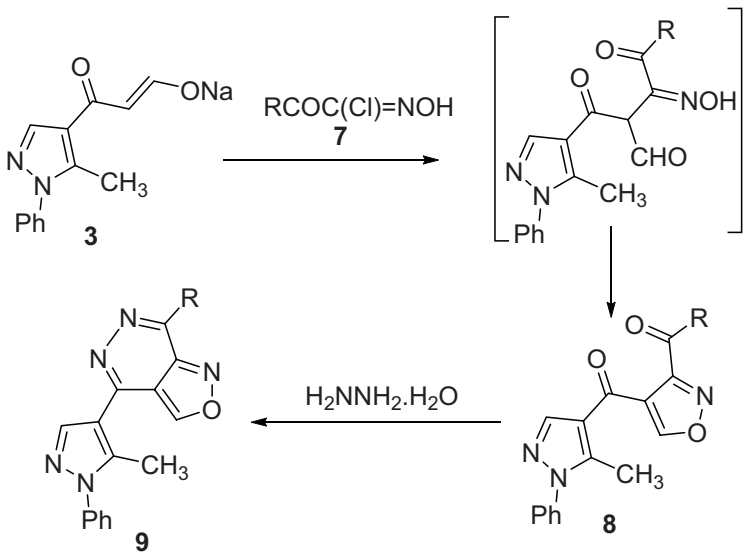
For example, the IR spectra of all compounds revealed a common C=O band in the region υ 1630–1658 cm^{-1}. In addition, the IR spectra of compounds **5a**–**f** exhibited an acetyl C=O band in the region υ 1685–1691 cm^{-1} and compounds **5g**–**i** and **5j**–**l** showed their ester and anilide C=O bands near 1716 and 1681 cm^{-1}, respectively. The ^{1}H NMR spectra of compounds **5** revealed, in addition to the aromatic proton signals, a characteristic singlet signal near δ 8.95 assignable to H-5 of the pyrazole ring residue.[13] In addition,

the assigned structures for the isolated products were confirmed by the similarity of the physical properties of compounds **5a**–**c** and **5g**–**i** with those previously reported.[14]

Furthermore, the structures of the products **5** were established by their chemical reaction with hydrazine hydrate. Thus, grinding each of the 2 products **5a** and **5g** with hydrazine hydrate resulted in their conversion into the pyrazolo[3,4-*d*]pyridazine derivatives **6a** and **6g**, respectively (Scheme 1).

The structures of the products **6a** and **6g** were elucidated on the basis of their spectra (IR, MS, ^{1}H NMR) and elemental analytical data (see Experimental). For example, while the IR spectrum of **6a** revealed the absence of carbonyl absorption bands, the spectrum of **6g** showed an OH band near 3521 cm^{-1}. The ^{1}H NMR spectrum of **6g** revealed the absence of the triplet and quartet signals of the – $COOCH_2CH_3$ group present in the spectrum of **5g**.

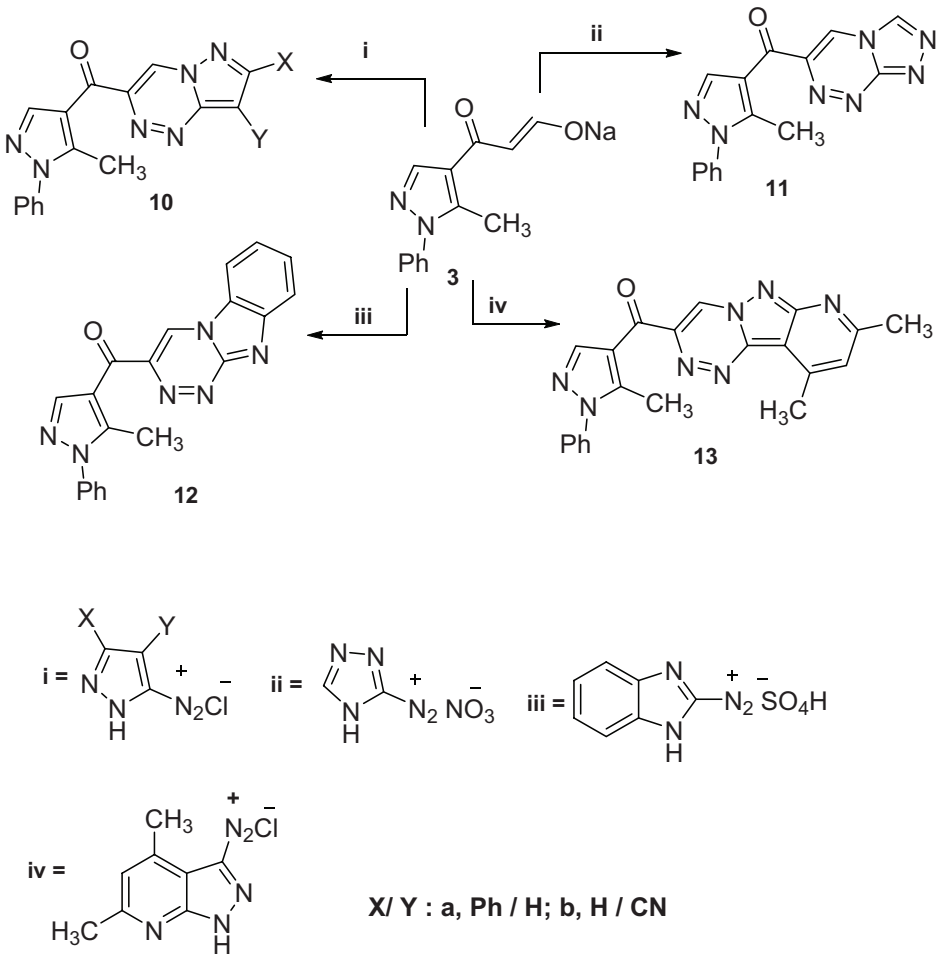
Similarly, reactions of the salt **3** with each of the hydroximoyl chlorides **7** under the same reaction conditions furnished the products **8** (Scheme 2). The assigned structures of the latter new products **8** were consistent with their spectroscopic data (IR, MS, ^{1}H NMR) and elemental analyses (see Experimental). For example, the IR spectra exhibited, in each case, 2 common C=O absorption bands in the regions υ 1636–1638 and υ 1690–1697 cm^{-1}. Moreover, the ^{1}H NMR spectra of compounds **8** revealed, in addition to the aromatic proton signals, a characteristic singlet signal in the region δ 10.02–10.12 assignable to H-5 of the isoxazole ring residue.[13] This finding indicates that reactions of **3** with **7** follow a regioselective pathway similar to that found for the reactions of **3** with hydrazonoyl halides **4**. This conclusion was further confirmed by our finding that grinding each of the products **8** with hydrazine hydrate afforded the corresponding isoxazolo[3,4-*d*]pyridazine derivatives **9** (Scheme 2). The structures of the latter products **9** were also consistent with their spectral data (IR, ^{1}H NMR, and MS) and elemental analyses (see Experimental). For example, while their IR spectra revealed no C=O absorption bands, their ^{1}H NMR spectra exhibited signals in the region δ 2.57– 2.62 (CH_3), 8.09–8.14 (pyrazole H-3), and 10.10–10.15 (isoxazole H-5).



