DOI 10.1007/s10593-019-02400-0

Chemistry of Heterocyclic Compounds **2018**, *54*(12), 1111–1116

Facile one-pot synthesis of N-fused 1,2,4-triazoles *via* oxidative cyclization using manganese dioxide

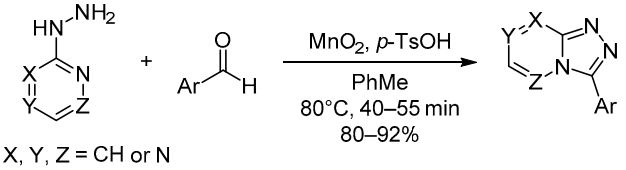
Ashish Bhatt[1]*, Rajesh K. Singh[2], Ravi Kant[1]

[1] *Department of Chemistry, Mewar University, Chittorgarh (Rajasthan) 312901, India; e-mail: itsbhatt2007@yahoo.co.in*

[2] *Department of Pharmacy, Mewar University, Chittorgarh (Rajasthan) 312901, India*

Published in Khimiya Geterotsiklicheskikh Soedinenii, 2018, *54*(12), 1111–1116

Submitted September 25, 2018
Accepted November 23, 2018



X, Y, Z = CH or N
Ar = Ph, 2-MeC_6H_4, 3-$F_3CC_6H_4$, 4-ClC_6H_4, 4-BrC_6H_4, 4-$MeOC_6H_4$, 4-HOC_6H_4, 4-NCC_6H_4, 2-furyl, 5-thiazolyl, 3-indolyl

A facile one-pot synthesis of N-fused 1,2,4-triazoles from heterocyclic hydrazines and aldehydes is reported. The reaction is efficiently promoted by manganese dioxide to afford the desired products mostly in high yields and in relatively short times. The mild nature of the synthesis, cheap oxidizing agent, and short reaction time are notable advantages of the developed protocol. This protocol is effective toward various substrates having different functionalities.

Keywords: manganese dioxide, toluene, 1,2,4-triazole, [1,2,4]triazolo[4,3-*a*]pyrazine, [1,2,4]triazolo[4,3-*b*]pyridazine, [1,2,4]triazolo-[4,3-*a*]pyridine, [1,2,4]triazolo[4,3-*a*]pyrimidine.

N-Fused aromatic nitrogen heterocycles are among the most important compound classes in drug discovery and also play a pivotal role in living organisms.[1,2] In particular, such scaffolds can be used as building blocks for DNA (guanine, adenine), they are also found in many approved drugs, including zolpidem and trazodone, and are featured in medicinal chemistry studies[3–6] (e.g., tyrosine kinase c-Src inhibitors[7,8] or p38α kinase inhibitors,[9] Fig. 1).

1,2,4-Triazoles have elicited considerable interest among medicinal chemists because they are considered to be privileged structural constituents of many pharmaceutical agents as well as natural products. In particular, compounds containing N-fused 1,2,4-triazoles substructures, such as triazolopyridine and triazolopyrazine moieties, exhibit a wide spectrum of biological activity including antifungal,[10] antimicrobial,[11] antiviral,[12] anti-inflammatory,[13] antiasthmatic,[14] antiproliferative,[15] and hypotonic.[16] In addition, they have often been used as bioisosteres of esters and amides, and as dipeptidomimetics in a number of pharmacologically important molecules.[17] On the other hand, they also play important roles as ligands in organometallic compounds, as precursors for N-heterocyclic carbenes, as ionic liquids, and as corrosion inhibitors.[18]

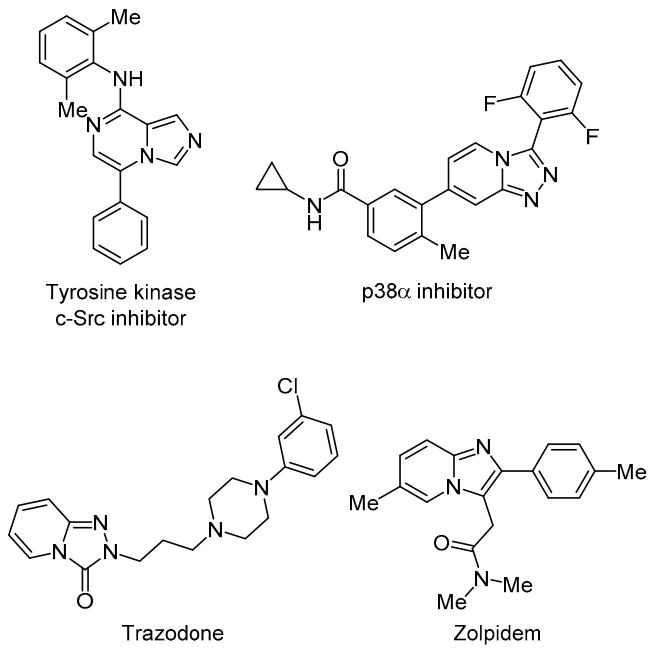
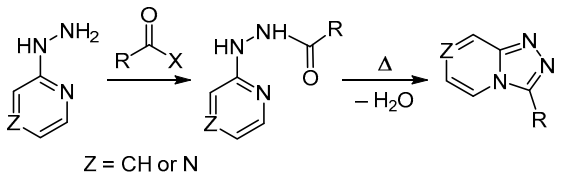


Figure 1. Representative bioactive molecules comprising fused heterocycles related to 1,2,4-triazoles.

