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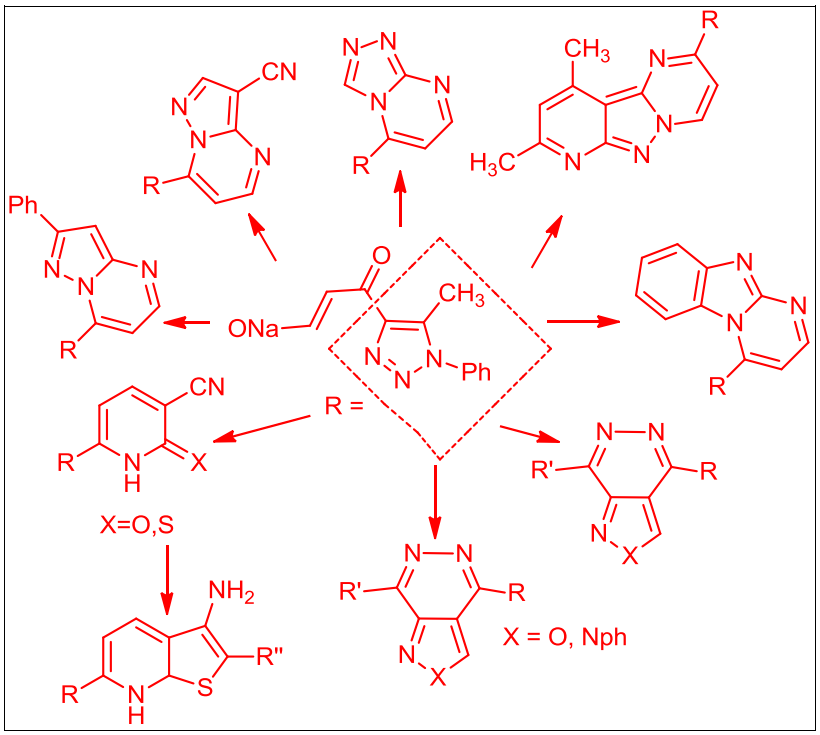

Synthesis of pyrazolo[1,5-*a*]pyrimidines, [1,2,4]triazolo[1,5-*a*]pyrimidine, 8,10-dimethyl-2-(5-methyl-1-phenyl-4,5-dihydro-1*H*-1,2,3-triazol-4-yl)pyrido[2′,3′:3,4]-pyrazolo[1,5-*a*]pyrimidine, benzo[4,5]imidazo [1,2-*a*]pyrimidine via heterocyclic amines, and sodium 3-hydroxy-1-(5-methyl-1-phenyl-1*H*-1,2,3-triazole-4-yl) prop-2-en-1-one were carried out. Also, synthesis of isoxazoles, and pyrazoles from sodium 3-hydroxy-1-(5-methyl-1-phenyl-1*H*-1,2,3-triazole-4-yl)prop-2-en-1-one and hydroxymoyl chlorides and hydrazonoyl halides, respectively, were made. Analogously, (1,2,3-triazol-4-yl)thieno[2,3-*b*]pyridine derivatives were obtained from sodium 3-hydroxy-1-(5-methyl-1-phenyl-1*H*-1,2,3- triazole-4-yl)prop-2-en-1-one and cyanothioacetamide followed by its reacting with active methylene compounds. In addition to full characterization of all synthesized compounds, they were tested to evaluate their antimicrobial activities, and some compounds showed competitive activities to those of tetracycline, the typical antibacterial drug, and clotrimazole, the typical antifungal drug.

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INTRODUCTION

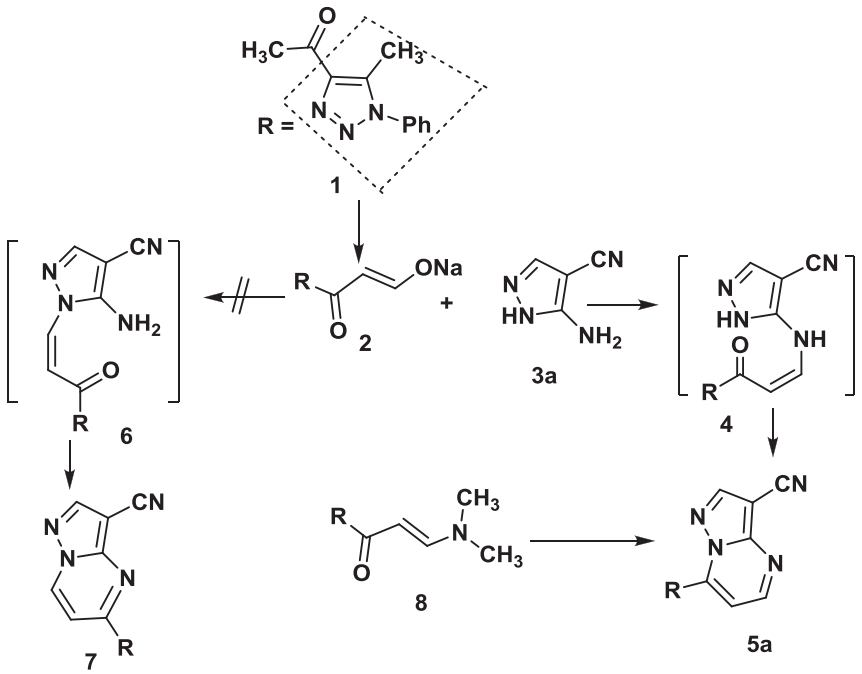
The increasing demand on a clean and efficient synthetic methodology represents a challenge of great interest in heterocyclic chemistry. The use of nontoxic organic solvents or even the exclusion of solvents in chemical reactions represents one of the main criteria for green chemistry [1,2]. Many synthetic chemical procedures that were carried out in hazardous organic solvents are now replaced by reactions in the absence of solvents, and "solvent-free reactions" is now a common terminology in literature not only from the environmental side but also from an economic advantageous standpoint [3–13]. Among various classes of heterocyclic compounds, 1,2,3-triazole derivatives occupy an important place in the realm of synthetic organic chemistry because of their therapeutic and pharmacological properties. Many compounds possessing this nucleus have been reported to exhibit antibacterial [14], antifungal [15], antiviral [16], anti-inflammatory, and analgesic activities [17]. Other derivatives possessing this moiety were also found to inhibit tumor proliferation, invasion, and metastasis and have anti-HIV activity [18–22].

We report herein on a mild, efficient, and green experimental synthetic procedure to synthesize various new heterocyclic compounds of antimicrobial biological interest and possessing 1,2,3-triazole moiety.

RESULTS AND DISCUSSION

Motivated by the statement "the best solvent is no solvent" [23], we tried our solvent-free approach for the synthesis of new heterocycles of pharmaceutical interest. Thus, azolo [1,5-*a*]pyrimidines, isoxazolo[3,4-*d*]pyridazines, pyrazolo [3,4-*d*]pyridazines, and thieno[2,3-*b*]pyridine derivatives were synthesized by the new solvent-free protocol and compared with the traditional synthetic methodology by refluxing in solvents. All solvent-free reactions were carried out by the following protocol: (1) grind up moist reagents with a pestle in an open mortar under ambient temperature for a reaction time up to only 15 min; (2) digest the paste with water then filter; (3) crystallize from suitable solvent if needed. The new synthetic approach can be used to carry

Scheme 1. Synthesis of **7**-(5-methyl-1-phenyl-1*H*-1,2,3-triazol-4-yl)pyrazolo[1,5-a]pyrimidine-3-carbonitrile.



