DOI 10.1007/s10593-018-2229-7

Chemistry of Heterocyclic Compounds **2018**, *54*(1), 51–57

One-pot three-component synthesis of a series of 4-aroyl-1,6-diaryl-3-methyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitriles in the presence of aluminum oxide as a nanocatalyst

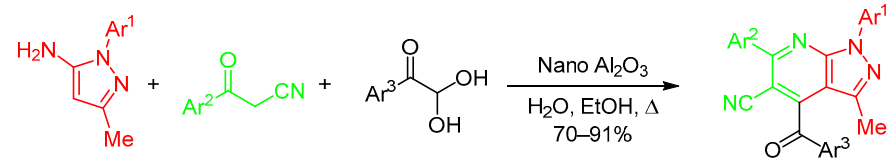
Fatemeh Majidi Arlan[1]*, Jabbar Khalafy[1], Ramin Maleki[2]

[1] *Department of Organic Chemistry, Faculty of Chemistry, Urmia University, P. O. Box 57153-165, Urmia, Iran; e-mail: majiidi@yahoo.com*

[2] *Research Department of Analytical Chemistry, Iranian Academic Center for Education, Culture and Research, P. O. Box 57155-397, Urmia, Iran; e-mail: malekichem@gmail.com*

Published in Khimiya Geterotsiklicheskikh Soedinenii, 2018, *54*(1), 51–57

Submitted July 25, 2017
Accepted after revision December 21, 2017



Ar^1 = Ph, 3-ClC_6H_4; Ar^2 = 4-ClC_6H_4, 4-MeC_6H_4; Ar^3 = Ph, 4-ClC_6H_4, 4-FC_6H_4, 4-$MeOC_6H_4$

One-pot three-component reaction of arylglyoxals, 3-aryl-3-oxopropanenitriles, and 5-amino-1-aryl-3-methylpyrazoles using various solvent systems and different catalysts under reflux conditions afforded the corresponding 4-aroyl-1,6-diaryl-3-methyl-1*H*-pyrazolo[3,4-*b*]-pyridine-5-carbonitrile derivatives. The best yields (70–91%) were obtained using Al_2O_3 as a nanocatalyst in H_2O–EtOH, 1:1, under reflux conditions. The simplicity of workup procedure, the novelty of pyrazolopyridines, green solvent system, easy preparation of a nanocatalyst, and good to excellent yields of the products are the advantages of this synthetic strategy. The structures of all products were confirmed by FT-IR, ^{1}H and ^{13}C NMR, and mass spectral data.

Keywords: arylglyoxals, pyrazolo[3,4-*b*]pyridines, multicomponent reaction, nanocatalyst, one-pot reaction.

The synthesis of nitrogen-containing heterocyclic compounds have attracted much attention due to their wide biological and pharmaceutical activities.[1–3] The presence of two or more different heterocyclic moieties in a single molecule unites properties of all the heterocyclic skeletons present and may enhance the pharmacological or biological activity. Therefore, the design of novel polycyclic heterocycles by combining various structurally diverse motifs have recently received considerable attention due to numerous applications.[4–7]

Fused heterocyclic compounds such as pyrazolopyridines are an important class of organic compounds with biological and pharmacological activities, such as antibacterial,[8] antimicrobial,[9,10] antileishmanial,[11,12] antiproliferative,[13] cytotoxic and anti-biofilm,[14] antioxidant,[15] antimalarial,[16] anticancer,[17] and GSK-3 inhibiting.[18]

Multicomponent reactions (MCRs) play an important role in the synthesis of heterocyclic compounds by multiple bond-making or bond-breaking through environmentally and economically useful one-pot procedures.[19–23] MCRs in green solvents and using green catalysts can be a powerful tool in organic synthesis.

In continuation of our studies in the field of new heterocyclic compound synthesis,[24–30] herein, we report a one-pot three-component procedure toward a series of new 4-aroyl-1,6-diaryl-3-methyl-1*H*-pyrazlo[3,4-*b*]pyridine-5-carbonitriles in the presence of different catalysts under reflux conditions. In comparison to the methods reported before, our method provides pyrazolo[3,4-*b*]pyridines in good to high yields and using green solvent system.[4,5]

In our initial studies, 1-(3-chlorophenyl)-3-methyl-1*H*-pyrazol-5-amine (**1b**), 3-(4-chlorophenyl)-3-oxopropanenitrile (**2a**), and phenylglyoxal hydrate (**3a**) were chosen as starting compounds for the test reaction (Scheme 1). We did not observe the formation of the desired product even after 24 h upon stirring the reaction mixture in the absence of a catalyst at room temperature. Refluxing the reaction mixture using various catalysts and different solvent systems (Table 1) gave solid precipitate, which was separated in 15–89% yield. It was characterized by IR, NMR spectroscopy and MS spectrometry to be the desired 1*H*-pyrazolo[3,4-*b*]pyridine **4i**.

To study the effect of the amount of catalyst, the reaction was carried out in the presence of various amounts

Scheme 1. One-pot synthesis of 1*H*-pyrazolo[3,4-*b*]pyridine derivative **4i**

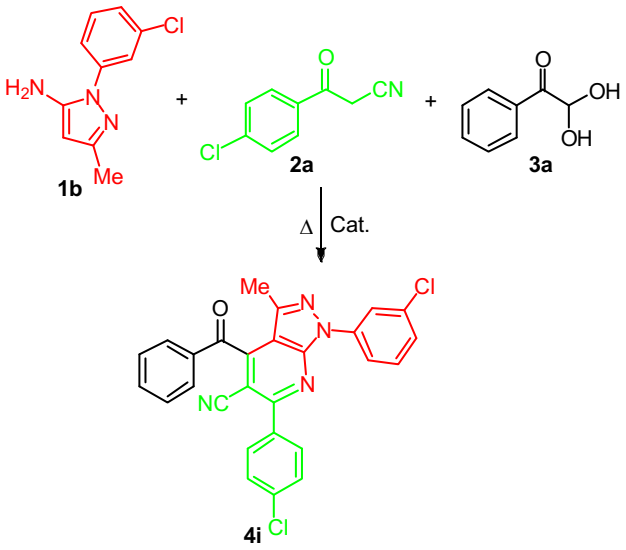


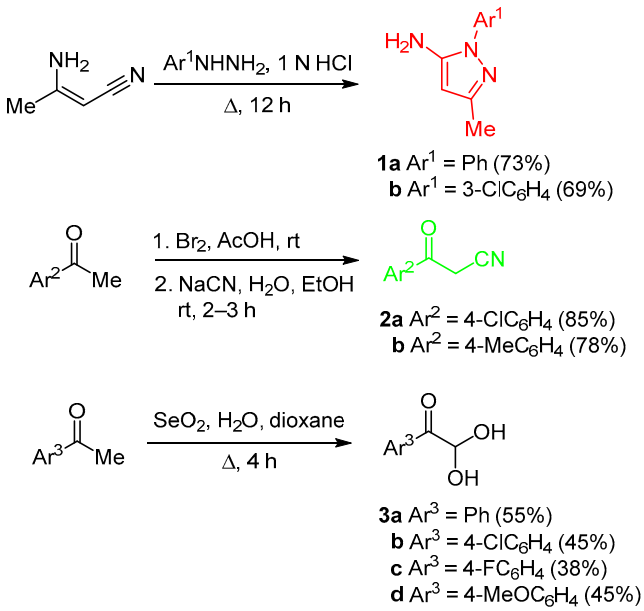
Table 1. Optimization of the reaction conditions