7-9 : R : a, Ph; b, 2-thienyl; c, 2-furyl; d, 2-naphthyl

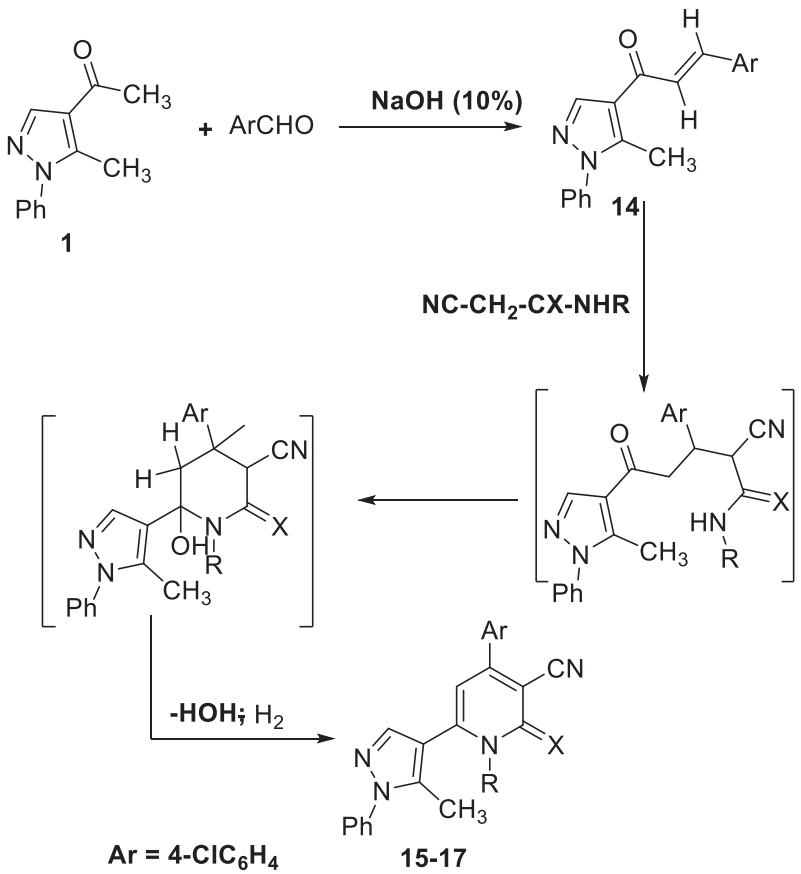
Scheme 2. Synthesis of isoxazolo[3,4-*d*]pyridazines.

Next, reactions of **3** with diazotized substituted 5-amino-pyrazoles were examined. Thus, reaction of **3** with each of diazotized 5-amino-substituted pyrazoles, 3-amino-1,2,4-triazole, 2-aminobenzimidazole, and 5-amino-2,4-dimethyl-pyrazolo[3,4-*b*]pyridine in ethanol in the presence of sodium acetate at 0–5 °C yielded the corresponding pyrazolo[5,1-*c*][1,2,4]triazene, 1,2,4-triazolo[3,4-*c*][1,2,4]triazene, benzoimidazo[2,1-*c*][1,2,4]triazene, and pyrazolo[3,4-*b*]pyrido[7,1-*c*][1,2,4]triazene derivatives **10**–**13**, respectively (Scheme 3). The formation of such products seems to result via initial substitution of the α-hydrogen in the 3-oxopropanol **3** to form the respective azo coupling intermediate, which then undergoes in situ dehydrative cyclization. This suggested pathway is consistent with that reported for coupling diazotized heterocyclic amines with enaminones.[15,16] Structures of the products **10**–**13** were assigned on the basis of their elemental and spectral (MS, IR, and ^{1}H NMR) analyses (see Experimental). The IR spectra of the isolated products **10**–**13** showed absorption bands characteristic for a C=O group in the region 1630–1660 cm^{-1}. Their mass spectra gave the molecular ion peaks at m/z (%): 380 (65), 329 (22), 305 (76), 354 (8), 383 (87), for compounds **10a**, **10b**, **11**–**13**, respectively.



Scheme 3. Synthesis of pyrazolo[5,1-*c*]triazines, [1,2,4] triazolo[5,1-*c*][1,2,4]triazine, benzo[4,5]imidazo[2,1-*c*][1,2,4]triazine, and pyrido[2',3':3,4]pyrazolo[5,1-*c*][1,2,4]triazines.

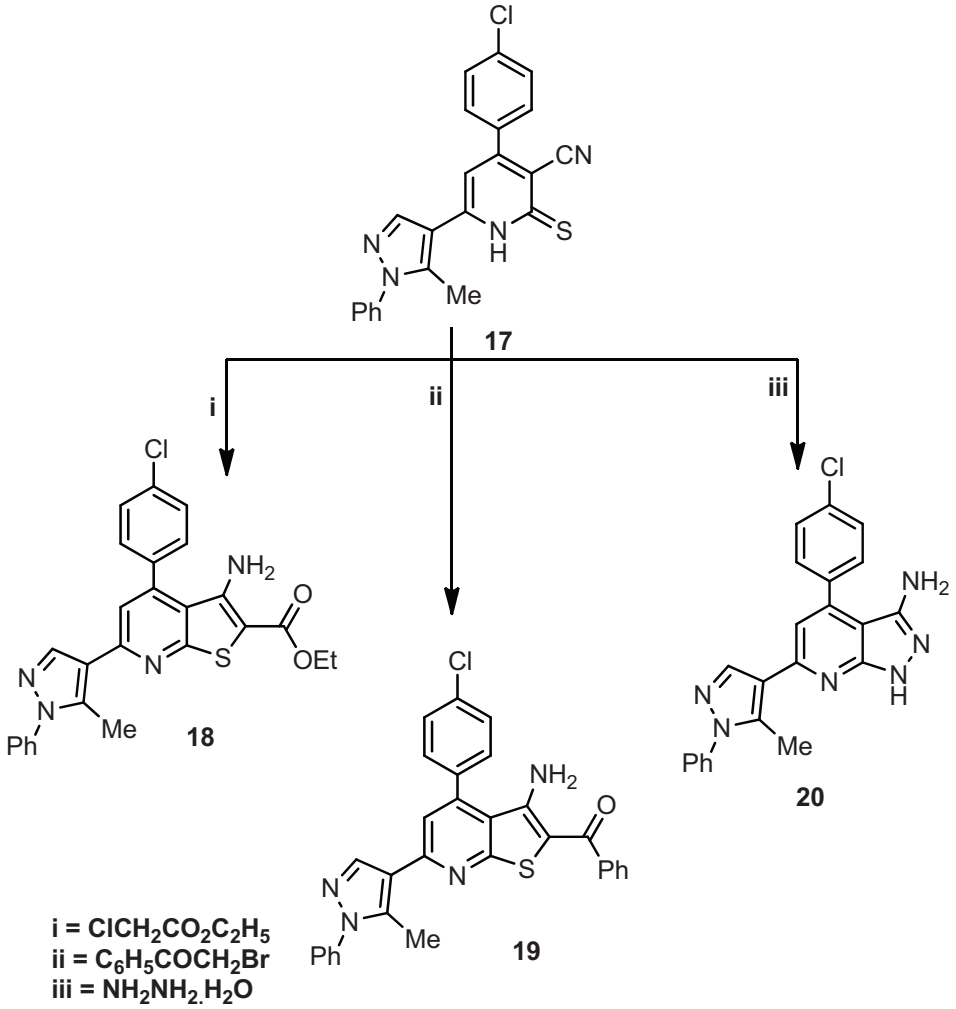
Furthermore, condensation of compound **1** with 4-chlorobenzaldehyde in ethanol in the presence of sodium hydroxide afforded 4-(4-chlorocinnamoyl)-5-methyl-1-phenylpyrazole[17] (**14**) (Scheme 4). Grinding of **14** with each of 2-cyanoacetamide, 2-cyanoacetohydrazide, and 2-cyanoethanethioamide yielded products whose elemental analyses and spectral (IR, ^{1}H NMR, and MS) data were consistent with the structures **15**–**17**, respectively (Scheme 4).