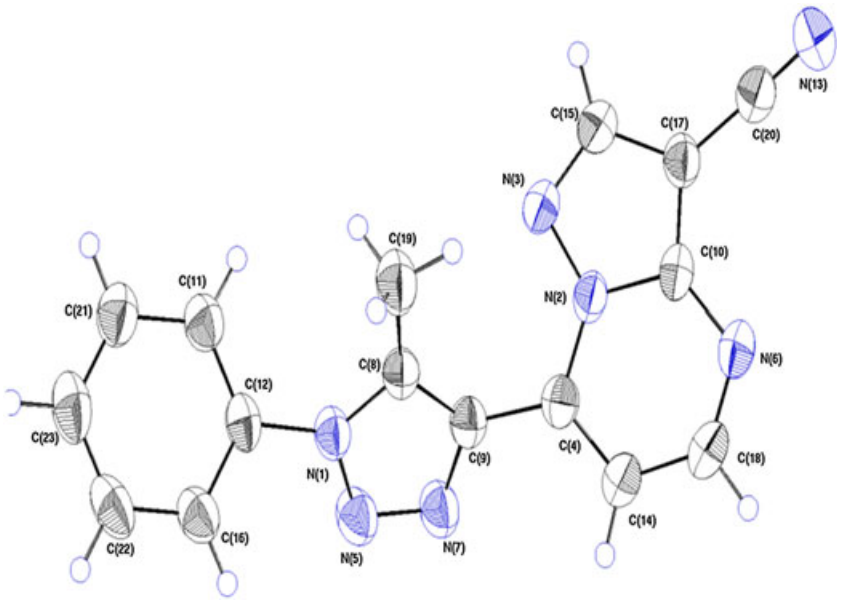


Figure 1. X-ray of **5a**. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

out a wide range of reactions in short times and with high conversions and selectivity, without the need for solvents. This approach can prove advantageous because (i) there is no reaction medium to collect, work up, and purify; (ii) the reactions are clean where the formed compounds are often sufficiently pure to circumvent extensive purification techniques such as chromatography, and in some cases there is even no need for recrystallization; (iii) sequential solvent-free reactions are possible in high-yielding reactions; and (iv) the reactions are more rapid, sometimes reaching substantial completion in several minutes compared with hours in case of reactions in organic solvents.

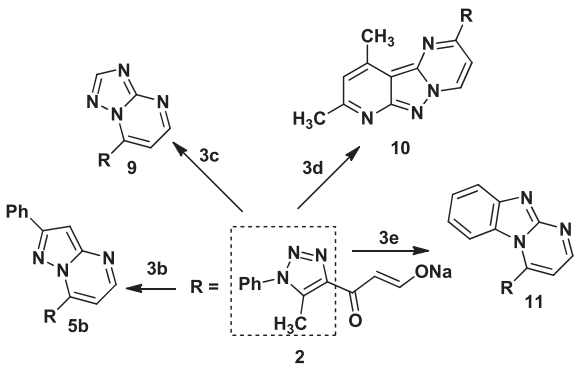
The first reaction involves grinding of sodium 3-hydroxy-1-(5-methyl-1-phenyl-1*H*-1,2,3-triazole-4-yl)prop-2-en-1-one (**2**) and 5-amino-1*H*-pyrazole-4-carbonitrile (**3a**) with a few catalytic drops of glacial acetic acid for 15 min at room temperature resulting in one spot on TLC corresponding to one isolable product that is formed in good yield (Scheme 1). Two regioisomeric products **5a** and **7** were suggested on the basis of the first attacking nucleophile. The reaction may proceed through the nucleophilic attack of the less sterically hindered exocyclic primary amino group or by the more sterically hindered endocyclic pyrazole nitrogen. The two possible isomers cannot be distinguished by spectroscopic data; however, unambiguous confirmation of the product structure was achieved by X-ray crystallography [24] (Fig. 1) that revealed the formation of **5a** and not **7** as a result of the first attacking of more nucleopholic exocyclic primary amino group.

The formation of the product was also confirmed on the basis of alternative synthetic pathways. The salt **2** reacted with **3a** in acetic acid and in the presence of piperidinium acetate catalyst at the reflux temperature to afford **5a**. Also, in another synthetic procedure, heating 3-(dimethylamino)-1-(5-methyl-1-phenyl-1*H*-1,2,3-triazol-4-yl)prop-2-en-1-one (**8**) with **3a** in refluxing acetic acid and in the presence of ammonium acetate for 2 h resulted in the formation of the same product that is identical in all aspects (mp, mixed mp, ^{1}H-NMR, IR, and mass spectrometry) with the products from the previous methods. The grinding method proves to be more superior to the other experimental procedures leading to complete conversion to **5a** within only 15 min. In a similar manner, the reaction of **2** with 3-phenyl-1*H*-pyrazol-5-amine (**3b**), 4*H*-1,2,4-triazol-3-amine (**3c**), 4,6-dimethyl-1*H*-pyrazolo[3,4-*b*]pyridin-3-amine (**3d**), or 1*H*-benzo[*d*]imidazol-2-amine (**3e**) resulted in excellent yields of the corresponding 7-(5-methyl-1-phenyl-1*H*-1,2,3-triazol-4-yl)-2-phenylpyrazolo[1,5-*a*]pyrimidine (**5b**), 7-(5-methyl-1-phenyl-1*H*-1,2,3-triazol-4-yl)-[1,2,4]triazolo[1,5-*a*]pyrimidine (**9**), 8,10-dimethyl-2-(5-methyl-1-phenyl-1*H*-1,2,3-triazol-4-yl)pyrido[2′,3′:3,4]pyrazolo[1,5-*a*]pyrimidine (**10**), and 4-(5-methyl-1-phenyl-1*H*-1,2,3-triazol-4-yl)benzo[4,5]imidazo[1,2-*a*]pyrimidine (**11**), respectively (Scheme 2).

Also, compound **2** reacted with hydroxymoyl chloride **12a** in the presence of sodium carbonate to give the 3,4-disubstituted isoxazole regioisomer (3-benzoylisoxazol-4-yl)-(5-methyl-1-phenyl-1*H*-[1,2,3]triazol-4-yl)-methanone (**13a**) and not the 3,5-disubstituted product (**14a**) (Scheme 3). The structure of the product was confirmed on the basis of the chemical transformation of **13a** to give 7-(5-methyl-1-phenyl-1*H*-1,2,3-triazol-4-yl)-4-phenylisoxazolo[4,3-*d*]pyridazine (**15a**) in good yield treatment with hydrazine hydrate. The ^{1}H-NMR spectrum of **13a** showed a singlet at $\delta = 8.79$ corresponding to the characteristic signal of the proton at the isoxazole H5. Similar treatment of compound **2** with the appropriate hydroxymoyl chlorides **12b–d** resulted in the corresponding isoxazoles **13b–d** that were converted to the corresponding isoxazolo[4,3-*d*]pyridazine **15b–d**, respectively.

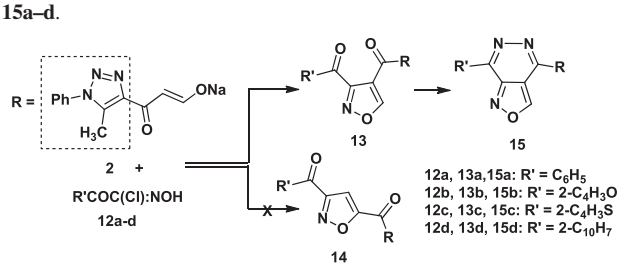
Analogously, compound **2** reacted with the appropriate hydrazonoyl halides **16a–d** via grinding with moist sodium carbonate to afford the pyrazoles **17a–d**, respectively. Structures **17a–d** were elucidated on the basis of elemental analysis, spectral data, and chemical transformation. ^{1}H-NMR spectrum of **17a** showed signals at $\delta = 1.38$ (t, 3H, $CH_2\mathbf{CH_3}$), 2.54 (s, 3H, CH_3), 4.28 (q, 2H, $\mathbf{CH_2}CH_3$), 7.27–8.0 (m, 10H, ArH's), and 8.32 (s, 1H, pyrazole H-5). The regioselectivity of the reaction was confirmed by reacting the pyrazoles **17a–d** with hydrazine hydrate, which gave the corresponding pyrazolo[3,4-*d*]pyridazines **19a–c**, respectively (Scheme 4).

Scheme 2. Synthesis of azolo[1,5-a]pyrimidine derivatives **5b** and **9–11**.

