Received: 6 October 2019 | Revised: 5 November 2019 | Accepted: 11 November 2019

DOI: 10.1002/jhet.3835

WILEY

ARTICLE

Synthesis, reactions, and antimicrobial activity of some novel pyrazolo[3,4-*d*]pyrimidine, pyrazolo[4,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidine, and pyrazolo[4,3-*e*][1,2,4]triazolo[3,4-*c*]pyrimidine derivatives

Hamdi M. Hassaneen[1] | **Fatma M. Saleh**[1] | **Tayseer A. Abdallah**[1] | **Yasmin Sh. Mohamed**[2] | **Enas M. Awad**[3]

[1]Department of Chemistry, Faculty of Science, Cairo University, Giza, Egypt

[2]National Organization for Drug Control and Research, Dokki, Giza, Egypt

[3]Chemistry of Natural and Microbial Products Department, Pharmaceutical and Drug Industries Research Division, National Research Centre, Cairo, Egypt

Correspondence
Hamdi M. Hassaneen, Department of Chemistry, Faculty of Science, Cairo University, Giza 12613, Egypt.
Email: hamdi_251@yahoo.com

Abstract

Treatment of *N*-phenyl-substituted benzenecarbo-hydrazonoyl chlorides **1a-d** with malononitrile in sodium ethoxide solution gave 5-amino-4-cyanopyrazole derivatives **2-5**. Compounds **2-5** were converted to formidate derivatives **6-9** upon treatment with TEOF in acetic anhydride. The reaction of the latter products **6-9** with hydrazine hydrate gave imino-amino derivatives **10-13**, which was converted to hydrazino derivatives **14-17** by refluxing with hydrazine hydrate. Hydrazino as well as imino-amino derivatives undergo condensation, cyclization, and cycloaddition reactions to give pyrazolo[3,4-*d*]pyrimidine **18-21**, pyrazolo[4,3-*e*][1,2,4]triazolo-[3,4-*c*]pyrimidine **22-27**, and pyrazolo[3′,4′:4,5]pyrimido[1,6-*b*][1,2,4]triazine **42-44** derivatives. Antimicrobial studies are performed using two Gram-positive bacteria and two Gram-negative bacteria. Data indicated that compounds **5**, **28D**, **29B**, and **31D** are exploring elevated antibacterial effects against all strains tested. Compound **28D** is the most promising antibacterial agent against the delicate bacterial strain *Bacillus subtilis* and *Pseudomonas aeruginosa* with high effectiveness (low minimum inhibitory concentration [MIC] value) 40 and 60 μg/mL, respectively.

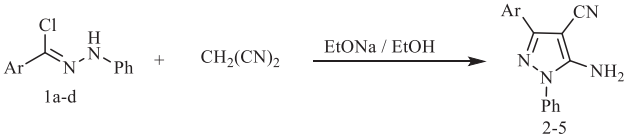
1 | INTRODUCTION

A survey of literature reveals that pyrazolo[3,4-*d*]pyrimidine derivatives have attracted considerable interest because of their biological activity as purine analogs.[1–3] In addition, compounds containing 1,2,4-triazolo[1,5-*c*] pyrimidine moiety were reported to exhibit remarkable adenosine receptor affinity.[4] Reports from our laboratory[5] and from others[6] revealed that the possible route for the synthesis of pyrazolo[4,3-*e*][1,2,4]triazolo[1,5-*c*] pyrimidine derivatives involves reaction of 5-amino-4-imino-pyrazolo[3,4-*d*]pyrimidine with one-carbon cyclizing agents. Furthermore, attempts to prepare the isomeric pyrazol[4,3-*e*][1,2,4]triazolo[4,3-*c*] pyrimidines via dehydrative cyclization of the 4-acylhydrazino-pyrazolo[3,4-*d*]pyrimidines were reported to give the corresponding pyrazolo[4,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidines.[7] In the light of these findings and in continuation of our ongoing research work on the chemistry of hydrazonoyl halides,[8–23] it was thought interesting to synthesize new series of pyrazolo[3,4-*d*]pyrimidine and pyrazolo[4,3-*e*][1,2,4]triazolo[3,4-*c*]pyrimidine derivatives. Evaluation of antimicrobial activity against some microorganisms was investigated.