Scheme 4. Synthesis of 3-cyanopyridine derivatives.

To account for the formation of the latter products, it is suggested, as depicted in Scheme 4, that the reactions started with the initial formation of the corresponding Michael adducts as intermediates, which in turn undergo tandem in situ cyclization, dehydration, and oxidation to give the corresponding **15**–**17** as end products.

Finally, we studied the reactions of pyridinethione **17** with ethyl chloroactate, ω-bromoacetophenone, and hydrazine hydrate. In our hands, grinding of **17** with each of such reagents in the presence of potassium carbonate yielded the products **18**–**20**, respectively (Scheme 5). The structures of **18**–**20** were confirmed by elemental analyses and spectral data (see Experimental).



Scheme 5. Synthesis of thieno[2,3-*b*]pyridines and pyrazolo[3,4-*b*]pyridine.

2.1. Antimicrobial activity

The synthesized products **5a**, **5b**, **6a**, **6g**, **8a**, **9a**, **13**, and **17** were screened for their antimicrobial activities in vitro against the gram-positive bacterium *Staphylococcus aureus* (*S. aureus*), gram-negative bacterium *Escherichia coli* (*E. coli*), and the fungus *Candida albicans* (*C. albicans*) under the same conditions using trimethoprim as reference. The bacteria and fungus were subjected to susceptibility testing on Mueller-Hinton agar medium by the disk agar diffusion method.[18,19] The results are summarized in the Table.

Such results indicate the following:

1. Compounds **5a**, **6a**, **9a**, and **13** exhibit high inhibitory effects against *S. aureus* and *E. coli*, while compounds **5b**, **8a**, and **17** have moderate inhibitory effect. On the other hand, compound **6g** has no inhibitory effect towards either species, while compound **17** has no inhibitory effect towards *E. coli*.

2. Compounds **6a** and **13** exhibit high inhibitory activities against *C. albicans*, while compounds **5a**, **8a**, and **9a** have moderate inhibitory activity and compounds **5b**, **6g**, and **17** have no activity against this species.

Table. Antimicrobial activity of the tested compounds.

Sample number	Inhibition zone diameter (mm/mg sample)		
	S. aureus	*E. coli*	*C. albicans*
5a	16	17	10
5b	12	10	-
6a	17	16	16
6g	-	-	-
8a	12	14	12
9a	17	15	14
13	16	19	18
17	12	-	-
Trimethoprim	19	21	21

(-) No inhibition zone

3. Experimental

All melting points were measured on Electrothermal IA 9000 series digital melting point apparatus. The IR spectra were recorded in potassium bromide disks on a Pye Unicam SP 3300 and Shimadzu FT IR 8101 PC infrared spectrophotometer. The ^{1}H and ^{13}C NMR spectra were recorded at 270 MHz on a Varian Mercury VX-300 NMR spectrometer. ^{1}H NMR (300 MHz) was run in $CDCl_3$ and $(CD_3)_2SO$ solutions and chemical shifts are expressed in ppm units using TMS as an internal reference. Mass spectra were recorded on a Shimadzu GCMS-QP1000 EX mass spectrometer at 70 eV. Elemental analyses and the biological evaluation of the products were carried out at the Microanalytical Center of Cairo University, Giza, Egypt. All reactions were followed by TLC (Silica gel, Aluminum Sheets 60 F254, Merck). 4-Acetyl-5-methyl-1-phenyl-pyrazole[11] **1**, 3-(4-chlorophenyl)-1-(5-methyl-1-phenyl-1*H*-pyrazol-4-yl)prop-2-en-1-one[17] **14**, hydrazonoyl halides[20,21] **4a**–**l** and hydroximoyl chlorides[22–25] **7a**–**d** were prepared as previously reported in the literature.

3.1. Synthesis of pyrazoles (5a–l) and isoxazoles derivatives (8a–d)

General procedure:

A mixture of sodium salt **3** (0.25 g, 1 mmol) and each of the appropriate hydrazonoyl halides **4a**–**d** or hydroximoyl chlorides **7a**–**d** (1 mmol) and sodium carbonate (0.3 g) was thoroughly ground with a pestle in an open mortar at room temperature for 3–5 min until the mixture turned into a melt and grinding was continued for further 5–10 min and the reaction was monitored by TLC. The solid formed was washed with water and crystallized from the appropriate solvent to give corresponding pyrazole **5a**–**l** and isoxazoles **8a**–**d** derivatives**,** respectively. The synthesized compounds **5a**–**l** and **8a**–**d** together with their physical and spectral data are listed below.

3.1.1. 3-Acetyl-4-(5'-methyl-1'-phenyl-pyrazol-4'-oyl)-1-phenyl-pyrazole (5a)

. Pale yellow solid; Yield 86%; mp 179 °C (Lit.[26] mp 178–179 °C).

3.1.2. 3-Acetyl-1-(4-methylphenyl)-4-(5'-methyl-1'-phenyl-pyrazol-4'-oyl)pyrazole (5b)

Pale yellow solid; Yield 84%; mp 160–161 °C (Lit.[26] mp 160–161 °C).

3.1.3. 3-Acetyl-1-(4-chlorophenyl)-4-(5'-methyl-1'-phenyl-pyrazol-4'-oyl)pyrazole (5c)

Pale yellow solid; Yield 84%; mp 197–198 °C (Lit.[26] mp 197–198 °C).

3.1.4. 3-Acetyl-1-(4-bromophenyl)-4-(5'-methyl-1'-phenyl-pyrazol-4'-oyl)pyrazole (5d)

Pale yellow solid; Yield 87%; mp 164–166 °C. IR (KBr): υ 1687, 1656 (2C=O), 1591 (C=N) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.38 (s, 3H, CH_3CO), 2.54 (s, 3H, CH_3), 7.21–7.67 (m, 9H, ArH's), 8.08 (s, 1H, pyrazole H-3), 8.95 (s, 1H, pyrazole H-5); ^{13}C NMR (DMSO-d_6): δ 12.34, 27.24, 121.55, 125.26, 126.00, 128.59, 133.70, 136.42, 140.63, 141.76, 142.58, 144.18, 150.94, 176.46, 195.12; MS m/z(%): 449 (M^+, 48), 406 (24), 292 (63), 185 (92), 78 (100), 51 (52). Anal. Calcd for: $C_{22}H_{17}BrN_4O_2$ (449.30): C, 58.81; H, 3.81; N, 12.47. Found: C, 58.68; H, 3.65; N, 12.37%.

3.1.5. 3-Acetyl-1-(4-methoxyphenyl)-4-(5'-methyl-1'-phenyl-pyrazol-4'-oyl)pyrazole (5e)

Pale yellow solid; Yield 84%; mp 144–146 °C. IR (KBr): υ 1686, 1632 (2C=O), 1592 (C=N) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.54 (s, 3H, CH_3CO), 2.59 (s, 3H, CH_3), 3.54 (s, 3H, OCH_3) 7.22–7.68 (m, 9H, ArH's), 8.04 (s, 1H, pyrazole H-3), 8.96 (s, 1H, pyrazole H-5); ^{13}C NMR (DMSO-d_6): δ 11.45, 27.12, 55.75, 113.42, 122.63, 125.74, 126.27, 128.54, 136.12, 138.86, 140.65, 141.74, 142.24, 150.75, 160.32, 178.46, 194.67; MS m/z(%): 400 (M^+, 81), 243 (100), 130 (16), 78 (32), 51 (15). Anal. Calcd for: $C_{23}H_{20}N_4O_3$ (400.43): C, 68.99; H, 5.03; N, 13.99. Found: C, 68.76; H, 5.01; N, 13.87%.