Due to their importance, many efficient methods have been developed to access N-fused 1,2,4-triazoles.[19] Among them, coupling of carboxylic acids or their derivatives with amidrazones, followed by cyclodehydration is the most common explored strategy (Scheme 1).[20] However, some of these protocols suffer from the limitations of harsh conditions, tedious synthetic procedures, time-consuming reactions, and unsatisfactory yields. Hence, the development of milder and more general procedures to access N-fused 1,2,4-triazoles with high yields in short reaction time remains desirable.

Scheme 1. General synthesis of N-fused 1,2,4-triazoles



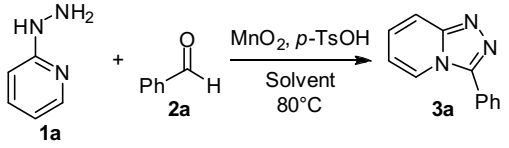
The described oxidative cyclization has previously been reported for the preparation of triazoloquinoxalines.[21–27] Other methods reported in the literature for the cyclization of the triazole ring usually require a combination of NBS and base,[28] refluxing orthoesters,[29,30] acids,[30,31] desulfurization of thiosemicarbazides,[32] or cyclization of hydrazides in polyphosphoric acid.[30] A few examples of oxidative cyclizations using chloramine-T have previously been reported.[33]

MnO_2 has been used for the oxidation of varieties of functional groups in various organic solvents and also in aqueous solution. MnO_2 is a cheap oxidant, therefore, studies for the development of the new methods for using this reagent in a more efficient way are of practical importance. Our continued interest in the development of useful synthetic methodologies prompted us to explore the feasibility of MnO_2 for the one-pot synthesis of N-fused 1,2,4-triazoles. However, it has not been investigated as a catalyst in the synthesis of 1,2,4-triazoles until now.

Our preliminary investigation began with the reaction of 2-hydrazinopyridine (**1a**) and benzaldehyde (**2a**) in the presence of MnO_2 (1 equiv) and a catalytic amount of *p*-TsOH (2 mol %) in ethanol at 80°C. We were delighted to observe the formation of the desired fused heterocyclic product 3-phenyl[1,2,4]triazolo[4,3-*a*]pyridine (**3a**), albeit in a moderate yield of 65% (Table 1, entry 1). Next, we optimized the reaction conditions in order to increase the yield. Thus, different solvents were screened, and the results are summarized in Table 1. It was found that toluene was the best solvent in terms of the reaction time and yield of the product (Table 1, entry 3).

Once we had established a suitable solvent for the synthesis of N-fused 1,2,4-triazoles, we then focused on the quantity of MnO_2 and *p*-TsOH. An increase in the amount of MnO_2 (from 1 to 4 equiv) and *p*-TsOH (from 2 to 5 mol %) not only decreased the reaction time from two hours to 45 min, but also increased the product yield from 80 to 95% (Table 1, entry 7). Further increasing the quantity of MnO_2 to 5 equiv and that of *p*-TsOH to 10 mol % led to a decrease in the yield (Table 1, entry 8). Therefore, we

Table 1. Optimization of the reaction conditions for synthesis of compound **3a**



Entry	Solvent	MnO_2, equiv	*p*-TsOH, mol %	Time, h	Yield, %
1	EtOH	1	2	3.5	65
2	1,4-Dioxane	1	2	3.5	60
3	PhMe	1	2	2	80
4	DCE	1	2	4	55
5	MeCN	1	2	4	50
6	PhMe	2	5	1.5	90
7	PhMe	4	5	0.75	95
8	PhMe	5	10	0.5	82

decided to perform the subsequent reactions of the heterocyclic hydrazines with different aldehydes in the presence of MnO_2 (4 equiv) and *p*-TsOH (5 mol %) as the catalyst in toluene at 80°C. The effect of temperature on the yields of the products was also investigated, but increasing the temperature did not produce satisfactory yields.