Our interest in developing a new synthsis of these two ring systems results from the fact that some derivatives of both pyrazolo[3,4-*d*][1,2,4]triazolo[1,5-*c*]pyrimidine and pyrazolo[4,3-*e*][1,2,4]triazolo[3,4-*c*]pyrimidine derivatives exhibit interesting pharmacological activities[24]; for example, several 3- and/or 5-substituted 7*H*-pyrazolo[4,3-*e*][1,2,4]triazolo[3,4-*c*]pyrimidines were reported to be potent xantheine oxidase (XO) inhibitors.[24] Also, pyrazolo[3,4-*d*][1,2,4]triazolo[1,5-*c*]pyrimidine is one of the structural requirements for compounds that have as selective antagonists for human A_{2A} and A_3 adenosine receptor subtypes.[6]

2 | RESULTS AND DISCUSSION

The starting compounds, namely, 5-amino-1,3-diarylpyrazole-4-carbonitrile **2**-**5**, were prepared via reaction of the corresponding *N*-phenyl-substituted benzenecarbohydrazonoyl chlorides **1a**-**d** (prepared by stirring of the corresponding hydrazide with carbon tetrachloride and triphenylphosphine in acetonitrile)[25] with malononitrile in ethanol in the presence of sodium ethoxide following the procedure we have previously reported for synthesis of 5-amino-1,3-diphenyl-pyrazole-4-carbonitrile **2** (Scheme 1).[26] Elemental and spectral information verified the structures of the latter products (see Section 4). For example, IR spectrum of **3** showed bands at ν 3430, 3320 (NH_2) and 2238 (CN) cm^{-1}. Its ^1H NMR spectrum revealed the presence of two singlet signals at δ 3.81 (3H, CH_3O) and at δ 6.75 (2H, NH_2), in addition to multiplet signal at δ 7.04-7.85 (9H) revealed to aromatic protons.

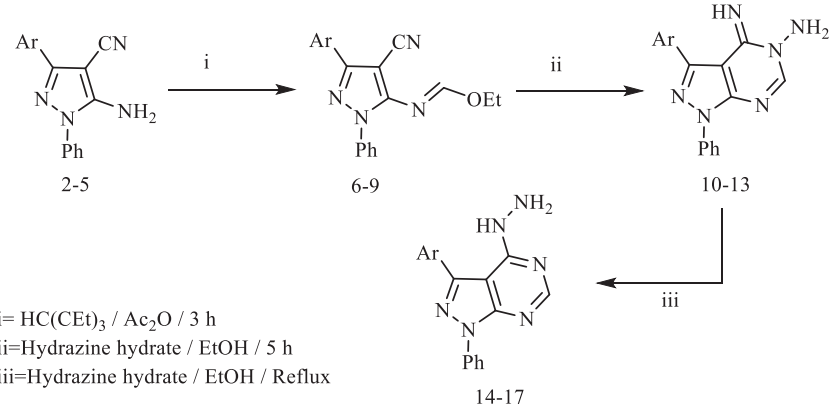


	Ar
1a, 2	Ph
1b, 3	4-$CH_3OC_6H_4$
1c, 4	4-$CH_3C_6H_4$
1d, 5	4-ClC_6H_4

SCHEME 1 Synthesis of 5-amino-1,3-diarylpyrazole-4-carbonitriles

Reaction of the compounds **2**-**5** with triethylorthoformate in acetic anhydride at reflux yielded the corresponding *N*-ethoxymethylene derivatives **6**-**9** (Scheme 2). Elemental and spectral information verified the structures of the latter products (see Section 4). For example, ^1H NMR spectrum of **7** revealed the presence of triplet signal at δ 1.27 (3H, J = 7 Hz, $\underline{CH_3}CH_2$), quartet signal at δ 4.30 (2H, J = 7 Hz, $\underline{CH_2}CH_3$), and two singlet signals at δ 3.80 (3H, CH_3O) and 8.59 (s, 1H, CH), in addition to multiplet signal at δ 7.07-7.91 (9H) assignable to aromatic protons.