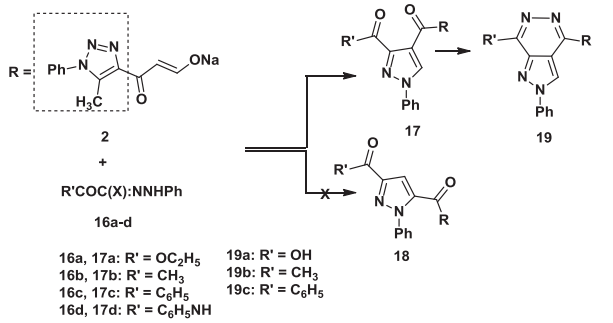


3b: 3-amino-5-phenyl-1*H*-pyrazole
3c: 3-amino-4*H*-1,2,4-triazole
3d: 4,6-dimethyl-2*H*-pyrazolo[3,4-*b*]pyridin-3-amine
3e: 2-amino-1*H*-benzo[*d*]imidazole

Scheme 3. Synthesis of isoxazoles **13a–d** and isoxazolo[3,4-d]pyridazines **15a–d**.



Scheme 4. System of pyrazoles **17a–d** and pyrazo[3,4-d]pyridazines **19a–c**.



Furthermore, 2-mercapto-6-(5-methyl-1-phenyl-1*H*-1,2,3-triazol-4-yl)pyridine-3-carbonitrile (**20**) was synthesized by treating **2** with cyanothiocetamide in the presence of ammonium acetate via the new grinding method. Structure **20** was confirmed on the basis of elemental analysis, spectral data, and chemical transformation. The appropriate ethyl chloroacetate, chlorocetone, ω-bromoacetophenone, and chloroacetonitrile were reacted with **20** and potassium hydroxide to give the corresponding ethyl 3-amino-6-(5-methyl-1-phenyl-1*H*-1,2,3-triazol-4-yl)thieno[2,3-*b*]pyridine-2-carboxylate (**21a**), 1-(3-amino-6-(5-methyl-1-phenyl-1*H*-1,2,3-triazol-4-yl)thieno[2,3-*b*]pyridin-2-yl)ethanone (**21b**), (3-amino-6-(5-methyl-1-phenyl-1*H*-1,2,3-triazol-4-yl)thieno [2,3-*b*]pyridin-2-yl)(phenyl)-methanone (**21c**), and 3-amino-6-(5-methyl-1-phenyl-1*H*-1,2,3-triazol-4-yl)thieno[2,3-*b*]pyridine-2-carbonitrile (**21d**), respectively (Scheme 5). Also, when **2** reacted with each of cyanoacetamide and 2-cyanoacetohydrazide, it afforded 1,2-dihydro-6-(5-methyl-1-phenyl-1*H*-1,2,3-triazol-4-yl)-2-oxopyridine-3-carbonitrile (**22**) and 1-amino-6-(5-methyl-1-phenyl-1*H*-[1,2,3]triazol-4-yl)-2-oxo-1,2-dihydropyridine-3-carbonitrile (**23**), respectively (Scheme 5).

In all previous reactions, the solvent-free protocol was more advantageous than the in-solvent procedure, giving the products in higher chemical yields and shorter reaction times (Table 1).

Scheme 5. Synthesis of 1,2-dihydropyridine-3-carbonitrile derivatives **20**, **22**, and **23** and thieno[2,3-b]pyridin-3-amine derivatives **21a–d**.

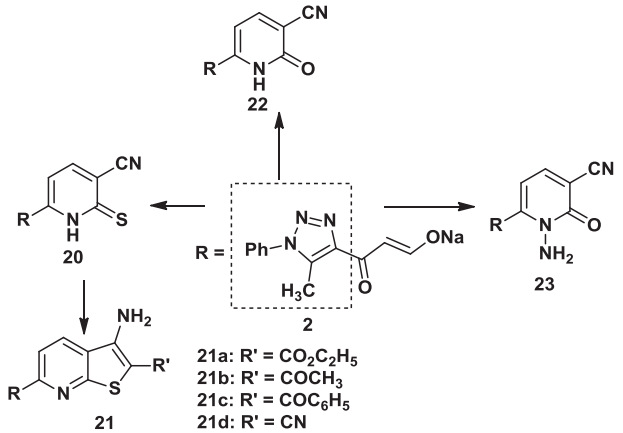


Table 1

Comparison of solvent-free and in-solvent synthetic approaches of the newly synthesized compounds.

		Solvent-free reaction (Method A)		In-solvent reaction (Method B)	
Entry	Product	Time (min)	Isolated yield (%)	Time (min)	Isolated yield (%)
1	**5a**	15	92	10	73
2	**5b**	15	93	10	81
3	**9**	15	96	10	70
4	**10**	15	94	10	83
5	**11**	15	90	10	77
6	**13a**	15	92	120	74
7	**13b**	15	96	120	83
8	**13c**	15	95	120	70
9	**13d**	15	95	120	84
10	**15a**	15	92	120	69
11	**15b**	15	94	120	67
12	**15c**	15	91	120	72
13	**15d**	15	94	120	82
14	**17a**	15	89	120	69
15	**17b**	15	95	120	67
16	**17c**	15	93	120	70
17	**17d**	15	91	120	82
18	**19a**	15	91	120	71
19	**19b**	15	96	120	83
20	**19c**	15	94	120	85
21	**20**	15	93	10	85
22	**21a**	15	92	300	78
23	**21b**	15	94	300	74
24	**21c**	15	96	300	85
25	**21d**	15	94	300	80
26	**22**	15	95	10	86
27	**23**	15	90	10	72

Finally, the antibacterial and antifungal activities of many of the synthesized compounds were tested, and some showed good pharmacological properties. Compounds **5a** and **22** exhibit competitive antibacterial activities to those of tetracycline, the typical antibacterial drug, whereas compounds **20** and **22** exhibit competitive antifungal activities to those of clotrimazole, the typical antifungal drug. The results are summarized in Table 2.

CONCLUSION

In conclusion, the presented solvent-free grinding procedure provides an efficient and much improved modification of the traditional in-solvent synthetic methodology. Several heterocyclic classes like azolo[1,5-*a*]pyrimidines, isoxazolo [3,4-*d*]pyridazines, pyrazolo[3,4-*d*]pyridazines, and thieno [2,3-*b*]pyridine derivatives were used to probe the applicability of the new method. This green grinding method is milder, more efficient, and simpler in workup and needs shorter reaction time. Antibacterial and antifungal activities of many of the synthesized compounds were tested, and some showed good pharmacological properties that are competitive to those

Table 2

Antibacterial and antifungal activities of some synthesized compounds.

	Inhibition zone diameter (mm/mg sample)					
	Antimicrobial activity % (Inhibition zone %)					
Sample	*A. fumigatus*	*C. albicans*	*S. aureus*	*B. subtilis*	*E. coli*	*S. typhimurium*
DMSO (positive control)	0.0	0.0	0.0	0.0	0.0	0.0
Tetracycline (antibacterial agent)	–	–	30	29	31	30
Clotrimazole (antifungal agent)	24	22	–	–	–	–
5a	0.0	0.0	17	21	18	27
5b	0.0	0.0	15	9	17	20
11	0.0	9	5	7	12	10
20	21	17	0.0	0.0	0.0	0.0
22	22	20	18	21	25	27
23	7	9	0.0	0.0	0.0	0.0

of tetracycline, the typical antibacterial drug, and clotrimazole, the typical antifungal drug.

EXPERIMENTAL

All melting points were determined on an electrothermal apparatus and are uncorrected. IR spectra were recorded (KBr discs) on a Shimadzu FTIR 8201 PC spectrophotometer. NMR spectra were recorded in $CDCl_3$ and $(CD_3)_2SO$ solutions on a JNM-LA 400 FT-NMR system and a Varian Gemini 300 MHz spectrometer, and chemical shifts were expressed in δ ppm units using TMS as an internal reference. Mass spectra were recorded on a GC-MS QP1000 EX Shimadzu. Elemental analyses were carried out at the Microanalytical Center of Cairo University. 1-(5-Methyl-1-phenyl-1*H*-1,2,3-triazol-4-yl)ethanone (**1**) was synthesized as previously reported [25].