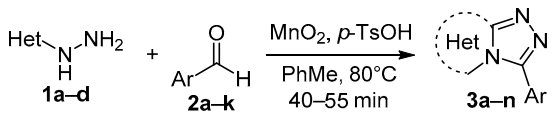
With optimized conditions in hand, the scope of the reaction was investigated, and the results are summarized in Table 2. As expected, aldehydes **2a**–**k** gave with pyridine derivative **1a** the corresponding N-fused 1,2,4-triazoles: [1,2,4]triazolo[4,3-*a*]pyridines **3a**–**k**, [1,2,4]triazolo-[4,3-*a*]pyrazine **3l**, [1,2,4]triazolo[4,3-*b*]pyridazine **3m**, and [1,2,4]triazolo[4,3-*a*]pyrimidine **3n** in good to excellent yields. Benzaldehydes with electron-donating groups such as *o*-tolualdehyde (**2b**) and *p*-anisaldehyde (**2f**) gave the desired [1,2,4]triazolo[4,3-*a*]pyridines **3b**,**f** in very good yields. Aromatic aldehydes with an electron-withdrawing groups **2c**–**e**,**h** and heteroaryl aldehydes **2i**–**k** gave only slightly lower yields. Pyrazine, pyridazine, and pyrimidine derivatives **1b**–**d** have also been successfully coupled with benzaldehyde (**2a**) affording the corresponding N-fused 1,2,4-triazoles **3l**–**n** in good yields.

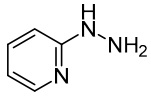
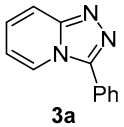
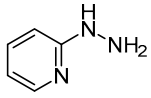
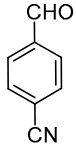
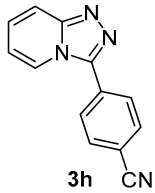
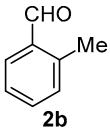
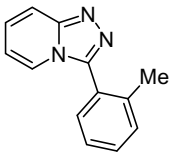
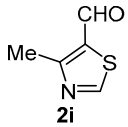
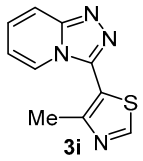
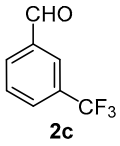
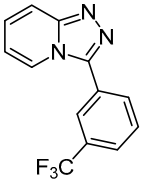
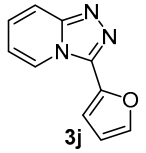
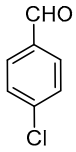
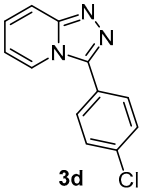
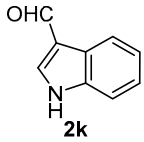
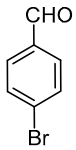
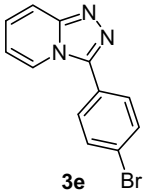
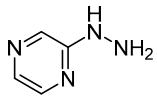
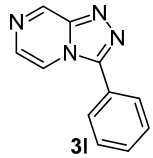
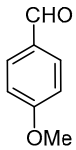
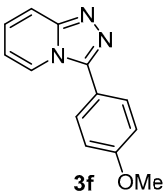
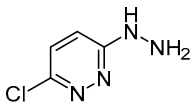
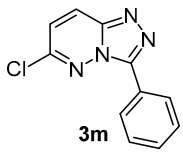
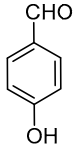
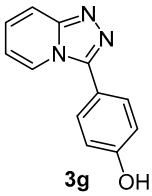
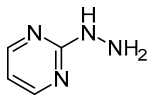
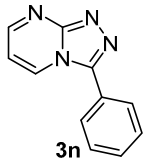
In conclusion, we have developed a short and efficient synthesis of N-fused 1,2,4-triazoles using a mild and straightforward one-pot condensation/oxidative cyclization of aldehydes and hetaryl hydrazines with manganese dioxide as oxidant. A variety of substituents are tolerated allowing the synthesis of diverse products in good to excellent yields at short reaction times. The newly developed synthetic route is believed to be valuable not only for the construction of building blocks, but also for medicinal chemistry studies of N-fused 1,2,4-triazole moiety.

Experimental

^1H and ^{13}C NMR spectra were recorded on an AV-500 Bruker spectrometer (500 and 126 MHz, respectively) in $CDCl_3$ or DMSO-d_6 with TMS as internal standard. High-resolution mass spectra were recorded on a Thermo Finnigan MAT95XP microspectrometer using electron

Table 2. Synthesis of [1,2,4]triazolo[4,3-*a*(*b*)]azines **3a**–**n**



HetNHNH$_2$	ArCHO	Product	Yield, %	HetNHNH$_2$	ArCHO	Product	Yield, %
 **1a**	PhCHO **2a**	 **3a**	95	 **1a**	 **2h**	 **3h**	85
	 **2b**	 **3b**	98		 **2i**	 **3i**	80
	 **2c**	 **3c**	85		 **2j**	 **3j**	88
	 **2d**	 **3d**	90		 **2k**	 **3k**	82
	 **2e**	 **3e**	91	 **1b**	**2a**	 **3l**	92
	 **2f**	 **3f**	98	 **1c**	**2a**	 **3m**	90
	 **2g**	 **3g**	90	 **1d**	**2a**	 **3n**	86

impact ionization. Elemental analyses were performed on a VarioEL analyzer. Melting points were determined on a Stuart SMP3 melting point apparatus. The progress of the reactions was monitored by TLC on silica gel 60 F254 (Merck) TLC plates, eluent hexane–EtOAc, 6:4. Column chromatography was carried out using Merck silica gel (200–300 mesh), eluent hexane–EtOAc, 6:4. All solvents and reagents were purchased from commercial sources and used without further purification.