3.1.6. 3-Acetyl-1-(4-nitrophenyl)-4-(5'-methyl-1'-phenyl-pyrazol-4'-oyl)pyrazole (5f)

Pale yellow solid; Yield 84%; mp 160–162 °C. IR (KBr): υ 1688, 1658 (2C=O), 1593 (C=N) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.46 (s, 3H, CH_3CO), 2.59 (s, 3H, CH_3), 7.26-7.65 (m, 9H, ArH's), 8.02 (s, 1H, pyrazole H-3), 8.97 (s, 1H, pyrazole H-5); ^{13}C NMR (DMSO-d_6): δ 11.85, 27.11, 122.21, 124.85, 125.88, 126.66, 128.89, 136.24. 140.47, 141.62, 142.17, 146.77, 147.54, 150.85, 178.65, 194.77; MS m/z(%): 415 (M^+, 67), 371 (19), 185 (69), 78 (100), 51 (38). Anal. Calcd for: $C_{22}H_{17}N_5O_4$ (415.40): C, 63.61; H, 4.12; N, 16.86. Found: C, 63.46; H, 4.10; N, 16.76%.

3.1.7. Ethyl 1-phenyl-4-(5'-methyl-1'-phenyl-pyrazol-4'-oyl)pyrazole 3-carboxylate (5g)

Pale yellow solid; Yield 88%; mp 165–167 °C (Lit.[26] mp 165–166 °C).

3.1.8. Ethyl 1-(4-methylphenyl)-4-(5'-methyl-1'-phenyl-pyrazol-4'-oyl)pyrazole 3-carboxylate (5h)

Pale yellow solid; Yield 86%; mp 162–163 °C (Lit.[26] mp 162–163 °C).

3.1.9. Ethyl 1-(4-chlorophenyl)-4-(5'-methyl-1'-phenyl-pyrazol-4'-oyl)pyrazole 3-carboxylate (5i)

Pale yellow solid; Yield 82%; mp 195–196 °C (Lit.[26] mp 195–196 °C).

3.1.10. *N*-Phenyl-(1-phenyl-4-(5'-methyl-1'-phenyl-pyrazol-4'-oyl)pyrazole-3- carboxamide (5j)

Pale yellow solid; Yield 86%; mp 167–168 °C. IR (KBr): υ 3346 (NH), 1684, 1631 (2C=O), 1600 (C=N) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.54 (s, 3H, CH_3), 7.19–7.73 (m, 15H, ArH's), 8.24 (s, 1H, pyrazole H-3), 9.08 (s, 1H,

pyrazole H-5), 11.63 (s, 1H, br, NH); ^{13}C NMR (DMSO-d_6): δ 12.11, 118.65, 119.25, 122.78, 125.79, 126.11, 127.86, 129.24, 129.88, 130.56, 136.58, 136.94, 137.68, 141.68, 142.79, 150.38, 152.66, 176.67; MS m/z(%): 447 (M^+, 53), 341 (24), 185 (67), 118 (77), 92 (84), 78 (100), 51 (54). Anal. Calcd for $C_{27}H_{21}N_5O_2$ (447.49): C, 72.47; H, 4.73; N, 15.65. Found: C, 72.38; H, 4.56; N, 15.34%.

3.1.11. *N*-Phenyl-(1-(4-methylphenyl)-4-(5'-methyl-1'-phenyl-pyrazol-4'-oyl)pyrazole-3-carboxamide (5k)

Pale yellow solid; Yield 88%; mp 178–179 °C. IR (KBr): v 3389 (NH), 1681, 1637 (2C=O), 1601 (C=N) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.28 (s, 3H, CH_3), 2.52 (s, 3H, CH_3), 7.16–7.78 (m, 14H, ArH's), 8.24 (s, 1H, pyrazole H-3), 9.10 (s, 1H, pyrazole H-5), 11.67 (s, 1H, br, NH); ^{13}C NMR (DMSO-d_6): δ 12.60, 21.37, 119.80, 120.12, 122.45, 125.22, 126.00, 128.74, 130.01, 130.45, 132.78, 136.42, 136.57, 137.12, 141.08, 142.13, 150.00, 152.77, 176.51; MS m/z(%): 461 (M^+, 73), 341 (24), 186 (42), 118 (91), 92 (84), 66 (100), 51 (38). Anal. Calcd for $C_{28}H_{23}N_5O_2$ (461.51): C, 72.87; H, 5.02; N, 15.17. Found: C, 72.76; H, 5.00; N, 15.05%.

3.1.12. *N*-Phenyl-(1-(4-chlorophenyl)-4-(5'-methyl-1'-phenyl-pyrazol-4'-oyl)-pyrazole-3-carboxamide (5l)

Pale yellow solid; Yield 86%; mp 185–187 °C. IR (KBr): v 3378 (NH), 1686, 1634 (2C=O), 1597 (C=N) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.54 (s, 3H, CH_3), 7.13–7.86 (m, 14H, ArH's), 8.26 (s, 1H, pyrazole H-3), 9.12 (s, 1H, pyrazole H-5), 11.82 (s, 1H, br, NH); ^{13}C NMR (DMSO-d_6): δ 11.85, 27.22, 122.34, 124.78, 125.89, 126.54, 128.35, 136.54, 140.32, 141.54, 142.45, 145.89, 147.57, 150.37, 178.88.95.12; MS m/z(%): 481 (M^+, 100), 306 (54), 185 (37), 118 (80), 66 (16), 51 (38). Anal. Calcd for $C_{27}H_{20}ClN_5O_2$ (481.93): C, 67.29; H, 4.18; N, 14.53. Found: C, 67.21; H, 4.12; N, 14.36%.

3.1.13. 3-Benzoyl-4-(5'-Methyl-1'-phenyl-*1*H-pyrazol-4'-yl)isoxazole (8a)

Yield 86%; Pale yellow solid; mp 220 °C (Lit.[26] mp 219–220 °C).

3-(2-Thienyl)-4-(5'-methyl-1'-phenyl-1*H*-pyrazol-4'-oyl)isoxazole (8b). Yellow solid; Yield 86%; mp 234–236 °C. IR (KBr): v 1692, 1633 (2 C=O), 1590 (C=N) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.57 (s, 3H, CH_3), 7.52–8.12 (m, 9H, ArH's and pyrazole H-3), 10.03 (s, 1H, isoxazole H-5); ^{13}C NMR (DMSO-d_6): δ 12.12, 113.74, 122.89, 125.75, 126.10, 129.24, 132.77, 136.89, 142.68, 147.99, 150.67, 158.23, 178.87, 178.41, 180.32; MS m/z(%): 363 (M^+, 100), 319 (22), 212 (60), 51 (65). Anal. Calcd for $C_{19}H_{13}N_3O_3S$ (363.39): C, 62.80; H, 3.61; N, 11.56. Found: C, 62.76; H, 3.45; N, 11.48%.