Antimicrobial activity. The antimicrobial activity of the tested samples was carried out in the Faculty of Agriculture, Cairo University, Giza, Egypt, and was determined using the modified Kirby–Bauer disc diffusion method [26]. Briefly, 100 μL of the test bacteria/fungi were grown in 10 mL of fresh media until they reached a count of approximately 108 cells/mL for bacteria or 105 cells/mL for fungi [27]. One hundred microliters of microbial suspension was spread onto agar plates corresponding to the broth in which they were maintained. Isolated colonies of each organism that might be playing a pathogenic role should be selected from primary agar plates and tested for susceptibility by disc diffusion method [28].

Plates were inoculated with the filamentous fungus *Aspergillus fumigatus* (incubated at 25°C for 48 h), the Gram (+) bacteria *Staphylococcus aureus* and *Bacillus subtilis* and Gram (−) bacteria *Escherichia coli* and *Salmonella typhimurium* (incubated at 35–37°C for 24–48 h), and the diploid fungus *Candida albicans* (incubated at 30°C for 24–48 h); then the diameters of the inhibition zones were measured in millimeters. Standard discs of tetracycline (antibacterial agent) and clotrimazole (antifungal agent) served as positive controls for antimicrobial activity, and filter discs impregnated with 10 μL of solvent (distilled water, chloroform, and DMSO) were used as a negative control.

General procedure for the synthesis of pyrazolo[1,5-*a*]pyrimidines 5a–c, [1,2,4]triazolo[1,5-*a*]pyrimidine (9), 8,10-dimethyl-2-(5-methyl-1-phenyl-4,5-dihydro-1*H*-1,2,3-triazol-4-yl)pyrido[2′,3′:3,4]pyrazolo[1,5-*a*]pyrimidine (10), and benzo[4,5]imidazo[1,2-*a*]pyrimidine (11).

Method A—A mixture of sodium salt of 3-hydroxy-1-(5-methyl-1-phenyl-1*H*-1,2,3-triazol-4-yl)prop-2-en-1-one (**2**) (1.2 g, 5 mmol), the appropriate heterocyclic amines **3a–f** (5 mmol), and few catalytic 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. Grinding of the initial syrup was continued for 5–10 min, and the reaction was monitored by TLC. The solid was washed with water and recrystallized from the appropriate solvent to give the corresponding fused pyrimidines **5a**, **5b**, and **9–11**, respectively.

Method B—A mixture of the appropriate sodium salt **2** (10 mmol) and the appropriate heterocyclic amines **3a–e** (10 mmol) in a solution of piperidinium acetate (piperidine (2.5 mL), water (5 mL), and acetic acid (2 mL)) was heated under reflux for about 10 min; acetic acid (1.5 mL) was added to the reaction mixture while boiling. Then the mixture was cooled, and the resulting solid was collected and recrystallized from the appropriate solvent to give **5a**, **5b**, and **9–11**, respectively.

Method C—A mixture of 3-(dimethylamino)-1-(5-methyl-1-phenyl-1*H*-1,2,3-triazol-4-yl)prop-2-en-1-one (**8**) (10 mmol) and the appropriate heterocyclic amines **3a–e** (10 mmol) in acetic acid were stirred at room temperature for 2 h. The resulting solid was collected and recrystallized from the appropriate solvent to give **5a**, **5b**, and **9–11**, respectively.

***7-(5-Methyl-1-phenyl-1H*-1,2,3-triazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carbonitrile (5a).** Mp 218–220°C (AcOH), orange, IR (cm-1): 3066 (CH), 2923 (CH), 2229 (CN), 1643 (C=N), 1569 (C=C).

^{1}H-NMR (DMSO-d_6), $\delta = 2.62$ (s, 3H, CH_3), 7.17–7.34 (m, 5H, ArH's), 7.66–7.69 (m, 1H, ArH), 8.45 (s, 1H, pyrazole H-3), 9.55 (s, 1H, pyrimidine H-6).

^{13}C-NMR (DMSO-d_6), $\delta = 7.58$ (CH3), 99.89, 110.32, 118.82, 127.28, 127.40, 128.15, 128.40, 130.13, 132.12, 132.89, 133.56, 141.72, 144.76, 145.58, 148.42, 152.35.

MS: 301 (M+, 23.8%), 272 (47%), 149 (23.8%), 135 (23.8%), 134 (14.3%), 130 (33.3%), 104 (23.8%), 77 (81%).

Calcd., %: C 63.78, H 3.68, N 32.54. $C_{16}H_{11}N_7$. Found, %: C 63.82, H 3.57, N 32.44.

7-(5-Methyl-1-phenyl-1H-1,2,3-triazol-4-yl)-2-phenylpyrazolo [1,5-a]pyrimidine (5b). Mp 232–234°C (EtOH), brown, IR (cm-1): IR (cm^{-1}): 3070 (CH), 2923 (CH), 1627 (C=N), 1566 (C=C).

^{1}H-NMR (DMSO-d_6), $\delta = 2.63$ (s, 3H, CH_3), 6.65 (s, 1H, pyrazole H-4), 7.02–7.03 (d, 1H, $J = 4$ Hz, ArH), 7.17–7.19 (m, 2H, ArH's), 7.31–7.34 (m, 2H, ArH's), 7.45–7.80 (m, 6H, ArH's), 9.21 (d, 1H, pyrimidine H-6).

MS: 353 (M + 1, 14%), 352 (M^+, 29.8%), 324 (42.6%), 220 (19.1%), 134 (17%), 130 (17%), 104 (35%), 77 (100%).

Calcd., %: C 71.58, H 4.58, N 23.85. $C_{21}H_{16}N_6$. Found, %: C 71.62, H 4.60, N 23.74.

7-(5-Methyl-1-phenyl-1H-1,2,3-triazol-4-yl)-[1,2,4]triazolo [1,5-a]pyrimidine (9). Mp 226–228°C (EtOH), brown, IR (cm^{-1}): 3066 (CH), 2924 (CH), 1651 (C=N), 1596 (C=C).

^{1}H-NMR (DMSO-d_6), $\delta = 2.62$ (s, 3H, CH_3), 6.62–6.63 (d, 1H, pyrimidine H-5), 7.14–7.67 (m, 5H, ArH), 8.58 (s, 1H, triazole H-3), 9.27–9.28 (d, 1H, $J = 4$ Hz), pyrimidine H-6).

^{13}C-NMR (DMSO-d_6), $\delta = 7.58$, 117.25, 118.82, 126.52, 127.28, 128.40, 132.26, 140.58, 153.07, 155.01, 156.83.

MS: 277 (M^+, 4.8%), 276 (M-1, 22.5%), 220 (17.3%), 219 (100%), 60 (5.9%). Calcd., %: C 60.64, H 4.00, N 35.36. $C_{14}H_{11}N_7$. Found, %: C 60.54, H 3.88, N 35.20.

8,10-Dimethyl-2-(5-methyl-1-phenyl-1H-1,2,3-triazol-4-yl)pyrido [2′,3′:3,4]pyrazolo[1,5-a]pyrimidine (10). Mp 260–262°C (AcOH), yellow, IR (cm^{-1}): 3070 (CH), 2920, 2850 (CH).

^{1}H-NMR (DMSO-d_6), $\delta = 2.62$ (s, 3H, CH_3), 2.67 (s, 3H, CH_3), 2.92 (s, 3H, CH_3), 6.53–6.54 (d, 1H, pyridine H-4), 7.01–7.66 (m, 6H, ArH), 9.10–9.11 (d, 1H, $J = 4$ Hz), pyrimidine H-6).

^{13}C-NMR (DMSO-d_6), $\delta = 10.81$, 19.57, 21.54, 106.14, 114.31, 115.52, 122.06, 126.69, 130.45, 132.27, 140.70, 150.28, 254.98, 164.96.