Synthesis of N-fused 1,2,4-triazoles 3a–**n** (General method). *p*-TsOH (9.5 mg, 55 μmol, 5 mol %) and MnO_2 (348 mg, 4.00 mmol) were added to a stirred solution of heterocyclic hydrazine **1a**–**d** (1 mmol) and aldehyde **2a**–**k** (1.2 mmol) in PhMe (10 ml). The mixture was heated at 80°C until the starting material was completely consumed (monitored by TLC, 40–55 min) and then cooled down to room temperature. After filtration and evaporation of solvent from the filtrate, the resulting residue was purified by silica gel column chromatography affording pure products.

3-Phenyl[1,2,4]triazolo[4,3-*a*]pyridine (3a). Yield 85 mg (95%), white solid, mp 171–173°C (mp 175–176°C[34a]). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 6.89 (1H, td, *J* = 6.8, *J* = 1.1, H Py); 7.31 (1H, ddd, *J* = 9.3, *J* = 6.5, *J* = 1.1, H Py); 7.55–7.63 (3H, m, H Ph); 7.82–7.88 (3H, m, 1H Py, 2H Ph); 8.30 (1H, dt, *J* = 7.0, *J* = 1.2, H Py). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 114.5; 116.7; 122.7; 126.5; 127.5; 128.3; 129.4; 130.3; 146.8; 150.3. Found, *m*/*z*: 195.0792 $[M]^+$. $C_{12}H_9N_3$. Calculated, *m*/*z*: 195.0791. Found, %: C 73.80; H 4.61; N 21.48. $C_{12}H_9N_3$. Calculated, %: C 73.83; H 4.65; N 21.52.

3-(2-Methylphenyl)[1,2,4]triazolo[4,3-*a*]pyridine (3b). Yield 94 mg (98%), white solid, mp 148–150°C (mp 149–150°C[34b]). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 2.27 (3H, s, CH_3); 6.84 (1H, td, *J* = 6.7, *J* = 1.1, H Py); 7.30 (1H, ddd, *J* = 9.3, *J* = 6.5, *J* = 1.2, H Py); 7.37 (1H, td, *J* = 7.3, *J* = 1.4, H Ar); 7.40–7.45 (1H, m, H Ar); 7.45–7.51 (2H, m, H Ar); 7.80 (1H, d, *J* = 7.0, H Py); 7.84 (1H, d, *J* = 9.3, H Py). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 19.8; 113.9; 116.6; 122.7; 125.6; 126.3; 127.1; 130.3; 130.6; 131.1; 138.6; 146.4; 149.8. Found, *m*/*z*: 209.0949 $[M]^+$. $C_{13}H_{11}N_3$. Calculated, *m*/*z*: 209.0948. Found, %: C 74.59; H 5.28; N 20.05. $C_{13}H_{11}N_3$. Calculated, %: C 74.62; H 5.30; N 20.08.

3-[3-(Trifluoromethyl)phenyl][1,2,4]triazolo[4,3-*a*]-pyridine (3c). Yield 103 mg (85%), light-yellow solid, mp 154–156°C (mp 154–155°C[34c]). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 6.97 (1H, td, *J* = 6.8, *J* = 1.1, H Py); 7.36 (1H, ddd, *J* = 9.3, *J* = 6.5, *J* = 1.1, H Py); 7.76 (1H, t, *J* = 7.8, H Ar); 7.84 (1H, d, *J* = 7.9, H Ar); 7.89 (1H, d, *J* = 9.3, H Py); 8.05–8.11 (1H, m, H Ar); 8.14 (1H, d, *J* = 1.7, H Ar); 8.28 (1H, d, *J* = 7.0, H Py). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 114.9; 117.0; 122.3; 125.1 (q, J_{CF} = 3.9); 126.9 (q, J_{CF} = 3.9); 127.5; 127.6; 130.0; 131.3; 131.9 (q, J_{CF} = 33.1); 145.4; 150.7. Found, *m*/*z*: 263.0668 $[M]^+$. $C_{13}H_8F_3N_3$. Calculated, *m*/*z*: 263.0665. Found, %: C 59.30; H 3.01; N 15.93. $C_{13}H_8F_3N_3$. Calculated, %: C 59.32; H 3.06; N 15.96.