Solvents	Catalyst (mol %)	Time, h	Yield, %
AcOH	–	8	54
H_2O–AcOH	–	6	63
EtOH	Nano Al_2O_3 (10)	7	78
H_2O	Nano Al_2O_3 (20)	24	–
H_2O–EtOH	Nano Al_2O_3 (5)	7	66
H_2O–EtOH	**Nano Al_2O_3 (10)**	**7**	**89**
H_2O–EtOH	Nano Al_2O_3 (20)	7	86
H_2O–EtOH	–	7	15
H_2O–EtOH	$ZnCl_2$ (20)	10	53
H_2O–EtOH	*p*-TSA (20)	8	71
H_2O–EtOH	L-proline (20)	8	46
H_2O–EtOH	concd HCl	7	57
$CHCl_3$	Al_2O_3 (20)	14	42
H_2O–EtOH	Al_2O_3 (10)	7	57

of Al_2O_3 ranging from 5 to 20 mol %, and increasing the amount of catalyst did not improve the yield. To find the best solvent for this reaction, we carried out the trial reaction using various solvent systems such as AcOH, H_2O–AcOH, H_2O–EtOH, EtOH, H_2O, and $CHCl_3$. Among all these solvents, H_2O–EtOH, 1:1, was proved to be the best in terms of yield. The acid nature catalysts, such as concentrated HCl, *p*-TSA, $ZnCl_2$, AcOH, and L-proline as an amino acid, gave lower yields. The best result, in terms of yield (89%) and reaction time (7 h), was obtained when the reaction was performed using 10 mol % Al_2O_3 as a nanocatalyst in H_2O–EtOH, 1:1.

After optimizing the reaction conditions, we next determined the scope of this reaction with diverse arylglyoxals, 5-amino-1-aryl-3-methylpyrazoles, and 3-aryl-3-oxopropanenitriles. Starting materials, including 1-aryl-5-amino-3-methylpyrazoles **1a**,**b**,[31] 3-oxo-3-phenylpropanenitriles **2a**,**b**,[32,33] and arylglyoxal monohydrates **3a**–**d**,[34] were prepared by the literature-reported methods (Scheme 2).

Scheme 2. Preparation of the starting compounds **1a**,**b**, **2a**,**b**, **3a**–**d**



The sol-gel procedure was used for synthesis of nano-Al_2O_3 according to the literature method with some modifications.[35] The SEM image of desired nanocatalyst is shown in Figure 1.

The one-pot three component reaction of 1-aryl-5-amino-3-methylpyrazoles **1a**,**b**, 3-oxo-3-phenylpropanenitriles **2a**,**b**, and arylglyoxal hydrates **3a**–**d** in H_2O–EtOH, 1:1, under reflux conditions in the presence of Al_2O_3 nanocatalyst gave the desired 1*H*-pyrazolo[3,4-*b*]pyridines **4a**–**p** in 70–91% yield (Scheme 3). The reaction times and the yields of products **4a**–**p** are listed in Table 2. The structures of substituted 4-aroyl-3-methyl-1,6-diaryl-1*H*-pyrazolo[3,4-*b*]-pyridine-5-carbonitriles **4a**–**p** were characterized using FT-IR, ^1H and ^{13}C NMR, and mass spectral data and microanalysis. The characteristic singlet at around 2.29–2.32 ppm was ascribed to the methyl group of the pyrazole moiety and was present in all new products. In the ^{13}C NMR spectra of products, signals located around

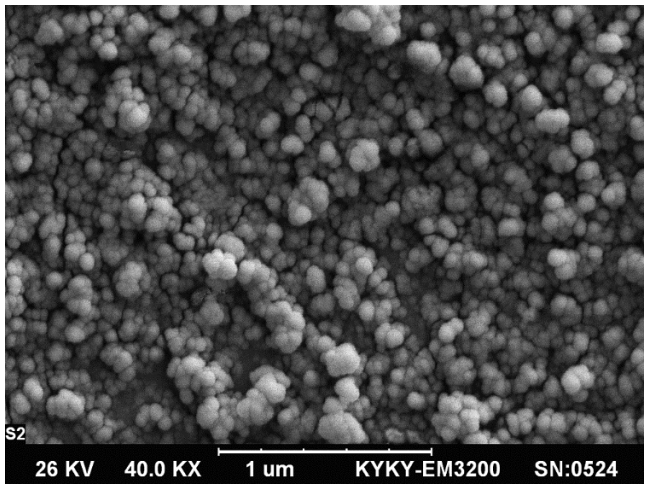


Figure 1. The SEM image of Al_2O_3 nanocatalyst. Particle size 34.9–74.1 nm.

Scheme 3. One-pot synthesis of substituted 1*H*-pyrazolo[3,4-*b*]pyridine derivatives **4a**–**p**

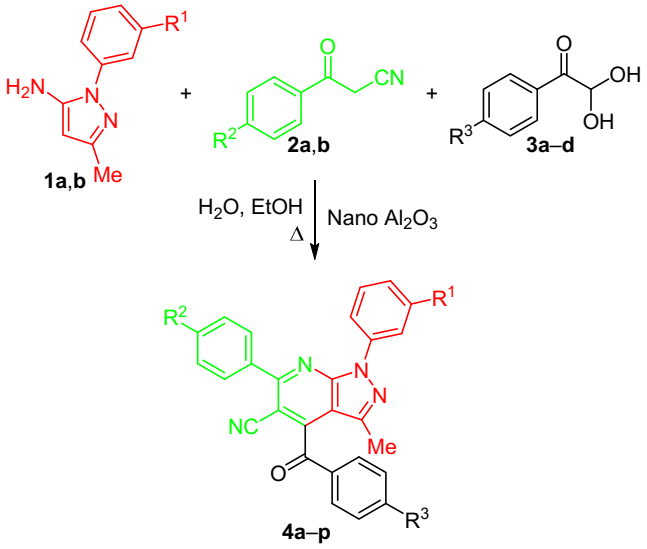


Table 2. Reaction conditions and yields of substituted 1*H*-pyrazolo[3,4-*b*]pyridines **4a**–**p**

Compound	R^1	R^2	R^3	Reaction time, h	Yield*, %
4a	H	Cl	H	6	91
4b	H	Cl	F	8	86
4c	H	Cl	OMe	6	75
4d	H	Cl	Cl	7	79
4e	H	Me	H	8	84
4f	H	Me	F	8	81
4g	H	Me	OMe	7	70
4h	H	Me	Cl	8	79
4i	Cl	Cl	H	7	89
4j	Cl	Cl	F	7	78
4k	Cl	Cl	OMe	6	76
4l	Cl	Cl	Cl	7	85
4m	Cl	Me	H	8	83
4n	Cl	Me	F	8	80
4o	Cl	Me	OMe	8	76
4p	Cl	Me	Cl	8	81

* The isolated yields are referred to the recrystallized products.