3.1.14. 3-(2-Furyl)-4-(5'-methyl-1'-phenyl-1*H*-pyrazol-4'-oyl)isoxazole (8c)

Yellow solid; Yield 88%; Pale yellow solid; mp 247–249 °C. IR (KBr): v 1697, 1638 (2C=O), 1596 (C=N) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.59 (s, 3H, CH_3), 6.90–8.14 (m, 9H, ArH's and pyrazole H-3), 10.12 (s, 1H, isoxazole H-5); ^{13}C NMR (DMSO-d_6): δ 11.97, 111.12, 122.54, 126.00, 127.58, 129.11, 135.99, 137.56, 142.57, 146.32, 150.54, 152.12, 152.89, 176.95, 178.22, 180.49; MS m/z(%): 347 (M^+, 90), 319 (34), 212 (100), 51 (84). Anal. Calcd for $C_{19}H_{13}N_3O_4$ (347.32): C, 65.70; H, 3.77; N, 12.10. Found: C, 65.61; H, 3.56; N, 11.92%.

3.1.15. 3-(2-Naphthyl)-4-(5'-methyl-1'-phenyl-1*H*-pyrazol-4'-oyl)isoxazole (8d)

Pale yellow solid; Yield 83%; mp 242–244 °C. IR (KBr): υ 1697, 1638 (2 C=O), 1596 (C=N) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.55 (s, 3H, CH_3), 7.51–8.11 (m, 12H, ArH's and pyrazole H-3), 8.44 (s, 1H, naphthalene H-1), 10.13 (s, 1H, isoxazole H-5); ^{13}C NMR (DMSO-d_6): δ 11.82, 118.11, 122.45, 124.42, 126.00, 126.98, 128.10, 128.64, 128.95, 130.21, 131.62, 132.78, 134.13, 134.86, 135.75, 142.82, 150.94, 152.58, 177.95, 185.74, 187.53; MS m/z(%): 407 (M^+, 100), 337 (45), 164 (53), 105 (100). Anal. Calcd for $C_{25}H_{17}N_3O_3$ (407.42): C, 73.70; H, 4.21; N, 10.31. Found: C, 73.58; H, 4.13; N, 10.22%.

3.2. Synthesis of pyrazolo[3,4-*d*]pyridazines (6a,g) and isoxazolo[3,4-*d*]-pyridazines (9a–d)

A mixture of the appropriate pyrazoles **5a** and **5g** (5 mmol) and hydrazine hydrate (1 g, 10 mmol) was thoroughly ground with a pestle in an open mortar at room temperature for 3–5 min until the mixture turned into a melt. The initial syrupy consistency continued for 5–10 min and the reaction was monitored by TLC. The solid was washed with water and crystallized from the appropriate solvent to give the corresponding pyrazolo[3,4-*d*]pyridazines **6a** and **6g.** When the above procedure was repeated using the appropriate isoxazole **8a**–**5** in place of the pyrazole **5**, the corresponding isoxazolo[3,4-*d*]pyridazines **9a**–**d**, respectively were obtained. The physical constants of the products **6a** and **6g** and **9a**–**d** are given below.

3.2.1. 7-Methyl-4-(5-methyl-1-phenyl-1*H*-pyrazol-4-yl)-2-phenyl-2*H*-pyrazolo[3,4-d]pyridazine (6a)

Pale yellow solid; Yield 89%; mp 232 °C (Lit.[26] mp 231–232 °C).

3.2.2. 4-(5-Methyl-1-phenyl-1*H*-pyrazol-4-yl)-2-phenyl-2*H*-pyrazolo[3,4-*d*]-pyridazin-7-ol (6g)

Pale yellow solid; Yield 88%; mp 266–268 °C. IR (KBr): υ 1612 (C=N), 3521(OH) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.61 (s, 3H, CH_3), 7.40–7.89 (m, 11H, ArH's and OH), 8.13 (s, 1H, pyrazole H-3), 8.96 (s, 1H, pyrazole H-5); ^{13}C NMR (DMSO-d_6): δ 11.82, 116.50, 119.94, 121.02, 125.71, 126.00, 127.51, 129.27, 129.98, 138.21, 140.02, 146.63, 146.57, 146.99, 156.12; MS m/z(%): 369 (M^++1, 11), 368 (M^+, 26), 352 (100), 105 (42), 77 (34), 51 (75). Anal. Calcd for $C_{21}H_{16}N_6O$ (368.39): C, 68.47; H, 4.38; N, 22.81. Found: C, 68.58; H, 4.30; N, 22.57%.

3.2.3. 4-(5-Methyl-1-phenyl-1*H*-pyrazol-4-yl)-7-phenylisoxazolo[3,4-*d*]pyridazine (9a)

Pale yellow solid; Yield 90%; mp 277–279 °C. IR (KBr): υ 1604 (C=N) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.57 (s, 3H, CH_3), 7.43–7.94 (m, 10H, ArH's), 8.12 (s, 1H, pyrazole H-3), 10.10 (s, 1H, isoxazole H-5); ^{13}C NMR (DMSO-d_6): δ 10.84, 112.41, 116.03, 121.81, 126.00, 128.32, 128.67, 128.98, 131.15, 135.48, 137.22, 141.24, 143.18, 150.43, 152.13, 156.78; MS m/z(%): 353 (M^+, 47), 277 (42), 158 (67), 78 (100). Anal. Calcd for: $C_{21}H_{15}N_5O$ (353.38): C, 71.38; H, 4.28; N, 19.82. Found: C, 71.31; H, 4.18; N, 19.67%.

3.2.4. 4-(5-Methyl-1-phenyl-1*H*-pyrazol-4-yl)-7-(thien-2-yl)isoxazolo[3,4-*d*]-pyridazine (9b)

Pale yellow solid; Yield 88%; mp 255–257 °C. IR (KBr): υ 1599 (C=N) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.60 (s, 3H, CH_3), 7.43–7.92 (m, 8H, ArH's), 8.09 (s, 1H, pyrazole H-3), 10.05 (s, 1H, isoxazole H-5); ^{13}C NMR (DMSO-d_6): δ 10.89, 112.71, 116.03, 121.35, 126.00, 128.32, 128.67, 129.98, 132.11, 135.89, 141.35, 143.55,

148.12, 152.92, 157.92, 162.89; MS m/z(%): 359 (M^+, 64), 277 (100), 212 (53), 84 (42), 51 (65). Anal. Calcd for $C_{19}H_{13}N_5OS$ (359.40): C, 63.49; H, 3.65; N, 19.49. Found: C, 63.34; H, 3.72; N, 19.37%.

3.2.5. 7-(Furan-2-yl)-4-(5-methyl-1-phenyl-1*H*-pyrazol-4-yl)isoxazolo[3,4-*d*]-pyridazine (9c)

Pale yellow solid; Yield 88%; mp 269–271 °C. IR (KBr): v 1602 (C=N) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.62 (s, 3H, CH_3), 7.52–7.94 (m, 8H, ArH's), 8.14 (s, 1H, pyrazole H-3), 10.06 (s, 1H, isoxazole H-5); ^{13}C NMR (DMSO-d_6): δ 10.54, 112.26, 112.62, 114.78, 116.32, 121.28, 126.00, 130.42, 136.24, 141.25, 146.88, 149.57, 151.28, 154.32, 155.89, 157.87; MS m/z(%): 343 (M^+, 40), 277 (100), 212 (94), 51 (84). Anal. Calcd for $C_{19}H_{13}N_5O_2$ (343.34): C, 66.47; H, 3.82; N, 20.40. Found: C, 66.23; H, 3.65; N, 20.24%.