3-(4-Chlorophenyl)[1,2,4]triazolo[4,3-*a*]pyridine (3d). Yield 95 mg (90%), white solid, mp 198–200°C (mp 196–197°C[34d]). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 6.91 (1H, ddd, *J* = 7.5, *J* = 6.6, *J* = 1.1, H Py); 7.31 (1H, ddd, *J* = 9.3, *J* = 6.5, *J* = 1.1, H Py); 7.53–7.60 (2H, m, H Ar); 7.76–7.81 (2H, m, H Ar); 7.84 (1H, dt, *J* = 9.3, *J* = 1.2, H Py); 8.25 (1H, dt, *J* = 7.0, *J* = 1.2, H Py). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 114.6; 116.9; 122.4; 125.1; 127.3; 129.5; 129.7; 136.4; 145.8; 150.6. Found, *m*/*z*: 229.0404 $[M]^+$. $C_{12}H_8ClN_3$. Calculated, *m*/*z*: 229.0401. Found, %: C 62.73; H 3.47; N 18.26. $C_{12}H_8ClN_3$. Calculated, %: C 62.76; H 3.51; N 18.30.

3-(4-Bromophenyl)[1,2,4]triazolo[4,3-*a*]pyridine (3e). Yield 114 mg (91%), white solid, mp 200–202°C (mp 198–200°C[34e]). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 6.92 (1H, ddd, *J* = 7.4, *J* = 6.6, *J* = 1.1, H Py); 7.32 (1H, ddd, *J* = 9.3, *J* = 6.5, *J* = 1.1, H Py); 7.74 (4H, s, H Ar); 7.86 (1H, d, *J* = 9.3, H Py); 8.26 (1H, d, *J* = 7.1, H Py). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 114.6; 117.0; 122.4; 124.7; 125.6; 127.2; 129.6; 132.6; 145.8; 150.7. Found, *m*/*z*: 272.9899 $[M]^+$. $C_{12}H_8BrN_3$. Calculated, *m*/*z*: 272.9896. Found, %: C 52.55; H 2.91; N 15.29. $C_{12}H_8BrN_3$. Calculated, %: C 52.58; H 2.94; N 15.33.

3-(4-Methoxyphenyl)[1,2,4]triazolo[4,3-*a*]pyridine (3f). Yield 101 mg (98%), white solid, mp 122–124°C (mp 123–125°C[34d]). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 3.89 (3H, s, OCH_3); 6.84 (1H, td, *J* = 6.8, *J* = 1.0, H Py); 7.09 (2H, d, *J* = 8.7, H Ar); 7.26 (1H, ddd, *J* = 9.3, *J* = 6.5, *J* = 1.1, H Py); 7.73–7.77 (2H, m, H Ar); 7.80 (1H, d, *J* = 9.3, H Py); 8.23 (1H, dt, *J* = 7.0, *J* = 1.2, H Py). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 55.5; 114.0; 114.8; 116.8; 118.9; 122.6; 126.9; 129.8; 146.7; 150.4; 161.1. Found, *m*/*z*: 225.0901 $[M]^+$. $C_{13}H_{11}N_3O$. Calculated, *m*/*z*: 225.0897. Found, %: C 69.29; H 4.89; N 18.62. $C_{13}H_{11}N_3O$. Calculated, %: C 69.32; H 4.92; N 18.66.

4-([1,2,4]Triazolo[4,3-*a*]pyridin-3-yl)phenol (3g). Yield 87 mg (90%), white solid, mp 248–250°C (mp 249–250°C[34f]). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 6.95–7.03 (3H, m, 2H Ar, 1H Py); 7.64–7.76 (2H, m, H Ar); 7.39 (1H, ddd, *J* = 9.2, *J* = 6.5, *J* = 1.1, H Py); 7.81 (1H, dd, *J* = 9.3, *J* = 1.2, H Py); 8.48 (1H, dd, *J* = 7.1, *J* = 1.2, H Py); 10.03 (1H, s, OH). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 114.1; 115.6; 116.0; 117.1; 123.8; 127.5; 129.7; 146.2; 149.6; 159.0. Found, *m*/*z*: 211.0743 $[M]^+$. $C_{12}H_9N_3O$. Calculated, *m*/*z*: 211.0740. Found, %: C 68.21; H 4.25; N 19.87. $C_{12}H_9N_3O$. Calculated, %: C 68.24; H 4.29; N 19.89.