189.8–191.7 ppm were attributed to the carbonyl groups of arylglyoxal moieties, and signals observed around 13.8–13.9 ppm were due to the methyl groups of pyrazole moiety. In the FT-IR spectra, the characteristic absorption bands at 2218–2222 and 1500–1676 cm^{-1} could be assigned to the vibrations of the nitrile and carbonyl groups, respectively.

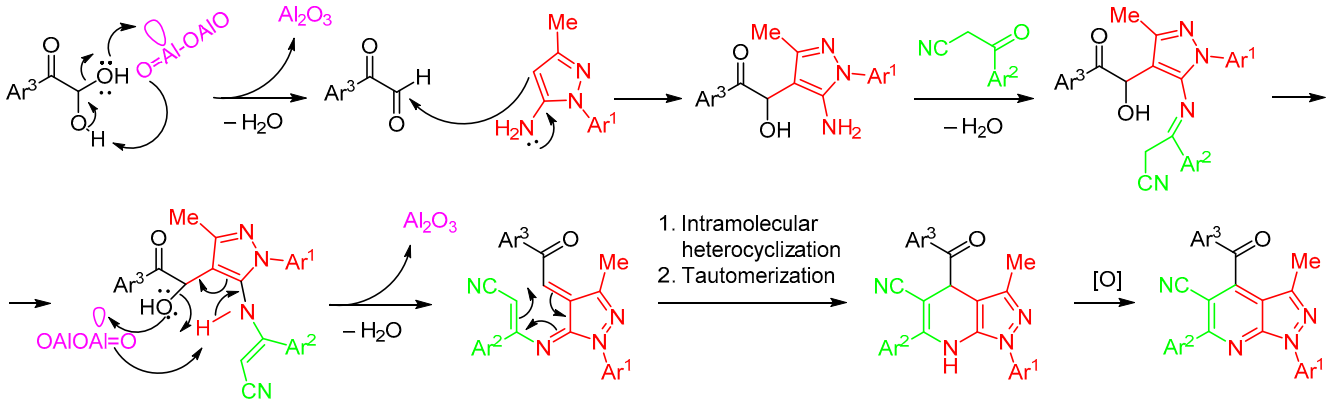
Mechanistically, the formation of products **4a**–**p** was achieved by a sequence of reactions involving the initial condensation of arylglyoxals with 5-amino-1-aryl-3-methylpyrazoles, followed by second condensation of the intermediate with 3-aryl-3-oxopropanenitriles, providing the corresponding dihydro-1*H*-pyrazolo[3,4-*b*]pyridines through intramolecular heterocyclization and subsequent tautomerization, which was finally dehydrogenated to the desired 4-aroyl-1,6-diaryl-3-methyl-1*H*-pyrazolo[3,4-*b*]-pyridine-5-carbonitriles *via* autoxidation (Scheme 4).

We have reported, one-pot three-component synthesis of a new series of 4-aroyl-1,6-diaryl-3-methyl-1*H*-pyrazolo-[3,4-*b*]pyridine-5-carbonitrile derivatives in the presence of Al_2O_3 as a nanocatalyst. These new pyrazolo[3,4-*b*]-pyridines may also have useful biological and pharmacological properties, and they could also serve as intermediates for new planar polycyclic heterocycles. The simplicity, ease of product and catalyst isolations, mild reaction conditions, using green solvents, and good yields are the main advantages of this procedure.

Experimental

Infrared spectra were recorded on a Thermo-Nicolet Nexus 670-FT-IR instrument using KBr pellets. ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance AQS 300 spectrometer (300 and 75.5 MHz, respectively) in $CDCl_3$. Chemical shifts were measured using TMS as internal standard. Mass spectra were recorded on a Agilent Technologies 5975C VL MSD instrument with Triple-Axis detector, electron impact (EI, 70 eV). Melting points were measured on a Philip Harris C4954718 apparatus and are uncorrected. The reaction monitoring was accomplished by TLC on silica gel PolyGram SILG/UV254 plates. The scanning electron microscopy (SEM) image was obtained from a JEOL JXA-840 Electron Microscopy Ltd.

Scheme 4. The proposed mechanism for synthesis of substituted 1*H*-pyrazolo[3,4-*b*]pyridines catalyzed by Al_2O_3 as a nanocatalyst



Preparation of Al_2O_3 nanocatalyst. A 0.05 M ethanolic solution of aluminum nitrate was prepared. The pH of solution was adjusted to 8.5 by addition of 25% NH_3 solution in order to form aluminum hydroxide gel. The formed gel was let to maturate for 24 h at room temperature, afterward dried at 110°C for 6 h, and then calcined in an electric furnace for 2 h at 700°C.

Synthesis of pyrazolopyridines 4a–p (General method). Arylglyoxal hydrate **3a**–**d** (1 mmol) was added to a solution of 3-oxo-3-phenylpropanenitrile **2a**,**b** (1 mmol) in H_2O–EtOH, 1:1 (5 ml), followed by the addition of 1-aryl-5-amino-3-methylpyrazole **1a**,**b** (1 mmol) and Al_2O_3 nanocatalyst (15–18 mg, 10 mol %). The resulting reaction mixture was refluxed for 6–8 h. The reaction completion was monitored by TLC (eluent EtOAc–hexane, 2:3). The precipitate was filtered, washed with water, dried, and recrystallized from ethanol to give the desired product **4a**–**p** as white or yellow needles.

6-(4-Chlorophenyl)-3-methyl-1-phenyl-4-(phenylcarbonyl)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitrile (4a). Yield 0.41 g (91%), white needles, mp 171–173°C. IR spectrum, ν, cm^{-1}: 3070, 2927, 2220, 1676, 1580, 1489, 1438, 1220, 1091, 783, 741, 676. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 8.27 (2H, d, *J* = 8.1, H Ar); 8.01–7.89 (4H, m, H Ar); 7.79–7.68 (1H, m, H Ar); 7.63–7.48 (6H, m, H Ar); 7.37 (1H, t, *J* = 7.5, H Ar); 2.31 (3H, s, CH_3). ^{13}C NMR spectrum, δ, ppm: 191.9; 162.3; 159.0; 150.2; 149.4; 143.1; 138.4; 137.0; 135.6; 134.9; 130.9; 130.1; 129.5; 129.3; 129.1; 126.9; 121.3; 116.1; 111.9; 97.7; 13.8. Mass spectrum, *m*/*z* (I_{rel}, %): 450 $[M(^{37}Cl)]^+$ (4), 448 $[M]^+$ (13), 347 (11), 346 (53), 345 $[M(^{37}Cl)–PhCO]^+$ (55), 344 (100), 343 $[(M)–PhCO]^+$ (64), 329 (18), 303 (10), 267 (14), 165 (10), 111 (23), 77 $[Ph]^+$ (73), 51 (34). Found, %: C 72.13; H 3.69; N 12.54. $C_{27}H_{17}ClN_4O$. Calculated, %: C 72.24; H 3.82; N 12.48.