MS: 356 (M + 1, 4.6%), 355 (M^+, 16.5%), 326 (21.4%), 253 (8.7%), 199 (10.5%), 184 (78%), 173 (14%), 118 (80.6%), 77 (100%).

Calcd., %: C 67.59, H 4.82, N 27.59. $C_{20}H_{17}N_7$. Found, %: C 67.48, H 4.75, N 27.44.

4-(5-Methyl-1-phenyl-1H-1,2,3-triazol-4-yl)benzo[4,5]imidazo [1,2-a]pyrimidine (11). Mp 248–250°C (EtOH), brown, IR (cm^{-1}): 3070 (CH), 2920, 2850 (CH). IR (cm^{-1}): 3070 (CH), 2931, 2858 (CH), 165139 (C=N), 1600 (C=C).

^{1}H-NMR (DMSO-d_6), $\delta = 2.63$ (s, 3H, CH_3), 7.10–7.98 (m, 10H, ArH's), 9.25–9.26 (d, 1H, $J = 4$ Hz), pyrimidine H-6).

MS: 327 (M + 1, 7.2%), 326 (M^+, 33.9%), 281 (11%), 177 (19%), 149 (100%), 103 (23%), 65 (8.9%).

Calcd., %: C 69.92, H 4.32, N 25.75. $C_{19}H_{14}N_6$. Found, %: C 70.10, H 4.45, N 25.68.

General procedure for the synthesis of isoxazole and pyrazole derivatives 13a–d and 17a–d.

Method A—A mixture of sodium salt of 3-hydroxy-1-(5-methyl-1-phenyl-1*H*-1,2,3-triazol-4-yl)prop-2-en-1-one (**2**) (1.2 g, 5 mmol), the appropriate hydroxymoyl chlorides, or hydrazonoyl halides (5 mmol), and sodium carbonate (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. Grinding of the initial syrup was continued for 5–10 min, and the reaction was monitored by TLC. The solid was washed with water and recrystallized from the appropriate solvent to give the corresponding isoxazoles **13a–e** and pyrazoles, **17a–d**, respectively.

Method B—A mixture of 3-(dimethylamino)-1-(5-methyl-1-phenyl-1*H*-1,2,3-triazol-4-yl)prop-2-en-1-one (**8**) (10 mmol) and the appropriate hydroxymoyl chlorides or hydrazonoyl halides (5 mmol) and triethylamine (0.75 g, 0.5 mL, 5 mmol) in dry toluene (20 mL) was stirred at room temperature for 2 h (or was boiled under reflux for 2 h in case of hydrazonoyl halides). The reaction mixture was evaporated under reduce pressure and triturated with petroleum ether 40/60. The resulting solid was collected and recrystallized from proper solvent to give isoxazoles **13a–d** and pyrazoles **17a–d**, respectively.

(3-Benzoylisoxazol-4-yl)(5-methyl-1-phenyl-1H-1,2,3-triazol-4-yl)methanone (13a). Mp 144–146°C (AcOH), beige, IR (cm^{-1}): 3074 (CH), 2924 (CH), 1681 (CO), 1643 (C=N), 1593 (C=C).

^{1}H-NMR (DMSO-d_6), $\delta = 2.54$ (s, 3H, CH_3), 7.41–7.46 (m, 4H, ArH's), 7.63–7.68 (m, 4H, ArH's), 8.34–8.35 (d, 2H, $J = 4$ Hz, ArH's), and 8.79 (s, 1H, isoxazole H-5).

^{13}C-NMR (DMSO-d_6), $\delta = 8.14$, 119.62, 119.64, 127.28, 128.65, 130.69, 132.95, 137.73, 141.88, 150.03, 154.37, 176.58, 186.88, 187.35.

MS: 359 (M + 1, 0.22%), 358 (M^+, 0.59%), 227 (5%), 105 (100%), 77 (61%).

Calcd., %: C 67.03, H 3.94, N 15.63. $C_{20}H_{14}N_4O_3$. Found, %: C 67.11, H 4.15, N 15.58.

(3-(Furan-2-carbonyl)isoxazol-4-yl)(5-methyl-1-phenyl-1H-1,2,3-triazol-4-yl)methanone (13b). Mp > 300°C (benzene), brown, IR (cm^{-1}): 3066, 3020 (CH), 2924, 2850 (CH), 1697 (CO), 1593 (C=C).

^{1}H-NMR (DMSO-d_6), $\delta = 2.54$ (s, 3H, CH_3), 6.62–6.63 (d, 1H, $J = 4$ Hz, furan H-4), 7.41–7.55 (m, 6H, ArH's), 8.03–8.04 (d, 1H, $J = 4$ Hz, furan H-5), and 8.79 (s, 1H, isoxazole H-5).

MS: 349 (M + 1, 7%), 348 (M^+, 8%), 317 (11%), 276 (12%), 269 (12%), 228 (11%), 207 (8%), 180 (12%), 158 (14%), 145 (13%), 130 (38%), 123 (16%), 112 (24%), 111 (26%), 105 (17%), 95 (100%), 83 (27%), 77 (66%), 71 (68%), 69 (39%), 67 (29%), 63 (18%).

Calcd., %: C 62.07, H 3.47, N 16.09. $C_{18}H_{12}N_4O_4$. Found, %: C 61.98, H 3.38, N 15.88.

(5-Methyl-1-phenyl-1H-1,2,3-triazol-4-yl)(3-(thiophene-2-carbonyl)isoxazol-4-yl)methanone (13c). Mp > 300°C (benzene), gray, IR (cm^{-1}): 3051 (CH), 2981, 2850 (CH), 1697 (CO), 1593 (C=C).

^{1}H-NMR (DMSO-d_6), $\delta = 2.54$ (s, 3H, CH_3), 6.69–6.70 (d, 1H, $J = 4$ Hz, thiophene H-4), 7.41–7.55 (m, 6H, ArH's), 8.00–8.01 (d, 1H, $J = 4$ Hz, thiophene H-5), and 8.78 (s, 1H, isoxazole H-5).

MS: 365 (M + 1, 0.4%), 364 (M^+, 0.9%), 240 (1.5%), 227 (3%), 139 (4%), 130 (11%), 118 (7%), 111 (100%), 83 (13%), 77 (29%), 71 (9%).

Calcd., %: C 59.33, H 3.32, N 15.38, S 8.80. $C_{18}H_{12}N_4O_3S$. Found, %: C 59.22, H 3.11, N 15.68, S 8.67.

(3-(2-Naphthoyl)isoxazol-4-yl)(5-methyl-1-phenyl-1H-1,2,3-triazol-4-yl)methanone (13d). Mp 168–188°C (dioxane), beige, IR (cm^{-1}): 3051 (CH), 2916 (CH), 1701 (CO), 1639 (C=N), 1573 (C=C).

^{1}H-NMR (DMSO-d_6), $\delta = 2.54$ (s, 3H, CH_3), 7.42–7.77 (m, 9H, ArH's), 8.45–8.72 (m, 3H, ArH's), and 9.78 (s, 1H, isoxazole H-5).

MS: 409 (M + 1, 4%), 408 (M^+, 13%), 227 (6%), 172 (11%), 155 (100%), 127(65%), 118 (8%), 77 (22%).

Calcd., %: C 70.58, H 3.95, N 13.72. $C_{24}H_{16}N_4O_3$. Found, %: C 70.47, H 4.09, N 13.72.

Ethyl 4-(5-methyl-1-phenyl-1H-1,2,3-triazole-4-carbonyl)-1-phenyl-1H-pyrazole-3-carboxylate (17a). Mp 254–256°C (benzene), yellow. IR (cm^{-1}): 3062 (CH), 2977 (CH), 1720, 1666 (CO), 1595 (C=C).

^{1}H-NMR (DMSO-d_6), δ = 1.38 (t, 3H, $CH_2\mathbf{CH_3}$), 2.54 (s, 3H, CH_3), 4.28 (q, 2H, $\mathbf{CH_2}CH_3$), 7.27–8.0 (m, 10H, ArH's), and 8.32 (s, 1H, pyrazole H-5).