3.2.6. 4-(5-Methyl-1-phenyl-1*H*-pyrazol-4-yl)-7-(naphth-2-yl)isoxazolo[3,4-*d*]- pyridazine (9d)

Pale yellow solid; Yield 89%; mp 280–282 °C. IR (KBr): v 1608 (C=N) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.59 (s, 3H, CH_3), 7.42–7.81 (m, 11H, ArH's), 8.16 (s, 1H, pyrazole H-3), 8.47 (s, 1H, naphthalene H-1), 10.15 (s, 1H, isoxazole H-5); ^{13}C NMR (DMSO-d_6): δ 10.54, 112.56, 121.62, 123.42, 125.67, 125.99, 126.18, 127.54, 128.64, 130.11, 130.68, 130.67, 131.47, 135.75, 136.77, 141.60, 141.89, 150.12, 152.33, 156.57; MS m/z(%): 403 (M^+, 15), 277 (87), 185 (60), 128 (100). Anal. Calcd for $C_{25}H_{17}N_5O$ (403.44): C, 74.43; H, 4.25; N, 17.36. Found: C, 74.23; H, 4.35; N, 17.24%.

3.3. Synthesis of pyrazolo[5,1-*c*]triazines, [1,2,4] triazolo[5,1-*c*][1,2,4]triazine, benzo[4,5]imidazo[2,1-*c*][1,2,4]triazine, and pyrido[2',3':3,4]pyrazolo[5,1-*c*][1,2,4]triazines 10–13.

A solution of the appropriate diazonium salt of the appropriate amine, namely 3-amino-5-phenylpyrazole (**ia**), 3-amino-4-cyanopyrazole (**ib**), 3-amino-1,2,4-triazole (**ii**), 2-amino-benzimidazole (**iii**), or 3-amino-4,6-dimethyl-2*H*-pyrazolo[3,4-b]pyridine (**iv**), prepared as previously reported,[23] was added to a cold mixture of the sodium salt (**3**) (5 mmol) and sodium acetate (0.65 g, 5 mmol) in ethanol (40 mL) at 0–5 °C, while stirring for 30 min. The reaction mixture was stirred for a further 3 h. The resulting solid was collected and crystallized from the appropriate solvent to give the corresponding **10a**,**b**, **11**, **12**, and **13**, respectively.

3.3.1. (5-Methyl-1-phenyl-1*H*-pyrazol-4-yl)(7-phenylpyrazolo[5,1-*c*][1,2,4]triazin-4-yl)methanone (10a)

Pale yellow solid; Yield 84%; mp 242–244 °C. IR (KBr): v 1622 (C=O), 1597 (C=N) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.56 (s, 3H, CH_3), 6.31 (s, 1H, pyrazole H-4), 7.33–8.12 (m, 10H, ArH's), 8.65 (s, 1H, pyrazole H-3), 9.64 (s, 1H, triazine H-5); ^{13}C NMR (DMSO-d_6): δ11.12, 105.65, 121.78, 122.43, 126.00, 127.79, 128.34, 129.12, 129.89, 134.88, 135.57, 140.55, 151.26, 152.07, 153.44, 154.29, 179.46; MS m/z(%): 380 (M^+, 65), 352 (34), 235 (22), 184 (61), 117 (75), 78 (100), 51 (74). Anal. Calcd for: $C_{22}H_{16}N_6O$ (380.40): C, 69.46; H, 4.24; N, 22.09. Found: C, 69.41; H, 4.17; N, 22.02%.

3.3.2. 4-(5-Methyl-1-phenyl-1*H*-pyrazole-4-carbonyl)pyrazolo[5,1-*c*][1,2,4]triazine-8-carbonitrile (10b)

Pale yellow solid; Yield 80%; mp 192–194 °C. IR (KBr): v 2231 (CN), 1639 (C=O) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.57 (s, 3H, CH_3), 7.31–7.82 (m, 5H, ArH's), 8.51 (s, 1H, pyrazole H-3), 8.87 (s, 1H, pyrazole H-3), 9.69

(s, 1H, triazine H-5); ^{13}C NMR (DMSO-d_6): δ 11.12, 84.97, 115.15, 121.58, 122.78, 126.00, 130.47, 140.58, 141.89, 143.98, 151.43, 154.23, 179.52; MS m/z(%): 329 (M^+, 22), 243 (27), 185 (100), 118 (51), 78 (74), 51 (60). Anal. Calcd for $C_{17}H_{11}N_7O$ (329.32): C, 62.00; H, 3.37; N, 29.77. Found: C, 61.87; H, 3.30; N, 29.62%.

3.3.3. [1,2,4]Triazolo[5,1-*c*][1,2,4]triazin-4-yl(5-methyl-1-phenyl-1H-pyrazol-4-yl)methanone (11)

Pale yellow solid; Yield 84%; mp 180–182 °C. IR (KBr): v 1639 (C=O) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.56 (s, 3H, CH_3), 7.30–7.77 (m, 5H, ArH's), 8.51 (s, 1H, pyrazole H-3), 8.65 (s, 1H, triazole H-5), 9.72 (s, 1H, triazine H-5); ^{13}C NMR (DMSO-d_6): δ 11.12, 121.57, 122.61, 126.00, 129.43, 131.00, 135.94, 140.67, 146.58, 153.11, 154.48, 155.21, 179.45; MS m/z(%): 305 (M^+, 76), 250 (22), 186 (20), 156 (45), 104 (18), 78 (100), 51 (98). Anal. Calcd for $C_{15}H_{11}N_7O$ (305.29): C, 59.01; H, 3.63; N, 32.12. Found: C, 58.87; H, 3.54; N, 32.01%.

3.3.4. Benzo[4,5]imidazo[2,1-c][1,2,4]triazin-4-yl(5-methyl-1-phenyl-1H-pyrazol-4-yl)methanone (12)

Pale yellow solid; Yield 80%; mp 346–348 °C. IR (KBr): v 1651 (C=O) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.51 (s, 3H, CH_3), 7.26–7.60 (m, 9H, ArH's), 8.37 (s, 1H, pyrazole H-3), 9.70 (s, 1H, triazine H-5); ^{13}C NMR (DMSO-d_6): δ 11.10, 120.47, 121.47, 122.61, 124.42, 126.00, 129.46, 129.89, 132.45, 140.48, 145.11, 149.23, 150.67, 150.98, 182.54; MS m/z(%): 354 (M^+, 8), 185 (100), 118 (43), 106 (15), 78 (64), 51 (59). Anal. Calcd for $C_{20}H_{14}N_6O$ (354.36): C, 67.79; H, 3.98; N, 23.72. Found C, 67.64; H, 3.92; N, 23.57%.

3.3.5. (8,10-Dimethylpyrido[2',3':3,4]pyrazolo[5,1-c][1,2,4]triazin-4-yl)(5-methyl-1-phenyl-1*H*-pyrazol-4-yl)methanone (13)

Pale yellow solid; Yield 80%; mp 174–176 °C. IR (KBr): v 1651 (C=O) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.50 (s, 3H, CH_3), 2.75 (s, 3H, CH_3), 2.88 (s, 3H, CH_3), 6.95 (s, 1H, pyridine H-5), 7.53–7.74 (m, 5H, ArH's), 8.68 (s, 1H, pyrazole H-3), 9.89 (s, 1H, triazine H-5); ^{13}C NMR (DMSO-d_6): δ 11.01, 20.32, 21.89, 101.88, 117.45, 119.61, 121.34, 122.36, 126.00, 126.89, 128.62, 129.16, 135.94, 140.58, 150.98, 154.22, 158.67, 165.24, 179.56; MS m/z(%): 383 (M^+, 87), 186 (76), 130 (55), 78 (100), 51 (77). Anal. Calcd for $C_{21}H_{17}N_7O$ (383.41): C, 65.79; H, 4.47; N, 25.57. Found: C, 65.56; H, 4.40; N, 25.44%.