6-(4-Chlorophenyl)-4-[(4-fluorophenyl)carbonyl]-3-methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitrile (4b). Yield 0.40 g (86%), yellow needles, mp 178–179°C. IR spectrum, ν, cm^{-1}: 3065, 2220, 1675, 1590, 1498, 1420, 1390, 1229, 1094, 750, 678. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 8.32–8.20 (2H, m, H Ar); 8.03–7.89 (4H, m, H Ar); 7.59–7.48 (4H, m, H Ar); 7.42–7.25 (3H, m, H Ar); 2.31 (3H, s, CH_3). ^{13}C NMR spectrum, δ, ppm: 190.0; 168.9; 159.3; 150.4; 148.9; 143.5; 139.4; 137.3; 135.2; 134.9; 133.1; 130.8; 130.7; 130.3; 129.2; 129.1; 126.7; 126.3; 121.0; 116.8; 112.1; 97.9; 13.8. Mass spectrum, *m*/*z* (I_{rel}, %): 468 $[M(^{37}Cl)]^+$ (5), 466 $[M]^+$ (14), 347 (11), 346 (48), 345 $[M(^{37}Cl)–(4\text{-}FC_6H_4)CO]^+$ (51), 344 (100), 343 $[M–(4\text{-}FC_6H_4)CO]^+$ (62), 330 (18), 267 (14), 123 (29), 95 (16), 77 $[Ph]^+$ (49), 51 (29). Found, %: C 69.32; H 3.69; N 12.41. $C_{27}H_{16}ClFN_4O$. Calculated, %: C 69.46; H 3.45; N 12.00.

6-(4-Chlorophenyl)-4-[(4-methoxyphenyl)carbonyl]-3-methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitrile (4c). Yield 0.36 g (75%), white needles, mp 206–207°C. IR spectrum, ν, cm^{-1}: 3055, 2218, 1655, 1583, 1500, 1430, 1261, 1170, 1017, 844, 755. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 8.27 (2H, d, *J*=7.8, H Ar); 8.00 (2H, d, *J* = 8.4, H Ar); 7.89 (2H, d, *J* = 8.1, H Ar); 7.51–7.58 (4H, m, H Ph); 7.37 (1H, t, *J* = 7.5, H Ph); 7.03 (2H, d, *J* = 8.7, H Ar); 3.92 (3H, s, OCH_3); 2.32 (3H, s, CH_3). ^{13}C NMR spectrum, δ, ppm: 190.0; 165.5; 159.0; 150.2; 149.8; 143.2; 138.5; 136.9; 135.6; 132.7; 130.9; 129.3; 129.0; 128.1; 126.8; 126.5; 121.3; 116.2; 114.8; 111.9; 55.8; 13.8. Mass spectrum, *m*/*z* (I_{rel}, %): 480 $[M(^{37}Cl)]^+$ (10), 478 $[M]^+$ (28), 344 (29), 343 $[M–(4\text{-}MeOC_6H_4)CO]^+$ (15), 267 (10), 136 (15), 135 $[4\text{-}MeOC_6H_4CO]^+$ (100), 107 $[4\text{-}MeOC_6H_4]^+$ (19), 92 (27), 77 $[Ph]^+$ (74), 51 (16). Found, %: C 70.09; H 3.82; N 11.41. $C_{28}H_{19}ClN_4O_2$. Calculated, %: C 70.22; H 4.00; N 11.70.

6-(4-Chlorophenyl)-4-[(4-chlorophenyl)carbonyl]-3-methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitrile (4d). Yield 0.38 g (79%), yellow needles, mp 170–172°C. IR spectrum, ν, cm^{-1}: 3070, 2927, 2220, 1676, 1580, 1489, 1438, 1220, 1091, 783, 741, 676. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 8.26 (2H, d, *J* = 7.8, H Ar); 7.98 (2H, d, *J* = 8.1, H Ar); 7.87 (2H, d, *J* = 8.4, H Ar); 7.59–7.48 (6H, m, H Ar, H Ph); 7.38 (1H, t, *J* = 7.2, H Ph); 2.32 (3H, s, CH_3). ^{13}C NMR spectrum, δ, ppm: 190.7; 159.0; 150.2; 148.6; 142.9; 142.5; 138.4; 137.1; 135.4; 133.3; 131.3; 130.9; 129.9; 129.3; 129.2; 129.1; 128.9; 126.9; 121.3; 116.0; 13.9. Mass spectrum, *m*/*z* (I_{rel}, %): 486 $[M+4]^+$ (1), 484 $[M(^{37}Cl)]^+$ (6), 482 $[M]^+$ (8), 346 (45), 345 (42), 344 (100), 343 (65), 329 (15), 267 (12), 200 (34), 141 $[^{37}ClC_6H_4CO]^+$ (12), 139 $[^{35}ClC_6H_4CO]^+$ (37), 111 (20), 77 $[Ph]^+$ (47), 51 (27). Found, %: C 66.91; H 3.26; N 11.71. $C_{27}H_{16}Cl_2N_4O$. Calculated, %: C 67.09; H 3.34; N 11.59.

3-Methyl-6-(4-methylphenyl)-1-phenyl-4-phenylcarbonyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitrile (4e). Yield 0.36 g (84%), pale-yellow needles, mp 175–176°C. IR spectrum, ν, cm^{-1}: 3058, 2923, 2219, 1672, 1590, 1499, 1425, 1387, 1216, 1022, 743, 681. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 8.35–8.28 (2H, m, H Ar); 7.99–7.87 (3H, m, H Ar); 7.72 (1H, t, *J* = 7.2, H Ar); 7.65–7.45 (4H, m, H Ar); 7.43–7.25 (4H, m, H Ar); 2.70 (3H, s, CH_3); 2.32 (3H, s, CH_3). ^{13}C NMR spectrum, δ, ppm: 192.1; 162.3; 159.8; 150.4; 143.5; 138.6; 136.9; 135.5; 135.1; 134.7; 130.1; 129.5; 129.4; 129.2 (2C); 126.6; 121.2; 116.4; 114.8; 100.6; 21.5; 13.9. Mass spectrum, *m*/*z* (I_{rel}, %): 429 $[M+H]^+$ (37), 428 $[M]^+$ (99), 399 (49), 105 $[PhCO]^+$ (81), 77 $[Ph]^+$ (100), 51 (20). Found, %: C 78.13; H 4.49; N 13.21. $C_{28}H_{20}N_4O$. Calculated, %: C 78.49; H 4.70; N 13.08.