4-([1,2,4]Triazolo[4,3-*a*]pyridin-3-yl)benzonitrile (3h). Yield 86 mg (85%), white solid, mp 261–263°C (mp 258–260°C[34d]). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 6.99 (1H, td, *J* = 6.8, *J* = 1.1, H Py); 7.38 (1H, ddd, *J* = 9.3, *J* = 6.6, *J* = 1.1, H Py); 7.90 (3H, dd, *J* = 8.8, *J* = 1.8, 2H Ar, 1H Py); 8.01–8.06 (2H, m, H Ar); 8.31–8.35 (1H, m, H Py). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 113.8; 115.1; 117.2; 118.0; 122.3; 127.7; 128.5; 131.1; 133.1; 145.0; 151.0. Found, *m*/*z*: 220.0744 $[M]^+$. $C_{13}H_8N_4$. Calculated, *m*/*z*: 220.0744. Found, %: C 70.88; H 3.62; N 25.41. $C_{13}H_8N_4$. Calculated, %: C 70.90; H 3.66; N 25.44.

3-(4-Methyl-1,3-thiazol-5-yl)[1,2,4]triazolo[4,3-*a*]-pyridine (3i). Yield 79 mg (80%), brown solid, mp 127–129°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 2.58

(3H, s, CH_3); 6.97 (1H, td, *J* = 6.7, *J* = 1.0, H Py); 7.38 (1H, ddd, *J* = 9.3, *J* = 6.5, *J* = 1.1, H Py); 7.89 (1H, dt, *J* = 9.3, *J* = 1.2, H Py); 8.01 (1H, dt, *J* = 6.9, *J* = 1.1, H Py); 9.00 (1H, s, H thiazole). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 16.6; 114.8; 115.0; 116.9; 122.6; 127.7; 139.2; 150.5; 154.1; 155.7. Found, *m*/*z*: 216.0467 $[M]^+$. $C_{10}H_8N_4S$. Calculated, *m*/*z*: 216.0464. Found, %: C 55.51; H 3.71; N 25.88. $C_{10}H_8N_4S$. Calculated, %: C 55.54; H 3.73; N 25.91.

3-(Furan-2-yl)[1,2,4]triazolo[4,3-*a*]pyridine (3j). Yield 75 mg (88%), light-brown solid, mp 92–94°C (mp 92–93°C[34b]). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 6.66 (1H, dd, *J* = 3.5, *J* = 1.8, H Py); 6.94 (1H, td, *J* = 6.8, *J* = 1.1, H Py); 7.20–7.34 (2H, m, H furan, H Py); 7.67–7.70 (1H, m, H furan); 7.83 (1H, d, *J* = 9.3, H Py); 8.75 (1H, d, *J* = 7.1, H furan). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 111.2; 112.1; 114.6; 116.6; 124.3; 127.5; 139.6; 143.0; 143.6; 149.9. Found, *m*/*z*: 185.0585 $[M]^+$. $C_{10}H_7N_3O$. Calculated, *m*/*z*: 185.0584. Found, %: C 64.82; H 3.79; N 22.65. $C_{10}H_7N_3O$. Calculated, %: C 64.86; H 3.81; N 22.69.

3-(1*H*-Indol-3-yl)[1,2,4]triazolo[4,3-*a*]pyridine (3k). Yield 88 mg (82%), pinkish-white solid, mp 244–246°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 7.03 (1H, td, *J* = 6.7, *J* = 1.1, H Py); 7.19 (1H, ddd, *J* = 8.0, *J* = 7.0, *J* = 1.1, H Py); 7.26 (1H, ddd, *J* = 8.1, *J* = 7.0, *J* = 1.3, H indole); 7.40 (1H, ddd, *J* = 9.3, *J* = 6.5, *J* = 1.1, H Py); 7.55 (1H, dt, *J* = 8.0, *J* = 0.9, H indole); 7.84 (1H, dt, *J* = 9.3, *J* = 1.2, H Py); 8.16 (1H, dd, *J* = 7.8, *J* = 1.0, H indole); 8.26 (1H, d, *J* = 2.8, H indole); 8.65 (1H, dt, *J* = 7.1, *J* = 1.1, H indole); 11.89 (1H, br. s, NH). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 101.3; 111.9; 113.8; 115.6; 120.3; 120.8; 122.5; 124.3; 125.0; 125.6; 127.1; 136.1; 142.8; 148.8. Found, *m*/*z*: 234.0901 $[M]^+$. $C_{14}H_{10}N_4$. Calculated, *m*/*z*: 234.0900. Found, %: C 71.75; H 4.28; N 23.89. $C_{14}H_{10}N_4$. Calculated, %: C 71.78; H 4.30; N 23.92.

3-Phenyl[1,2,4]triazolo[4,3-*a*]pyrazine (3l). Yield 82 mg (92%), white solid, mp 161–163°C (mp 160–162°C[34d]). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 7.61–7.66 (3H, m, H Ph); 7.86–7.90 (2H, m, H Ph); 7.95 (1H, d, *J* = 4.8, H pyrazine); 8.23 (1H, dd, *J* = 4.9, *J* = 1.7, H pyrazine); 9.43 (1H, d, *J* = 1.6, H pyrazine). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 115.2; 125.6; 128.1; 129.6; 130.4; 130.9; 145.1; 146.0; 147.2. Found, *m*/*z*: 196.0745 $[M]^+$. $C_{11}H_8N_4$. Calculated, *m*/*z*: 196.0744. Found, %: C 67.31; H 4.09; N 28.51. $C_{11}H_8N_4$. Calculated, %: C 67.34; H 4.11; N 28.55.