3.4. Synthesis of pyridine derivatives (15-17)

Method A: A mixture of 4-(4-chlorocinnamoyl)-5-methyl-1-phenyl-pyrazole (**14**) (0.32 g, 1 mmol); the appropriate 2-cyanoacetamide, 2-cyanoacetohydrazide, or 2-cyanoethanethioamide (1 mmol); and few drops of acetic acid was thoroughly ground with a pestle in an open mortar at room temperature for 3–5 min until the mixture turned into a melt. The initial syrupy consistency continued for 5–10 min and the reaction was monitored by TLC. The solid was washed with water and crystallized from the appropriate solvent to give **15**–**17**, respectively.

Method B: A mixture of 4-(4-chlorocinnamoyl)-5-methyl-1-phenyl-pyrazole (**14**) (0.322 g, 1 mmol); 2-cyanoacetamide, 2-cyanoacetohydrazide, or 2-cyanoethanethioamide (1 mmol); and sodium hydroxide (0.3 g) in ethanol (20 mL) was refluxed for 6 h. The resulting solid was collected and crystallized from ethanol to give the respective pyridine derivatives (**15**–**17**).

3.4.1. 4-(4-Chlorophenyl)-1,2-dihydro-6-(5-methyl-1-phenyl-1*H*-pyrazol-4-yl)-2-oxopyridine-3-carbonitrile (15)

Pale yellow solid; Yield 78%; mp 116–118 °C. IR (KBr): υ 3412 (NH), 2219 (CN), 1652 (C=O) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.44 (s, 3H, CH_3), 6.91 (s, 1H, Pyridine H), 7.43–7.75 (m, 9H, ArH's), 7.96 (s, 1H, pyrazole H-3), 10.36 (s, br, 1H, NH); ^{13}C NMR (DMSO-d_6): δ 10.11, 91.87, 109.23, 111.96, 115.99, 122.37, 126.32, 128.35, 128.96, 132.71, 134.51, 136.52, 139.52, 142.57, 146.68, 156.21, 158.24; MS m/z(%): 386 (M^+, 19), 322 (68), 185 (100), 128 (65), 78 (75), 51 (47). Anal. Calcd for $C_{22}H_{15}ClN_4O$ (386.83): C, 68.31; H, 3.91; N, 14.48. Found C, 68.23; H, 3.98; N, 14.34%.

3.4.2. 1-Amino-4-(4-chlorophenyl)-6-(5-methyl-1-phenyl-1*H*-pyrazol-4-yl)-2-oxo-1,2-dihydropyridine-3-carbonitrile (16)

Pale yellow solid; Yield 76%; mp 178–179 °C. IR (KBr): υ 3422, 3184 (NH_2), 2213 (CN), 1632 (C=O) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.49 (s, 3H, CH_3), 6.87 (s, br, 2H, NH_2), 6.99 (s, 1H, Pyridine H), 7.43–7.75 (m, 9H, ArH's), 7.88 (s, 1H, pyrazole H-3); ^{13}C NMR (DMSO-d_6): δ 10.24, 91.75, 108.35. 114.27, 118.64, 121.32, 126.00, 128.45, 128.96, 132.45, 133.57, 135.67, 137.34, 139.84, 147.96, 150.23, 157.46; MS m/z(%): 401 (M^+, 100), 334 (31), 184 (29), 127 (28), 78 (46), 51 (21). Anal. Calcd for $C_{22}H_{16}ClN_5O$ (401.85): C, 65.76; H, 4.01; N, 17.43. Found C, 65.65; H, 4.01; N, 17.23%.

3.4.3. 4-(4-Chlorophenyl)-1,2-dihydro-6-(5-methyl-1-phenyl-1*H*-pyrazol-4-yl)-2-thioxopyridine-3-carbonitrile (17)

Pale yellow solid; Yield 86%; mp 266–268 °C. IR (KBr): υ 3446 (NH), 2218 (CN) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.48 (s, 3H, CH_3), 6.98 (s, 1H, Pyridine H), 7.40–7.79 (m, 9H, ArH's), 7.92 (s, 1H, pyrazole H-3), 13.86 (s, br, 1H, NH); ^{13}C NMR (DMSO-d_6): δ 10.24, 108.35. 110.45, 118.64, 121.32, 126.00, 128.45, 129.46, 132.45, 135.67, 137.23, 139.43, 140.76, 151.23, 154.46, 188.21; MS m/z(%): 402 (M^+, 18), 385 (52), 370 (87), 185 (67), 119 (39), 78 (100), 51 (44). Anal. Calcd for $C_{22}H_{15}ClN_4S$ (402.90): C, 65.58; H, 3.75; N, 13.91. Found: C, 65.51; H, 3.65; N, 13.86%.

3.5. Synthesis of thieno[2,3-*b*]pyridine derivatives (18 and 19)

Method A: A mixture of the thione **17** (0.40 g, 1 mmol), potassium carbonate (0.14 g, 1 mmol) and the appropriate ω-bromoacetophenone or ethyl chloroacetate (1 mmol each) was thoroughly ground with a pestle in an open mortar at room temperature for 3–5 min until the mixture turned into a melt. The initial syrupy consistency continued for 5–10 min and the reaction was monitored by TLC. The solid was washed with water and crystallized from the appropriate solvent to give **18** and **19**, respectively.

Method B: A mixture of the thione **17** (0.402 g, 1 mmol) and potassium hydroxide (0. 0.056 g, 1 mmol) in N,N-dimethylformamide (10 mL) was stirred for 2 h at room temperature. The appropriate ω-bromoacetophenone or ethyl chloroacetate (1 mmol each) was added and stirring was continued for 2 h. The resulting solid was collected and crystallized from ethanol to give **18** and **19**, respectively.

3.5.1. Ethyl 3-amino-4-(4-chlorophenyl)-6-(5-methyl-1-phenyl-1*H*-pyrazol-4-yl)thieno[2,3-*b*]pyridine-2-carboxylate (18)

Pale yellow solid; Yield 68%; mp 142–144 °C. IR (KBr): v 3434, 3312 (NH_2), 1714 (C=O) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 1.33 (t, J = 7.2 Hz, 3H, $CH_2\underline{CH_3}$), 2.48 (s, 3H, CH_3), 4.18 (q, J = 7.2 Hz, 2H, $\underline{CH_2}CH_3$), 7.82 (s, 1H, pyridine H-5), 7.41–7.86 (m, 11H, ArH's and NH_2), 7.93 (s, 1H, pyrazole H-3); ^{13}C NMR (DMSO-d_6): δ 11.75, 14.89, 60.30, 106.75, 119.58, 122.74, 126.00, 128.94, 132.17, 133.27, 135.69, 136.28, 136.32, 140.15, 144.58, 154.29, 155.78, 156.59, 164.00, 165.55; MS m/z(%): 488 (M^+, 19), 397 (51), 290 (39), 117 (100), 105 (80), 77 (63), 51 (58). Anal. Calcd for $C_{26}H_{21}ClN_4O_2S$ (488.99): C, 63.86; H, 4.33; N, 11.46. Found: C, 63.82; H, 4.18; N, 11.27%.