4-[(4-Fluorophenyl)carbonyl]-3-methyl-6-(4-methylphenyl)-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitrile (4f). Yield 0.36 g (81%), pale-yellow needles, mp 204–205°C. IR spectrum, ν, cm^{-1}: 3074, 2923, 2221, 1673, 1591, 1484, 1425, 1384, 1231, 1091, 776. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 8.37–8.25 (2H, m, H Ar); 8.08–7.86 (3H, m, H Ar); 7.60–7.45 (3H, m, H Ar); 7.43–7.31 (3H, m, H Ar); 7.31–7.18 (2H, m, H Ar); 2.47 (3H, s, CH_3); 2.31 (3H, s, CH_3). ^{13}C NMR spectrum, δ, ppm: 190.1; 165.4; 160.4; 143.5; 138.9; 136.9; 134.7; 133.0; 131.6; 129.5; 129.4; 129.3; 129.2 (2C); 126.7; 126.3; 120.8; 118.9; 116.3; 114.7; 100.5; 97.6; 21.5; 13.8. Mass spectrum, *m*/*z* (I_{rel}, %): 447 $[M+H]^+$ (12), 446 $[M]^+$ (36), 417 (24), 325 (27), 324 $[(M+H)–(4\text{-}FC_6H_4)CO]^+$ (100), 323 (71), 308 (16), 282 (11), 200 (12), 123 $[4\text{-}FC_6H_4CO]^+$ (43), 94 (29), 77 $[Ph]^+$ (37), 51 $[C_4H_3]^+$ (19). Found, %: C 75.21; H 4.18; N 12.68. $C_{28}H_{19}FN_4O$. Calculated, %: C 75.32; H 4.29; N 12.55.

4-[(4-Methoxyphenyl)carbonyl)-3-methyl-6-(4-methylphenyl)-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitrile (4g). Yield 0.32 g (70%), white needles, mp 184–186°C. IR spectrum, ν, cm^{-1}: 3057, 2924, 2220, 1675, 1590, 1500, 1426, 1388, 1259, 1171, 1020, 784, 676. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 8.31 (2H, d, *J* = 7.8, H Ar); 8.02–7.86 (4H, m, H Ar); 7.59–7.45 (4H, m, H Ar); 7.42–7.30 (3H, m, H Ar); 3.92 (3H, s, OCH_3); 2.47 (3H, s, CH_3); 2.32 (3H, s, CH_3). ^{13}C NMR spectrum, δ, ppm: 190.3; 165.4; 162.3; 159.8; 143.5; 138.6; 136.9; 134.7; 132.7; 129.5; 129.4; 129.3; 129.2; 128.2; 126.6; 126.3; 120.9; 118.9; 116.5; 114.7; 100.6; 55.8; 21.5; 13.8. Mass spectrum, *m/z* (I_{rel}, %): 458 $[M]^+$ (5), 325 (37), 324 $[(M+H)–(4\text{-}MeOC_6H_4)CO]^+$ (100), 323 (93), 309 (24), 283 (15), 282 (11), 135 $[4\text{-}MeOC_6H_4CO]^+$ (12), 77 $[Ph]^+$ (44), 51 (21). Found, %: C 75.84; H 4.97; N 12.31. $C_{29}H_{22}N_4O_2$. Calculated, %: C 75.97; H 4.84; N 12.22.

4-[(4-Chlorophenyl)carbonyl]-3-methyl-6-(4-methylphenyl)-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitrile (4h). Yield 0.37 g (79%), pale-yellow needles, mp 169–170°C. IR spectrum, ν, cm^{-1}: 3057, 2922, 2219, 1675, 1583, 11467, 1421, 1389, 1217, 1090, 1016, 747, 676. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 8.31 (2H, d, *J* = 7.2, H Ar); 7.94 (2H, d, *J* = 6.9, H Ar); 7.61–7.49 (5H, m, H Ar); 7.42–7.33 (4H, m, H Ar); 2.69 (3H, s, CH_3); 2.31 (3H, s, CH_3). ^{13}C NMR spectrum, δ, ppm: 190.9; 160.4; 150.4; 148.5; 143.5; 138.9; 138.5; 134.7; 134.2; 133.4; 131.4; 129.9; 129.5; 129.4; 129.2 (2C); 126.7; 126.3; 116.3; 97.6; 21.5; 13.9. Mass spectrum, *m/z* (I_{rel}, %): 464 $[M(^{37}Cl)]^+$ (7), 462 $[M]^+$ (20), 325 (31), 324 (100), 323 (79), 308 (17), 282 (12), 141 $[^{37}ClC_6H_4CO]^+$ (17), 140 (10), 139 $[^{35}ClC_6H_4CO]^+$ (35), 109 (10), 107 (24), 91 (13), 77 $[Ph]^+$ (55), 51 $[C_4H_3]^+$ (24). Found, %: C 72.46; H 4.05; N 11.95. $C_{28}H_{19}ClN_4O$. Calculated, %: C 72.65; H 4.14; N 12.10.

1-(3-Chlorophenyl)-6-(4-chlorophenyl)-3-methyl-4-phenylcarbonyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitrile (4i). Yield 0.43 g (89%), white needles, mp 178–179°C. IR spectrum, ν, cm^{-1}: 3079, 2934, 2220, 1661, 1585, 1488, 1260, 1169, 1094, 1017, 836, 777. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 8.37 (1H, s, H Ar); 8.29 (1H, d, *J* = 8.4, H Ar); 8.00 (2H, d, *J* = 8.1, H Ar); 7.92 (2H, d, *J* = 7.8, H Ar); 7.75 (1H, t, *J* = 7.2, H Ar); 7.65–7.52 (4H, m, H Ar); 7.45 (1H, t, *J* = 7.8, H Ar); 7.32 (1H, d, *J* = 7.8, H Ar); 2.29 (3H, s, CH_3). ^{13}C NMR spectrum, δ, ppm: 191.7; 159.3; 150.4; 149.5; 143.6; 139.5; 137.2; 135.7; 135.3; 134.9 (2C); 130.9; 130.7; 130.3; 130.1; 129.5; 129.1; 126.7; 126.3; 121.0; 118.8; 115.9; 13.8. Mass spectrum, *m/z* (I_{rel}, %): 486 $[M+4]^+$ (14), 484 $[M(^{37}Cl)]^+$ (82), 482 $[M]^+$ (94), 457 (5), 455 (28), 453 (43), 378 (16), 301 (15), 237 (20), 111 (26), 105 $[PhCO]^+$ (100), 77 $[Ph]^+$ (92), 51 (12). Found, %: C 66.87; H 3.45; N 11.79. $C_{27}H_{16}Cl_2N_4O$. Calculated, %: C 67.09; H 3.34; N 11.59.