^{13}C-NMR (DMSO-d_6), δ = 8.14, 14.40, 60.65, 119.82, 119.99, 124.33, 127.30, 128.65, 129.40, 135.09, 136.99, 139.93, 141.42, 141.88, 150.03, 160.79, 177.18.

MS: 401 (M^+, 0.2%), 101 (21%), 86 (100%).

Calcd., %: C 65.83, H 4.77, N 17.45. $C_{22}H_{19}N_5O_3$. Found, %: C 65.89, H 4.65, N 17.34.

1-(4-(5-Methyl-1-phenyl-1H-1,2,3-triazole-4-carbonyl)-1-phenyl-1H-pyrazol-3-yl)ethanone (17b). Mp 238–240°C (benzene), beige. IR (cm^{-1}): 3062 (CH), 2977 (CH), 11674, (CO), 1643 (C=N), 1554 (C=C).

^{1}H-NMR (DMSO-d_6), δ = 2.54 (s, 3H, CH_3), 2.88 (s, 3H, CH_3), 7.27–8.0 (m, 10H, ArH's), and 8.32 (s, 1H, pyrazole H-5).

MS: 371 (M^+, 0.6%), 101 (18%), 86 (100%).

Calcd., %: C 67.91, H 4.61, N 18.86. $C_{21}H_{17}N_5O_2$. Found, %: C 68.10, H 4.80, N 19.00.

(3-Benzoyl-1-phenyl-1H-pyrazol-4-yl)(5-methyl-1-phenyl-1H-1,2,3-triazol-4-yl)methanone (17c). Mp 180–182°C (EtOH), white. IR (cm^{-1}): 3062 (CH), 2977 (CH), 1678 (CO), 1639 (C=N), 1593 (C=C).

^{1}H-NMR (DMSO-d_6), δ = 2.54 (s, 3H, CH_3), 7.27–8.22 (m, 15H, ArH's), and 8.44 (s, 1H, pyrazole H-5).

MS: 433 (M^+, 0.7%), 300 (25%), 118 (54%), 105 (39%), 77 (100%).

Calcd., %: C 72.04, H 4.42, N 16.16. $C_{26}H_{19}N_5O_2$. Found, %: C 72.18, H 4.58, N 15.98.

4-(5-Methyl-1-phenyl-1H-1,2,3-triazole-4-carbonyl)-N,1-diphenyl-1H-pyrazole-3-carboxamide (17d). Mp 248–250°C, (dioxane). IR (cm^{-1}): 3780 (NH), 3062 (CH), 2977 (CH), 1670 (CO), 1596 (C=C).

^{1}H-NMR (DMSO-d_6), δ = 2.54 (s, 3H, CH_3), 7.10–8.20 (m, 16H, ArH's and pyrazole H-5), 8.81 (s, br., 1H, NH).

MS: 448 (M^+, 52%), 418(45%), 385 (49%), 344 (66%), 294 (50%), 279 (55%), 259 (64%), 210 (59%), 191 (78%), 141 (67%), 131 (51%), 109 (73%), 94 (73%), 74 (63%).

Calcd., %: C 69.63, H 4.50, N 18.74. $C_{26}H_{20}N_6O_2$. Found, %: C 69.60, H 4.35, N 18.67.

General procedure for the synthesis of isoxazolo[3,4-*d*] pyridazines 15a–d and pyrazolo[3,4-*d*]pyridazines 19a–c.

Method A—A mixture of the appropriate isoxazoles **13a–f**, pyrazoles **17a–c** (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. Grinding of the initial syrup was continued for 5–10 min, and the reaction was monitored by TLC. The solid was washed with water and recrystallized from the appropriate solvent to give the corresponding isoxazolo[3,4-*d*]pyridazines **15a–d** and pyrazolo[3,4-*d*]pyridazines **19a–c**, respectively.

Method B—A mixture of the appropriate isoxazoles **13a–f**, pyrazoles **17a–c** (5 mmol), and hydrazine hydrate (1 g, 10 mmol) in ethanol (20 mL) was heated under reflux for 2 h. The reaction mixture was cooled, and the resulting solid was collected and recrystallized from proper solvent to give isoxazolo[3,4-*d*]pyridazines **15a–d** and pyrazolo[3,4-*d*]pyridazines **19a–c**, respectively.

4-(5-Methyl-1-phenyl-1H-1,2,3-triazol-4-yl)-7-phenylisoxazolo [3,4-d]pyridazine (15a). Mp > 300°C (EtOH), white, IR (cm^{-1}): 3055 (CH), 2989 (CH), 1596 (C=C).

^{1}H-NMR (DMSO-d_6), δ = 2.62 (s, 3H, CH_3), 7.12–7.65 (m, 8H, ArH's), 8.16–8.18 (d, 2H, J = 8 Hz, ArH's), and 9.15(s, 1H, isoxazole H-5).

^{13}C-NMR (DMSO-d_6), δ = 6.89, 114.02, 118.63, 127.23, 127.28, 128.30, 128.76, 129.51, 131.02, 135.68, 137.56, 140.74, 146.56, 151.56, 151.29, 153.04.

MS: 354 (M^+, 46), 353 (M-1, 5%), 348 (18%), 334 (23%), 332 (26%), 319 (19%), 304 (30%), 265 (18%), 252 (14%), 210 (12%), 166 (11%), 149 (100%), 125 (89%).

Calcd., %: C 67.79, H 3.98, N 23.72. $C_{20}H_{14}N_6O$. Found, %: C 67.88, H 4.12, N 23.89.

7-(Furan-2-yl)-4-(5-methyl-1-phenyl-1H-1,2,3-triazol-4-yl) isoxazolo[3,4-d]pyridazine (15b). Mp 260–262°C (EtOH), beige, IR (cm^{-1}): 3062 (CH), 2989 (CH), 1597 (C=C).

^{1}H-NMR (DMSO-d_6), δ = 2.66 (s, 3H, CH_3), 6.67–6.68 (d, 1H, J = 4 Hz, furan H-4), 7.15–7.65 (m, 6H, ArH's), 7.66–8.67(d, 1H, J = 4 Hz, furan H-5), and 9.04 (s, 1H, isoxazole H-5).

MS: 345 (M + 1, 32), 353 (M^+, 38%), 341 (29%), 315 (22%), 292 (27%), 237 (29%), 246 (21%), 242 (27%), 239 (26%), 233 (35%), 139 (28%), 126 (15%), 105 (37%), 95 (100%, 85 (16%).

Calcd., %: C 62.79, H 3.51, N 24.41. $C_{18}H_{12}N_6O_2$. Found, %: C 62.86, H 3.48, N 24.30.

4-(5-Methyl-1-phenyl-1H-1,2,3-triazol-4-yl)-7-(thiophen-2-yl)isoxazolo[3,4-d]pyridazine (15c). Mp 248–250°C (EtOH), beige, IR (cm^{-1}): 3062 (CH), 2920 (CH), 1627 (C=N), 1589 (C=C).

^{1}H-NMR (DMSO-d_6), δ = 2.54 (s, 3H, CH_3), 6.69–6.70 (d, 1H, J = 4 Hz, thiophene H-4), 7.15–7.65 (m, 6H, ArH's and thiophene), 8.54–8.55 (d, 1H, J = 4 Hz, thiophene H-2), and 9.00 (s, 1H, isoxazole H-5).

MS: 360 (M^+, 0.3%), 215 (4%), 196 (3%), 159 (3%), 157 (26%), 142 (48%), 130 (16%), 118 (29%), 93 (19%), 77 (100%), 66 (9%).

Calcd., %: C 59.99, H 3.36, N 23.32, S 8.90. $C_{18}H_{12}N_6OS$. Found, %: C 60.10, H 3.20, N 23.10, S 8.79.