3.5.2. (3-Amino-4-(4-chlorophenyl)-6-(5-methyl-1-phenyl-1*H*-pyrazol-4-yl)thieno[2,3-*b*]pyridin-2-yl)(phenyl)methanone (19)

Pale yellow solid; Yield 88%; mp 124–126 °C. IR (KBr): v3435, 3268 (NH_2), 1666 (CO) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.49 (s, 3H, CH_3), 7.12 (s, 1H, pyridine H-5), 7.23–7.68 (m, 16H, ArH's, NH_2), 7.94 (s, 1H, pyrazole H-3); ^{13}C NMR (DMSO-d_6): δ 11.43, 118.33, 118.48, 122.89, 125.13, 126.00, 128.12, 128.64, 128.92, 132.19, 132.88, 123.98, 133.00, 133.28, 135.32, 136.27, 140.18, 144.85, 146.68, 154.89, 156.67, 162.38, 187.11; MS m/z(%): 522 (M+2, 5), 520 (M^+, 15), 415 (44), 305 (16), 185 (15), 151 (69), 77 (100), 51 (54). Anal. Calcd for $C_{30}H_{21}ClN_4OS$ (521.03): C, 69.16; H, 4.06; N, 10.75; S, 6.15. Found C, 69.43; H, 4.11; N, 10.94%.

3.5.3. Synthesis of 3-amino-4-(4-chlorophenyl)-6-(5-methyl-1-phenyl-1*H*-pyrazol-4-yl)-1*H*-pyrazolo[4',3':4,5]thieno[2,3-*b*]pyridine (20)

To a solution of the thione **17** (0.40 g, 1 mmol) in ethanol (10 mL) was added hydrazine hydrate (1 mL) and the mixture was heated under reflux for 20 h. The solution was poured over an ice-water mixture and then neutralized by HCl. The solid product was filtered off, dried, and crystallized from ethanol to afford compound **20**. Yellow crystals; Yield 67%; mp 316–318 °C; IR (KBr): v 3385, 3196 (NH_2 and NH), 1599 (C=N) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ2.53 (s, 3H, CH_3), 5.98 (s, br, 2H, NH_2), 7.23–7.78 (m, 10H, ArH's and pyridine H-5), 8.04 (s, 1H, pyrazole H-3), 11.43 (s, br, 1H, NH); ^{13}C NMR (DMSO-d_6): δ 11.38, 113.48, 114.99, 117.11, 126.00, 128.45, 128.98, 135.48, 136.07, 137.07, 137.95, 140.10, 141.67, 144.85, 151.89, 157.32, 162.16; MS m/z(%): 402 (M^++2, 37), 400 (M^+, 63), 183 (18), 117 (48), 77 (93), 51 (100). Anal. Calcd for $C_{22}H_{17}ClN_6$ (400.86): C, 65.92; H, 4.27; N, 20.96; Found: C, 65.77; H, 4.15; N, 20.76%.

3.6. Preliminary antimicrobial screening

Overnight culture was streaked on the surface of a Mueller-Hinton agar plate. A sterile filter paper disk was saturated with 10 μL of 0.5 mg/mL w/v solution of the compound under investigation in DMSO. The plates and disks were then incubated at 37 °C (for bacteria) and at 28 °C (for fungi) for 24 h and examined for inhibition zones to determine the activity of the tested compounds.

4. Conclusion

Compound **3** proved to be a useful precursor for synthesis of various fused heterocycles via its reactions with hydrazonoyl halides, hydroximoyl chlorides, and diazotized heterocyclic amines. Moreover, compound **14** proved

a useful precursor in the synthesis of various pyridine and thieno[2,3-*b*]pyridine derivatives. The structures of the newly synthesized compounds were confirmed by spectral data and elemental analyses. The results of the antimicrobial activity of the synthesized products were promising.

References

1. Tewari, A. K.; Mishra, A. *Bioorg. Med. Chem.* **2001**, *9*, 715–718.
2. Akbas, E.; Berber, I. *Eur. J. Med. Chem.* **2005**, *40*, 401–405.
3. Cornnello, M.; Ciciani, G.; Mini, E.; Guerrini, G.; Caciagli, B.; Selleri, S.; Costanzo, A.; Mazzei T. *Anticancer Drugs* **2005**, *16*, 645–661.
4. Ciciani, G.; Coronnello, M.; Guerrini, G.; Selleri, S.; Cantore, M.; Failli, P.; Mini, E.; Costanzo, A. *Bioorg. Med. Chem*. **2008**, *16*, 9409–9419.
5. Pevet, I.; Brulé, C.; Tizot, A.; Gohier, A.; Cruzalegui, F.; Boutin, J. A.; Goldstein, S. *Bioorg. Med. Chem.* **2011**, *19*, 2517–2528.
6. Lockman J. W.; Reeder, M. D.; Suzuki, K.; Ostanin; K., Hoff, R.; Bhoite, L.; Austin, H.; Baichwal, V.; Willardsen, J. A. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 2283–2286.
7. Tuccinardi, T.; Schenone, S.; Bondavalli, F.; Brullo, C.; Bruno, O.; Mosti, L.; Zizzari, A. T.; Tintori, C.; Manetti, F.; Ciampi, O.; et al. *Chem. Med. Chem.* **2008**, *3*, 898–913.
8. Shawali, A. S.; Parkanyi, C. *J. Heterocycl. Chem.* **1980**, *17*, 833–854.
9. Shawali, A. S.; Abdallah, M. A. *Adv. Heterocycl. Chem.* **1995**, *63*, 277–338.
10. Shawali, A. S.; Abdelhamid, A. O. *Current Org. Chem.* **2012**, *16*, 2673–2689.
11. Menichi, G.; Boutar, M.; Kokel, B.; Takagi, K.; Hubert-Habart, M. *J. Heterocycl. Chem.* **1986**, *23*, 275–279.
12. Abdelhamid, A. O.; Gomha, S. M. *J. Chem.* **2013**, *2013*, 1–7.
13. Abdelhamid, A. O.; Al-Atoom, A. A. *Synth. Comm.* **2006**, *36*, 97–110.
14. Ahmed, S. A.; Hussein, A. M.; Hozayen, W. G. M.; El-Ghandour, A. H. H.; Abdelhamid, A. O. *J. Heterocycl. Chem.* **2007**, *44*, 803–810.
15. Abdelhamid, A. O.; Shokry A. S.; Tawfiek, S. M. *J. Heterocycl. Chem.* **2012**, *49*, 116–124.
16. Abdelhamid, A. O.; Fahmi, A. A.; Alsheflo, A. A. M. *Eur. J. Chem.* **2012**, *3*, 129–137.
17. Ashok, D.; Pallavi, K.; Jagath Reddy, G.; Srinivasa Rao, K. *Heterocycl. Comm.* **2008**, *14*, 33–38.
18. Grayer, R. J.; Harborne, J. B. *Phytochemistry* **1994**, *37*, 19–42.
19. Irob, O. N.; Moo-Young, M.; Anderson, W. A. *Int. J. Pharm.* **1996**, *34*, 87–90.
20. Shawali, A. S.; Abdelhamid, A. O. *Bull. Soc. Japan* **1976**, *49*, 321–332.
21. Eweiss, N. F.; Osman, A. *J. Heterocycl. Chem.* **1980**, *17*, 1713–1717.
22. Parkanyi, C.; Abdelhamid, A. O.; Cheng, J. C. S.; Shawali, A. S. *J. Heterocycl. Chem.* **1948**, *21*, 1029–1035.
23. Abdelhamid, A. O.; Khalifa, F. A.; Ghabrial, S. S. *Phosphorus, Sulfur, and Silicon and the Related Elements* **1988**, *40*, 41–46.
24. Abdelhamid, A. O.; Abdou, S. E.; Mahgoub, S. A. *Arch. Pharm. Res.* **1992**, *15*, 317–321.
25. Abdelhamid, A. O.; Al-Hamidi, A. A. *J. Chin. Chem. Soc.* **1995**, *42*, 83–88.
26. Shaaban, M. R.; Eldebss, T. M. A.; Darweesh, A. F.; Farag, A. M. *J. Heteocycl. Chem.* **2008**, *45*, 1739–1744.