1-(3-Chlorophenyl)-6-(4-chlorophenyl)-4-[(4-fluorophenyl)carbonyl]-3-methyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitrile (4j). Yield 0.39 g (78%), white needles, mp 208–209°C. IR spectrum, ν, cm^{-1}: 3098, 2945, 2222, 1665, 1584, 1492, 1428, 1231, 1091, 1012, 844, 764, 677, 614. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 8.36 (1H, s, H Ar); 8.29 (1H, d, *J* = 7.8, H Ar); 8.08–7.91 (4H, m, H Ar); 7.57 (2H, d, *J* = 8.4, H Ar); 7.48 (1H, t, *J* = 8.1, H Ar); 7.35–7.26 (3H, m, H Ar); 2.31 (3H, s, CH_3). ^{13}C NMR spectrum, δ, ppm: 190.0; 168.9; 159.3; 150.4; 148.9; 143.5; 139.4; 137.3; 135.2; 134.9; 133.0; 130.8; 130.7; 130.3; 129.2; 129.1; 126.7; 126.3; 121.1; 116.9; 112.1; 97.9; 13.8. Mass spectrum, *m/z* (I_{rel}, %): 504 $[M+4]^+$ (4), 502 $[M(^{37}Cl)]^+$ (23), 500 $[M]^+$ (33), 382 (13), 380 (71), 378 $[(M+H)–4\text{-}FC_6H_4CO]^+$ (100), 377 (19), 343 (37), 267 (11), 176 (13), 165 (13), 148 (12), 123 $[4\text{-}FC_6H_4CO]^+$ (96), 111 $[^{35}ClC_6H_4]^+$ (47), 95 (58), 75 (55), 51 (11). Found, %: C 64.51; H 3.14; N 11.02. $C_{27}H_{15}Cl_2FN_4O$. Calculated, %: C 64.69; H 3.02; N 11.18.

1-(3-Chlorophenyl)-6-(4-chlorophenyl)-4-[(4-methoxyphenyl)carbonyl)]-3-methyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitrile (4k). Yield 0.39 g (76%), orange needles, mp 176–178°C. IR spectrum, ν, cm^{-1}: 3077, 2932, 2220, 1662, 1584, 1487, 1439, 1260, 1169, 1094, 1017, 836, 771, 672. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 8.36 (1H, s, H Ar); 8.27 (1H, d, *J* = 8.1, H Ar); 7.99 (2H, d, *J* = 6.9, H Ar); 7.88 (2H, d, *J* = 5.7, H Ar); 7.56–7.41 (4H, m, H Ar); 7.02 (2H, d, *J* = 8.1, Ar); 3.87 (3H, s, OCH_3); 2.31 (3H, s, CH_3). ^{13}C NMR spectrum, δ, ppm: 189.8; 165.5; 150.4; 149.9; 143.8; 139.5; 137.2; 135.4; 134.9; 132.7; 130.9; 130.7; 129.8; 129.4; 129.1; 126.6; 126.3; 120.9; 118.8; 116.6; 112.2; 55.8; 13.8. Mass spectrum, *m/z* (I_{rel}, %): 516 $[M+4]^+$ (10), 514 $[M(^{37}Cl)]^+$ (32), 512 $[M]^+$ (43), 139 (14), 136 (22), 135 $[4\text{-}MeOC_6H_4CO]^+$ (100), 111 $[ClC_6H_4]^+$ (28), 107 $[4\text{-}MeOC_6H_4]^+$ (29), 91 (32), 77 $[Ph]^+$ (49). Found, %: C 65.39; H 3.42; N 10.87. $C_{28}H_{18}Cl_2N_4O_2$. Calculated, %: C 65.51; H 3.53; N 10.91.

1-(3-Chlorophenyl)-6-(4-chlorophenyl)-4-[(4-chlorophenyl)carbonyl]-3-methyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitrile (4l). Yield 0.44 g (85%), light-orange needles, mp 191–193°C. IR spectrum, ν, cm^{-1}: 3079, 2932, 2219, 1674, 1581, 1487, 1483, 1220, 1090, 1007, 899, 770, 672. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 8.36 (1H, s, H Ar); 8.29 (1H, d, *J* = 8.1, H Ar); 7.99 (2H, d, *J* = 8.4, H Ar); 7.86 (1H, d, *J* = 8.1, H Ar); 7.60–7.50 (4H, m, H Ar); 7.51–7.41 (2H, m, H Ar); 7.33 (1H, d, *J* = 8.7, H Ar); 2.31 (3H, s, CH_3). ^{13}C NMR spectrum, δ, ppm: 190.5; 159.3; 150.4; 148.8; 143.4; 142.6; 139.4; 137.3; 135.2; 134.9; 130.8; 130.7; 130.3; 129.5; 129.2; 129.1; 126.7; 126.3; 118.8; 115.8; 112.1; 98.1; 13.9. Mass spectrum, *m/z* (I_{rel}, %): 522 $[M+6]^+$ (1), 520 $[M+4]^+$ (8), 518 $[M(^{37}Cl)]^+$ (22), 516 $[M]^+$ (22), 382 (19), 380 (74), 378 $[M(^{37}Cl)–^{35}ClC_6H_4CO]^+$ (100), 343 (36), 267 (11), 165 (13), 140 $[^{35}ClC_6H_4CO]^+$ (25), 138 (68), 134 (15), 113 $[^{37}ClC_6H_4]^+$ (27), 111 $[^{35}ClC_6H_4]^+$ (72), 75 (48), 51 $[C_4H_3]^+$ (10). Found, %: C 62.51; H 3.10; N 10.97. $C_{27}H_{15}Cl_3N_4O$. Calculated, %: C 62.63; H 2.92; N 10.82.

1-(3-Chlorophenyl)-3-methyl-6-(4-methylphenyl)-4-phenylcarbonyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitrile (4m). Yield 0.38 g (83%), pale-yellow needles, mp 201–202°C. IR spectrum, ν, cm^{-1}: 3061, 2923, 2221, 1673, 1590, 1483, 1385, 1027, 775, 742. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 8.37 (1H, s, H Ar); 8.30 (1H, d, *J* = 8.1, H Ar); 8.00–7.87 (4H, m, H Ar); 7.62–7.53 (1H, m, H Ar); 7.43–7.32 (4H, m, H Ar); 7.29–7.20 (2H, m, H Ar); 2.45 (3H, s, CH_3); 2.25 (3H, s, CH_3). ^{13}C NMR spectrum, δ, ppm: 195.1; 159.9; 150.5; 143.9; 143.5; 140.9; 139.9; 136.9; 134.9; 134.8; 131.2; 130.6; 129.4; 128.9; 128.2;

125.9; 121.0; 120.5; 118.4; 115.0; 100.9; 98.1; 21.5; 13.8. Mass spectrum, *m/z* (I_{rel}, %): 464 $[M(^{37}Cl)]^+$ (7), 462 $[M]^+$ (20), 436 (12), 358 (24), 346 (21), 236 (27), 234 (76), 119 (98), 111 (50), 105 $[PhCO]^+$ (99), 95 (64), 77 $[Ph]^+$ (100), 51 $[C_4H_3]^+$ (26). Found, %: C 72.71; H 4.06; N 12.19. $C_{28}H_{19}ClN_4O$. Calculated, %: C 72.65; H 4.14; N 12.10.