4-(5-Methyl-1-phenyl-1H-1,2,3-triazol-4-yl)-7-(naphthalen-2-yl)isoxazolo[3,4-d]pyridazine (15d). Mp 228–230°C (EtOH), yellow. IR (cm^{-1}): 3055 (CH), 2916 (CH), 1701 (CO), 1639 (C=N), 1573 (C=C).

^{1}H-NMR (DMSO-d_6), δ = 2.56 (s, 3H, CH_3), 7.21–8.00 (m, 12H, ArH's), and 9.00 (s, 1H, isoxazole H-5).

MS: 404 (M^+, 16%), 403 (M-1, 17%), 359 (14%), 320 (15%), 306 (16%), 284 (18%), 240 (15%), 230 (16%), 201 (23%), 194 (18%), 178 (13%), 171 (19%), 155 (20%), 127 (23%), 80 (89%).

Calcd., %: C 71.28, H 3.99, N 20.78. $C_{24}H_{16}N_6O$. Found, %: C 71.68, H 4.15, N 20.85.

4-(5-Methyl-1-phenyl-1H-1,2,3-triazol-4-yl)-2-phenyl-2,6-dihydro-7H-pyrazolo[3,4-d]pyridazin-7-one (19a). Mp > 300°C (AcOH), beige. IR (cm^{-1}): 3139 (NH), 3062 (CH), 2920 (CH), 11670, 1589 (C=C).

^{1}H-NMR (DMSO-d_6), δ = 2.57 (s, 3H, CH_3), 7.27–7.85 (m, 10H, ArH's), 8.12 (s, 1H, pyrazole H-5), and 12.26 (s, 1H, NH).

MS: 369 (M^+, 5%), 349 (5%), 326 (5%), 292 (7%), 255 (8%), 217 (5%), 196 (7%), 171 (8%), 111 (11%), 99 (16%), 85 (45%), 82 (10%), 71 (66%).

Calcd., %: C 65.03, H 4.09, N 26.54. $C_{20}H_{15}N_7O$. Found, %: C 65.22, H 4.18, N 26.54.

7-Methyl-4-(5-methyl-1-phenyl-1H-1,2,3-triazol-4-yl)-2-phenyl-2H-pyrazolo[3,4-d]pyridazine (19b). Mp 260–262°C (AcOH), yellow. IR (cm^{-1}): 3047 (CH), 2920 (CH), 1593 (C=C).

^{1}H-NMR (DMSO-d_6), δ = 2.54 (s, 3H, CH_3), 2.57 (s, 3H, CH_3), 7.20–7.45 (m, 10H, ArH's), and 8.14 (s, 1H, pyrazole H-5).

^{13}C-NMR (DMSO-d_6), δ = 8.15, 17.26, 118.65, 124.85, 126.88, 127.28, 129.51, 131.22, 138.31, 139.40, 143.33, 146.44, 160.84.

MS: 368, (M + 1, 8%), 467 (M^+, 30%), 338 (26%), 296 (7%), 118 (9%), 77 (100%).

Calcd., %: C 68.65, H 4.66, N 26.69. $C_{21}H_{17}N_7$. Found, %: C 68.39, H 4.75, N 26.82.

4-(5-Methyl-1-phenyl-1H-1,2,3-triazol-4-yl)-2,7-diphenyl-2H-pyrazolo[3,4-d]pyridazine (19c). Mp 228–230°C (AcOH), yellow. IR (cm^{-1}): 3062 (CH), 2916 (CH), 1589 (C=C).

^{1}H-NMR (DMSO-d_6), δ = 2.54 (s, 3H, CH_3), 7.20–7.65 (m, 13H, ArH's), 7.92 (s, 1H, pyrazole H-5), and 8.18–8.20 (d, 2H, J = 8 Hz, ArH's).

MS: 429 (M^+, 29%), 418 (17%), 392 (21%), 3767 (19%), 360 (22%), 354 (22%), 339 (25%), 295 (22%), 282 (30%), 277 (25%), 275 (30%), 220 (21%), 193 (20%), 175 (25%), 160 (25%), 156 (35%), 146 (26%), 132 (16%), 112 (31%), 91 (21%), 82 (20%), 71 (44%), 66 (16%).

Calcd., %: C 72.71, H 4.46, N 22.83. $C_{26}H_{19}N_7$. Found, %: C 72.85, H 4.31, N 22.76.

General procedure for the synthesis of 2-mercapto-6-(5-methyl-1-phenyl-1*H*-1,2,3-triazol-4-yl)pyridine-3-carbonitrile (20), 1,2-dihydro-6-(5-methyl-1-phenyl-1*H*-1,2,3-triazol-4-yl)-2-oxopyridine-3-carbonitrile (22), and 1-amino-6-(5-methyl-1-phenyl-1*H*-[1,2,3]triazol-4-yl)-2-oxo-1,2-dihydropyridine-3-carbonitrile (23).

Method A—A mixture of sodium salt of 3-hydroxy-1-(5-methyl-1-phenyl-1*H*-1,2,3-triazol-4-yl)prop-2-en-1-one (**2**) (1.2 g, 5 mmol), the appropriate cyanothioacetamide, cyanoacetamide, or 2-cyanoacetohydrazide (5 mmol), and few catalytic 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. Grinding of the initial syrup was continued for 5–10 min, and the reaction was monitored by TLC. The solid was washed with water and recrystallized from the appropriate solvent to give the corresponding fused pyridines **20**, **22**, and **23**, respectively.

Method B—A mixture of sodium salt of 3-hydroxy-1-(5-methyl-1-phenyl-1*H*-1,2,3-triazol-4-yl)prop-2-en-1-one (**2**) (1.2 g, 5 mmol) and the appropriate cyanothioacetamide, cyanoacetamide, or 2-cyanoacetohydrazide (5 mmol) in a solution of piperidine acetate (piperidine (2.5 mL), water (5 mL), and acetic acid (2 mL)) was heated under reflux for about 10 min; acetic acid (1.5 mL) was added to the reaction mixture while boiling. Then the mixture was cooled, and the resulting solid was collected and recrystallized from the appropriate solvent to give **20**, **22**, and **23**, respectively.

General procedure for the synthesis ethyl 3-amino-6-(5-methyl-1-phenyl-1*H*-1,2,3-triazol-4-yl)thieno[2,3-b]pyridine-2-carboxylate (21a), 1-(3-amino-6-(5-methyl-1-phenyl-1*H*-1,2,3-triazol-4-yl)thieno[2,3-b]pyridin-2-yl)ethanone (**21b**), (3-amino-6-(5-methyl-1-phenyl-1*H*-1,2,3-triazol-4-yl)thieno[2,3-b]pyridin-2-yl)-(phenyl)-methanone (**21c**), and 3-amino-6-(5-methyl-1-phenyl-1*H*-1,2,3-triazol-4-yl)thieno[2,3-b]pyridine-2-carbonitrile (**21d**).

Method A—A mixture of 2-mercapto-6-(5-methyl-1-phenyl-1*H*-1,2,3-triazol-4-yl)pyridine-3-carbonitrile (**20**) (1.46 g, 5 mmol), potassium carbonate (1.4 g, 10 mmol), and the appropriate of ethyl chloroacetate, chloroacetone, ω-bromoacetophenone, or chloroacetonitrile (5 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. Grinding of the initial syrup was continued for 5–10 min, and the reaction was monitored by TLC. The solid was washed with water and recrystallized from the appropriate solvent to give the corresponding thieno[2,3-*b*]pyridine derivatives **21a–d**, respectively.

Method B—A mixture of 2-mercapto-6-(5-methyl-1-phenyl-1*H*-1,2,3-triazol-4-yl)pyridine-3-carbonitrile (**20**) (1.46 g, 5 mmol) and potassium hydroxide (1.4 g, 10 mmol) in *N*,*N*-dimethylformamide (20 mL) was stirred for 2 h. The appropriate ethyl chloroacetate, chloroacetone, ω-bromoacetophenone, or chloroacetonitrile (5 mmol) was added to the above mixture, which was stirred for 3 h. The resulting solid was formed after dilution of water was collected and recrystallized from the proper solvent to give thieno [2,3-*b*]pyridine derivatives **21a–d**, respectively.