6-Chloro-3-phenyl[1,2,4]triazolo[4,3-*b*]pyridazine (3m). Yield 72 mg (90%), white solid, mp 197–199°C (mp 199–201°C[34g]). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 7.17 (1H, d, *J* = 9.6, H pyridazine); 7.54–7.61 (3H, m, H Ph); 8.17 (1H, d, *J* = 9.6, H pyridazine); 8.45–8.49 (2H, m, H Ph). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 121.8; 125.5; 126.6; 127.7; 128.8; 130.7; 143.6; 148.1; 149.4. Found, *m*/*z*: 230.0357 $[M]^+$. $C_{11}H_7ClN_4$. Calculated, *m*/*z*: 230.0354. Found, %: C 57.25; H 3.02; N 24.26. $C_{11}H_7ClN_4$. Calculated, %: C 57.28; H 3.06; N 24.29.

3-Phenyl[1,2,4]triazolo[4,3-*a*]pyrimidine (3n). Yield 77 mg (86%), white solid, mp 174–176°C (mp 182–184°C[34d]). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 6.98 (1H, dd, *J* = 7.0, *J* = 3.8, H pyrimidine); 7.55–7.64 (3H, m, H Ph); 7.81–7.87 (2H, m, H Ph); 8.64 (1H, dd, *J* = 7.0, *J* = 1.9, H pyrimidine); 8.70 (1H, dd, *J* = 3.8, *J* = 1.9, H pyrimidine). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 110.2; 125.9; 128.0; 129.5; 130.7; 130.8; 145.7; 153.9; 154.1. Found: 196.0745 $[M]^+$. $C_{11}H_8N_4$. Calculated, *m*/*z*: 196.0744. Found: C 67.31; H 4.09; N 28.52. $C_{11}H_8N_4$. Calculated, %: C 67.34; H 4.11; N 28.55.

Supplementary information file containing ^{1}H and ^{13}C NMR spectra of all synthesized compounds is available at the journal website at http://link.springer.com/journal/10593.

References

1. Bhadoriya, U.; Jain, D. K.; *Int. J. Pharm. Sci. Res.* **2016**, *7*, 1874.
2. Bhatt, A.; Singh, R. K.; Kant, R. *Chem. Biol. Lett.* **2017**, *4*, 73.
3. Endo, K.; Deguchi, K.; Matsunaga, H.; Tomaya, K.; Yamada, K. *Bioorg. Med. Chem.* **2014**, *22*, 3072.
4. Nagamatsu, T.; Fujita, T.; Endo, K. *J. Chem. Soc*., *Perkin Trans. 1* **2000**, *33*.
5. Nagamatsu, T.; Yamasaki, H.; Fujita, T.; Endo, K.; Machida, H. *J. Chem. Soc.*, *Perkin Trans. 1* **1999**, *3117*.
6. Kobe, B.; Kobe, J.; Smee, D. F.; Jerman-Blazic-Dzonova, B.; Solmajer, T. *Eur. J. Med. Chem.* **1992**, *27*, 259.
7. Mukaiyama, H.; Nishimura, T.; Kobayashi, S.; Ozawa, T.; Kamada, N.; Komatsu, Y.; Kikuchi, S.; Oonota, H.; Kusama, H. *Bioorg. Med. Chem.* **2007**, *15*, 868.
8. Ozawa, T.; Tsuji, E.; Ozawa, M.; Handa, C.; Mukaiyama, H.; Nishimura, T.; Kobayashi, S.; Okazaki, K. *Bioorg. Med. Chem.* **2008**, *16*, 10311.
9. Scheltens, P.; Prins, N.; Lammertsma, A.; Yaqub, M.; Gouw, A; Wink, A. M.; Chu, H. M.; van Berckel, B. N. M.; Alam, J. *Ann. Clin. Transl. Neurol.* **2018**, *5*, 464.
10. Collin, X.; Sauleau, A.; Coulon, J. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 2601.
11. Papakonstantinou-Garoufalias, S.; Pouli, N.; Marakos, P.; Chytyroglou-Ladas, A. *Farmaco* **2002**, *57*, 973.
12. De Clercq, E. *J. Clin. Virol.* **2004**, *30*, 115.
13. Navidpour, L.; Shadnia, H.; Shafaroodi, H.; Amini, M.; Dehpour, A. R.; Shafiee, A. *Bioorg. Med. Chem.* **2007**, *15*, 1976.
14. Naito, Y.; Akahoshi, F.; Takeda, S.; Okada, T.; Kajii, M.; Nishimura, H.; Sugiura, M.; Fukaya, C.; Kagitani, Y. *J. Med. Chem.* **1996**, *39*, 3019.
15. Saha, A. K.; Liu, L.; Simoneaux, R.; Decorte, B.; Meyer, C.; Skrzat, S.; Breslin, H. J.; Kukla, M. J.; End, D. W. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 5407.
16. Hester, J. B., Jr.; Rudzik, A. D.; Kamdar, B. V. *J. Med. Chem.* **1971**, *14*, 1078.
17. Hitotsuyanagi, Y.; Motegi, S.; Fukaya, H.; Takeya, K. *J. Org. Chem.* **2002**, *67*, 3266.
18. Dash, C.; Shaikh, M. M.; Ghosh, P. *J. Chem. Sci.* **2011**, *123*, 97.
19. Holm, S. C.; Straub, B. F. *Org. Prep. Proced. Int.* **2011**, *43*, 319.
20. Meanwell, N. A.; Romine, J. L.; Rosenfeld, M. J.; Martin, S. W.; Trehan, A. K.; Wright, J. J. K.; Malley, M. F.; Gougoutas, J. Z.; Brassard, C. L.; Buchanan, J. O.; Federic, M. E.; Fleming, J. S.; Gamberdella, M.; Hartl, K. S.; Zavoico, G. B.; Seiler, S. M. *J. Med. Chem.* **1993**, *36*, 3884.
21. Aggarwal, R.; Sumran, G.; Kumar, R.; Aggarwal, A.; Parkash, V. *Indian J. Heterocycl. Chem.* **2006**, *16*, 1.