1-(3-Chlorophenyl)-4-[(4-fluorophenyl)carbonyl]-3-methyl-6-(4-methylphenyl)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitrile (4n). Yield 0.38 g (80%), yellow needles, mp 185–187°C. IR spectrum, ν, cm^{-1}: 3074, 2923, 2221, 1673, 1591, 1484, 1384, 1231, 1091, 1031, 776, 743. ^1H NMR spectrum, δ, ppm (*J*, Hz): 8.41 (1H, s, H Ar); 8.40–8.29 (1H, m, H Ar); 8.01–7.91 (4H, m, H Ar); 7.52–7.35 (4H, m, H Ar); 7.37 (2H, m, H Ar); 2.48 (3H, s, CH_3); 2.30 (3H, s, CH_3). ^{13}C NMR spectrum, δ, ppm: 190.2; 165.4; 159.9; 150.6; 148.8; 143.9; 141.3; 139.6; 134.9; 134.5; 132.9; 131.6; 130.2; 129.6; 126.5; 126.0; 120.6; 118.6; 116.8; 115.0; 100.9; 98.0; 21.5; 13.8. Mass spectrum, *m/z* (I_{rel}, %): 482 $[M(^{37}Cl)]^+$ (10), 480 $[M]^+$ (29), 451 (20), 234 (26), 123 $[4\text{-}FC_6H_4CO]^+$ (100), 119 (27), 111 $[^{35}ClC_6H_4]^+$ (26), 95 (59), 91 $[Ar_2]^+$ (16), 75 (26). Found, %: C 69.81; H 3.91; N 11.82. $C_{28}H_{18}ClFN_4O$. Calculated, %: C 69.93; H 3.77; N 11.65.

1-(3-Chlorophenyl)-4-[(4-methoxyphenyl)carbonyl]-3-methyl-6-(4-methylphenyl)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitrile (4o). Yield 0.37 g (76%), pale-yellow needles, mp 205–206°C. IR spectrum, ν, cm^{-1}: 3061, 2923, 2221, 1653, 1592, 1483, 1385, 1264, 1172, 1088, 1024, 906, 776, 738. ^1H NMR spectrum, δ, ppm (*J*, Hz): 8.40 (1H, s, H Ar); 8.33 (1H, d, *J* = 8.1, H Ar); 7.94 (2H, d, *J* = 7.8, H Ar); 7.49–7.34 (5H, m, H Ar); 7.28 (1H, t, *J* = 7.2, H Ar); 6.99 (2H, d, *J* = 7.8, H Ar); 3.92 (3H, s, OCH_3); 2.68 (3H, s, CH_3); 2.48 (3H, s, CH_3). ^{13}C NMR spectrum, δ, ppm: 187.9; 159.9; 150.6; 143.9; 140.9; 139.9; 137.0; 136.9; 134.8; 134.5; 130.1; 129.9; 129.5; 129.3; 128.7; 126.0; 120.6; 120.5; 118.6; 118.4; 115.0; 100.9; 21.5; 13.9. Mass spectrum, *m/z* (I_{rel}, %): 494 $[M(^{37}Cl)]^+$ (7), 492 $[M]^+$ (20), 136 (12), 135 $[4\text{-}MeOC_6H_4CO]^+$ (100), 119 (13), 111 $[^{35}ClC_6H_4]^+$ (13), 107 $[4\text{-}MeOC_6H_4]^+$ (18), 92 (17), 77 $[Ph]^+$ (33). Found, %: C 70.45; H 4.15; N 11.47. $C_{29}H_{21}ClN_4O_2$. Calculated, %: C 70.66; H 4.29; N 11.37.

1-(3-Chlorophenyl)-4-[(4-chlorophenyl)carbonyl]-3-methyl-6-(4-methylphenyl)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitrile (4p). Yield 0.40 g (81%), yellow needles, mp 193–195°C. IR spectrum, ν, cm^{-1}: 3063, 2922, 2221, 1673, 1587, 1483, 1384, 1224, 1089, 1011, 907, 777, 729. ^1H NMR spectrum, δ, ppm (*J*, Hz): 8.47 (1H, s, H Ar); 8.45 (1H, d, *J* = 7.8, H Ar); 8.38–8.29 (1H, m, H Ar); 7.95 (2H, d, *J* = 8.4, H Ar); 7.86 (2H, d, *J* = 8.4, H Ar); 7.55 (2H, d, *J* = 8.4, H Ar); 7.39 (2H, d, *J* = 8.4, H Ar); 7.37–7.21 (1H, m, H Ar); 2.48 (3H, s, CH_3); 2.31 (3H, s, CH_3). ^{13}C NMR spectrum, δ, ppm: 191.1; 160.6; 148.6; 143.3; 141.3; 139.9; 139.6; 134.9; 134.0; 133.4; 130.9; 130.2; 129.9; 129.7; 129.6; 129.5; 129.0; 126.0; 125.3; 118.1; 115.0; 100.9; 21.5; 13.7. Mass spectrum, *m/z* (I_{rel}, %): 500 $[M+4]^+$ (3), 498 $[M(^{37}Cl)]^+$ (16), 496 $[M]^+$ (22), 467 (12), 236 (13), 234 (37), 141 $[^{37}ClC_6H_4CO]^+$ (24), 139 $[^{35}ClC_6H_4CO]^+$ (72), 133 (12), 119 (100), 113 $[^{37}ClC_6H_4]^+$ (21), 111 $[^{35}ClC_6H_4]^+$ (64), 91 (54), 75 (23), 65 (21). Found, %: C 67.54; H 3.51; N 11.14. $C_{28}H_{18}Cl_2N_4O$. Calculated, %: C 67.62; H 3.65; N 11.26.

Supplementary information file containing ^1H NMR spectra of compounds **4a**–**p** and mass spectrum of compound is available at the journal website at http://link.springer.com/journal/10593.

The authors are grateful for support from the Urmia University.

We also thank Prof. R. H. Prager from the Flinders University of Australia for proof-reading and language editing of this article.