6-(5-Methyl-1-phenyl-1H-1,2,3-triazol-4-yl)-2-thioxo-1,2-dihydropyridine-3-carbonitrile (20). Mp 262–264°C (EtOH), brown. IR (cm^{-1}): 3070 (CH), 2923 (CH), 2218 (CN), 1578 (C=C).

^{1}H-NMR (DMSO-d_6), δ = 2.54 (s, 3H, CH_3), 5.89 (s, 1H, SH), 7.10–7.65 (m, 6H, ArH's), 8.39–8.41 (d, 1H, pyridine H-4).

MS: 292 (M^+, 73%), 291 (M-1, 45%), 288 (63%), 223 (63%), 180 (63%), 148 (72%), 135 (63%), 131 (18%), 128 (63%), 120 (72%), 94 (63%), 92 (100%), 80 (18%), 75 (100%), 62 (66%).

Calcd., %: C 61.42, H 3.78, N 23.89, S 10.93. $C_{15}H_{11}N_5S$. Found, %: C 61.35, H 3.87, N 23.75, S 11.05.

Ethyl 3-amino-6-(5-methyl-1-phenyl-1H-1,2,3-triazol-4-yl) thieno[2,3-b]pyridine-2-carboxylate (21a). Mp 228–230°C (EtOH), beige. IR (cm^{-1}): 3460, 3355 (NH_2), 3062 (CH), 2970 (CH), 1666 (CO), 1604 (C=C).

^{1}H-NMR (DMSO-d_6), δ = 1.28 (t, 3H, $CH_2\mathbf{CH_3}$), 2.54 (s, 3H, CH_3), 4.21 (q, 2H, $\mathbf{CH_2}CH_3$), 5.89 (s, br., 2H, NH_2), 7.10–7.85 (m, 7H, ArH's).

^{13}C-NMR (DMSO-d_6), δ = 8.60, 14.60, 59.30, 105.44, 119.74, 120.96, 127.28, 128.15, 128.64, 133.57, 139.70, 143.67, 144.04, 144.16, 149.74, 155.25, 165.05

MS: 379 (100%), 351 (40%), 350 (13%), 323 (13%), 307 (6%), 306 (20%), 305 (77%), 304 (24%), 279 (11%), 278 (18%), 244 (43%), 235 (10%), 130 (54%), 103 (10%), 77 (62%).

Calcd., %: C 60.14, H 4.52, N 18.46, S 8.45. $C_{19}H_{17}N_5O_2S$. Found, %: C 60.005, H 4.62, N 18.34, S 8.35.

1-(3-Amino-6-(5-methyl-1-phenyl-1H-1,2,3-triazol-4-yl)thieno [2,3-b]pyridin-2-yl)ethanone (21b). Mp 276–278°C (EtOH), brown. IR (cm^{-1}): 3417, 3321 (NH_2), 3093 (CH), 2920 (CH), 1640 (CO), 1596 (C=C).

^{1}H-NMR (DMSO-d_6), δ = 2.35 (s, 3H, CH_3), 2.54 (s, 3H, CH_3), 5.79 (s, br., 2H, NH_2), 7.10–7.82 (m, 7H, ArH's).

^{13}C-NMR (DMSO-d_6), δ = 8.60, 30.94, 119.74, 120.74, 122.79, 127.28, 128.15, 134.17, 139.70, 144.16, 149.32, 156.02, 190.87.

MS: 349 (100%), 321 (58%), 320 (61%), 257 (60%), 229 (30%), 251 (14%), 237 (11%), 218 (13%), 154 (10%), 175 (10%), 130 (63%), 77 (62%), 63 (5%).

Calcd., %: C 61.87, H 4.33, N 20.04, S 9.18. $C_{18}H_{15}N_5OS$. Found, %: C 61.92, H 4.21, N 19.89, S 9.15.

(3-Amino-6-(5-methyl-1-phenyl-1H-1,2,3-triazol-4-yl)thieno [2,3-b]pyridin-2-yl)(phenyl) methanone (21c). Mp > 300°C (EtOH), gray. IR (cm^{-1}): 3402, 3286 (NH_2), 3066 (CH), 2920 (CH), 1645 (CO), 1608 (C=C).

^{1}H-NMR (DMSO-d_6), δ = 2.51 (s, 3H, CH_3), 5.82 (s, br., 2H, NH_2), 7.10–7.87 (m, 12H, ArH's).

MS: 411 (40%), 333 (74%), 130 (33%), 105 (38%), 77 (100%), 69 (5%).

Calcd., %: C 67.13, H 4.16, N 17.02, S 7.79. $C_{23}H_{17}N_5OS$. Found, %: C 67.00, H 3.98, N 16.89, S 7.85.

3-Amino-6-(5-methyl-1-phenyl-1H-1,2,3-triazol-4-yl)thieno [2,3-b]pyridine-2-carbonitrile (21d). Mp 244–246°C (AcOH),

brown. IR (cm^{-1}): 3344, 3236 (NH_2), 3058 (CH), 2923 (CH), 2194 (CN), 1639 (C=N), 1581 (C=C).

^{1}H-NMR (DMSO-d_6), $\delta = 2.51$ (s, 3H, CH_3), 7.10–7.87 (m, 8H, ArH's and NH_2), and 9.21–9.23 (d, 1H, $J = 8$ Hz, ArH).

MS: 332 (32%), 312 (51%), 283 (39%), 274 (36%), 267 (23%), 266 (41%), 243 (47%), 231 (20%), 222 (59%), 206 (19%), 198 (20%), 188 (46%), 181 (20%), 174 (16%), 162 (14%), 159 (20%), 149 (25%), 123 (28%), 113 (18%), 106 (29%), 100 (69%), 91 (61%), 87 (27%), 84 (57%), 77 (63%).

Calcd., %: C 61.43, H 3.64, N 25.28, S 9.65. $C_{17}H_{12}N_6S$. Found, %: C 61.34, H 3.74, N 25.12, S 9.55.

6-(5-Methyl-1-phenyl-1H-1,2,3-triazol-4-yl)-2-oxo-1,2-dihydropyridine-3-carbonitrile (22). Mp 250–252°C (EtOH), brown. IR (cm^{-1}): 3618 (OH), 3058 (CH), 2920 (CH), 2222 (CN), 1643 (C=N), 1546 (C=C).

^{1}H-NMR (DMSO-d_6), $\delta = 2.51$ (s, 3H, CH_3), 7.10–7.87 (m, 7H, ArH's), 14.25 (s, 1H, OH).

MS: 278 (M + 1, 5%), 277 (33%), 250 (9%), 248 (79%), 179 (25%), 146 (29%), 130 (68%), 104 (17%), 77 (95%), 51 (100%).

Calcd., %: C 64.97, H 4.00, N 25.26. $C_{15}H_{11}N_5O$. Found, %: C 65.12, H 3.88, N 25.15.

1-Amino-6-(5-methyl-1-phenyl-1H-1,2,3-triazol-4-yl)-2-oxo-1,2-dihydropyridine-3-carbonitrile (23). Mp 268–270°C (EtOH), yellow. IR (cm^{-1}): 3322, 3193 (NH_2), 3070 (CH), 2931 (CH), 1693 (CO), 1604 (C=C).

^{1}H-NMR (DMSO-d_6), $\delta = 2.39$ (s, 3H, CH_3), 6.22 (s, br., 2H, NH_2), 7.10–7.19 (m, 5H, ArH's), 7.64–7.71 (m, 1H, ArH), and 8.21–9.22 (d, 1H, $J = 4$ Hz, ArH).

MS: 293 (M + 1, 41%), 264 (83%), 248 (21%), 214 (50%), 162 (96%), 141 (100%), 114 54%), 90 (58%), 64 (75%), 51 (81%).

Calcd., %: C 61.64, H 4.14, N 28.75. $C_{15}H_{12}N_6O$. Found, %: C 61.93, H 4.00, N 28.67.

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