22. Hutchinson, J. H.; Seiders, T. J.; Stearns, B. A.; Wang, B.; Scott, J. M.; Truong, Y. P. US Patent 20070173508.
23. Jørgensen, M.; Bruun, A. T.; Rasmussen, L. K. WO Patent 2013034758.
24. Jørgensen, M.; Bruun, A. T.; Rasmussen, L. K.; Larsen, M. WO Patent 2013034755.
25. Kumar, D.; Chandra, S. K.; Dhillon, H.; Rao, V. S.; Varma, R. S. *Green Chem.* **2004**, *6*, 156.
26. Dubey, P. K.; Naidu, A.; Shiva Kumar, K. *Org. Chem.*: *Indian J.* **2008**, *4*, 475.
27. Aggarwal, R.; Sumran, G. *Synth. Commun.* **2006**, *36*, 1873.
28. Nitlikar, L. H.; Darandale, S. N.; Shinde, D. B. *Lett. Org. Chem.* **2013**, *10*, 348.
29. Graceffa, R.; Kaller, M.; La, D.; Lopez, P.; Patel, V. F.; Zhong, W. US Patent 20100120774.
30. Kim, D.; Wang, L.; Beconi, M.; Eiermann, G. J.; Fisher, M. H.; He, H.; Hickey, G. J.; Kowalchick, J. E.; Leiting, B.; Lyons, K.; Marsilio, F.; McCann, M. E.; Patel, R. A.; Petrov, A.; Scapin, G.; Patel, S. B.; Roy, R. S.; Wu, J. K.; Wyvratt, M. J.; Zhang, B. B.; Zhu, L.; Thornberry, N. A.; Weber, A. E. *J. Med. Chem.* **2005**, *48*, 141.
31. Guan, L. P.; Zhang, R. P.; Chang, Y.; Gan, X. X. *Asian J. Chem.* **2013**, *25*, 3660.
32. Comas, H.; Bernardinelli, G.; Swinnen, D. *J. Org. Chem.* **2009**, *74*, 5553.
33. Bourgeois, P.; Cantegril, R.; Chêne, A.; Gelin, J.; Mortier, J.; Moyroud, J. *Synth. Commun.* **1993**, *23*, 3195.
34. (a) Inturi, S. B.; Kalita, B.; Ahamed, A. J. *Org. Biomol. Chem.* **2016**, *14*, 11061. (b) Nakka, M.; Tadikonda, R.; Rayavarapu, S.; Sarakula, P.; Vidavalur, S. *Synthesis*, **2015**, 517. (c) Li, E.; Hu, Z.; Song, L.; Yu, W.; Chang, J. *Chem.–Eur. J.* **2016**, *22*, 11022. (d) Thiel, O. R.; Achmatowicz, M. M.; Reichelt, A.; Larsen, R. D. *Angew. Chem.*, *Int. Ed.* **2010**, *49*, 8395. (e) Srinivasan, R.; Sembian Ruso, J.; Nagarajan, N. S.; Senthil Kumaran, R.; Manickam, G. *J. Heterocycl. Chem.* **2016**, *53*, 606. (f) Ciesielski, M.; Pufky, D.; Döring, M. *Tetrahedron* **2005**, *61*, 5942. (g) Naqui, S.; Srinivasan, V. R. *Indian J. Chem.* **1965**, *3*, 162.