References

1. Hao, Y.; Xu, X.-P.; Chen, T.; Zhao, L.-L.; Ji, S.-J. *J. Org. Biomol. Chem*. **2012**, *10*, 724.
2. Tu, X.-J.; Hao, W.-J.; Ye, Q.; Wang, S.-S.; Jiang, B.; Li, G.; Tu, S.-J. *J. Org. Chem*. **2014**, *79*, 11110.
3. Lavecchia, G.; Berteina-Raboin, S. B.; Guillaumet, G. *Tetrahedron Lett.* **2004**, *45*, 2389.
4. Petrova, O. N.; Zamigajlo, L. L.; Gella, I. M.; Musatov, V. I.; Shishkina, S. V.; Shishkin, O. V.; Vashchenko, E. V.; Borisov, A. V.; Lipson, V. V. *Chem. Heterocycl. Compd.* **2014**, *50*, 514. [*Khim. Geterotsikl. Soedin.* **2014**, 562.]
5. Potapov, A. Yu.; Vandyshev, D. Yu.; Kosheleva, Y. A.; Polikarchuk, V. A.; Potapov, M. A.; Shikhaliev, Kh. S. *Chem. Heterocycl. Compd.* **2017**, *53*, 207. [*Khim. Geterotsikl. Soedin.* **2017**, *53*, 207.]
6. Govindaraju, S.; Tabassum, S.; Khan, R.-u.-R.; Afzal Pasha, M. *Chin. Chem. Lett.* **2017**, *28*, 437.
7. Abdel-Monem, Y. K.; El-Enein, S. A. A.; El-Sheikh-Amer, M. M. *J. Mol. Struct.* **2017**, *1127*, 386.
8. Leal, B.; Afonso, I. F.; Rodrigues, C. R.; Abreu, P. A.; Garrett, R.; Carlos, L.; Pinheiro, S.; Azevedo, A. R.; Borges, J. C.; Vegi, P. F.; Santos, C. C.; da Silveira, F. C. A.; Cabral, L. M.; Frugulhetti, I. C. P. P.; Bernardino, A. M. R.; Santos, D. O.; Castro, H. C. *Bioorg. Med. Chem.* **2008**, *16*, 8196.
9. Melha, S. A. *Arch. Pharm.* **2013**, *346*, 912.
10. Chandak, N.; Kumar, S.; Kumar, P.; Sharma, C.; Aneja, K. R.; Sharma, P. K. *Med. Chem. Res*. **2013**, *22*, 5490.
11. de Mello, H. D.; Echevarria, A.; Bernardino, A. M.; Canto-Cavalheiro, M.; Leon, L. L. *J. Med. Chem*. **2004**, *47*, 5427.
12. Anand, D.; Yadav, P. K.; Patel, O. P. S.; Parmar, N.; Maurya, R. K.; Vishwakarma, P.; Raju, K. S. R.; Taneja, S.; Wahajuddin, M.; Kar, S.; Yadav, P. P. *J. Med. Chem.* **2017**, *60*, 1041.
13. Salem, M. S.; Ali, M. A. M. *Biol. Pharm. Bull.* **2016**, *39*, 473.
14. Nagender, P.; Reddy, G. M.; Kumar, R. N.; Poornachandra, Y.; Kumar, C. G.; Narsaiah, B. *Bioorg. Med. Chem. Lett*. **2014**, *24*, 2905.
15. Gouda, M. A. *Arch. Pharm.* **2012**, *345*, 155.
16. Saini, D.; Jain, S.; Kumar, A.; Jain, N. *EXCLI J.* **2016**, *15*, 730.
17. Mohamed, M. S.; Awad, Y. E. E. D.; El-Hallouty, S. M.; El-Araby, M. *Open J. Med. Chem.* **2012**, *2*, 78.
18. Lavrard, H.; Popowycz, F. *Eur. J. Org. Chem*. **2017**, *2017*, 600.
19. Cioc, R.; Ruijter, E.; Orru, R. *Green Chem*. **2014**, *16*, 2958.
20. Sarkar, S.; Das, D. K.; Khan, A. T. *RSC Adv.* **2014**, *4*, 53752.
21. Petrova, O. N.; Zamigajlo, L. L.; Ostras, K. S.; Shishkina, S. Sh.; Shishkin, O. V.; Borisov, A. V.; Musatov, V. I.; Shirobokova, M. G.; Lipson, V. V. *Chem. Heterocycl. Compd.* **2015**, *51*, 310. [*Khim. Geterotsikl. Soedin.* **2015**, *51*, 310.]
22. Satish, G.; Sharma, A.; Gadidasu, K. K.; Vedula, R. R.; Penta, S. *Chem. Heterocycl. Compd.* **2016**, *52*, 409. [*Khim. Geterotsikl. Soedin.* **2016**, *52*, 409.]

23. Govindaraju, S.; Tabassum, S.; Khan, R.-u.-R.; Afzal Pasha, M. *Chem. Heterocycl. Compd.* **2016**, *52*, 964. [*Khim. Geterotsikl. Soedin.* **2016**, *52*, 964.]
24. Poursattar Marjani, A.; Khalafy, J.; Prager, R. H. *Chem. Heterocycl. Compd.* **2012**, *48*, 931. [*Khim. Geterotsikl. Soedin.* **2012**, 1001.]
25. Poursattar Marjani, A.; Khalafy, J.; Salami, F.; Mohammadlou, M. *Synthesis* **2015**, 1656.
26. Poursattar Marjani, A.; Khalafy, J.; Mahmoodi, S. *ARKIVOC* **2016**, (iii), 262.
27. Poursattar Marjani, A.; Khalafy, J.; Rostampoor, A. *J. Heterocycl. Chem.* **2017**, *54*, 648.
28. Poursattar Marjani, A.; Khalafy, J.; Chitan, M.; Mahmoodi, S. *Iran. J. Chem. Chem. Eng.* **2017**, *36*, 1.
29. Ezzati, M.; Khalafy, J.; Poursattar Marjani, A.; Prager, R. H. *Tetrahedron* **2017**, *73*, 6587.
30. Poursattar Marjani, A.; Khalafy, J.; Haghi, A. *J. Heterocycl. Chem.* **2017**, *54*, 3294.
31. Ganesan. A.; Heathcock. C. H. *J. Org. Chem.* **1993**, *58*, 6155.
32. Kordik, C. P.; Luo, C.; Zanoni, B. C.; Dax, S. L.; McNally, J. J.; Lovenberg, T. W.; Wilson, S. J.; Reitz, A. B. *Bioorg Med. Chem. Lett.* **2001**, *11*, 2283.
33. Lee, S.; Kim, T.; Lee, B. H.; Yoo, S.; Lee, K.; Yi, K. Y. *Bioorg. Med. Chem. Lett*. **2007**, *17*, 1291.
34. Riley, H. A.; Gray, A. R. In *Organic Syntheses*; Blatt, A. H., Ed.; Wiley & Sons: New York, 1943, Vol. 2, p 509.
35. Rogojan, R.; Andronescu, E.; Ghitulica, C.; Vasile, B. S. *Sci. Bull. – "Politeh." Univ. Bucharest*, *Ser. B* **2011**, *73*, 1454.