Stirring of the compound **6**-**9** in ethanol at room temperature with hydrazine hydrate furnished 3-amino-4-imino-pyrazolo[3,4-*d*]pyrimidines **10**-**13**, respectively (Scheme 2). Refluxing the mixture of each of the compounds **10**-**13** and hydrazine hydrate in ethanol for 2 hours, 4-hydrazino-1,3-diarylpyrazolo[3,4-*d*]pyrimidines **14**-**17** were produced, respectively (Scheme 2). The



	Ar
2, 6, 10, 14	Ph
3, 7, 11, 15	4-$CH_3OC_6H_4$
4, 8, 12, 16	4-$CH_3C_6H_4$
5, 9, 13, 17	4-ClC_6H_4

SCHEME 2 Synthesis of 4-hydrazino-1,3-diarylpyrazolo[3,4-*d*]pyrimidines

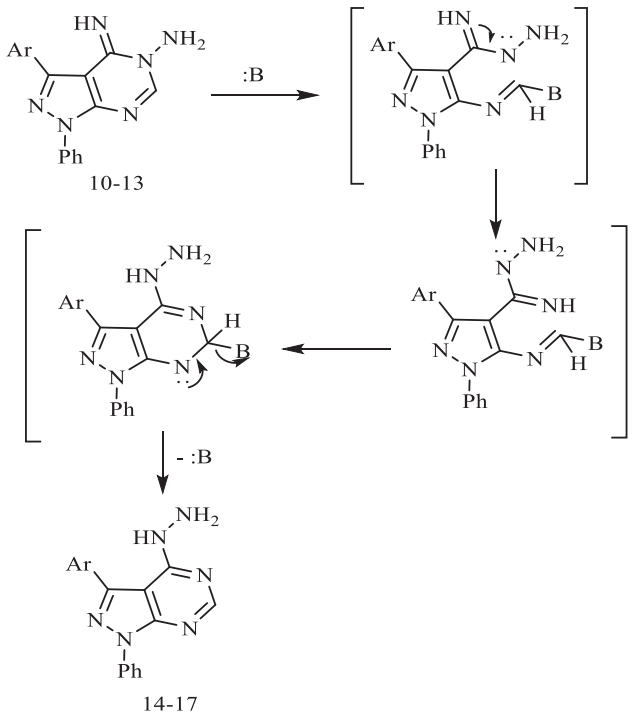
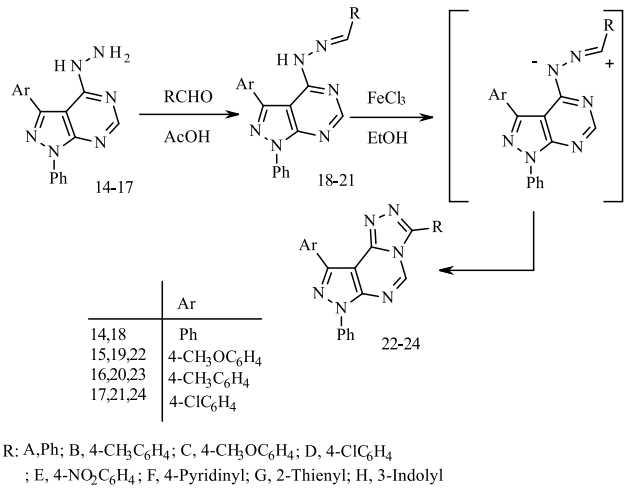


FIGURE 1 Mechanism of Dimroth rearrangement



SCHEME 3 Synthesis of 1,3,6-triarylpyrazolo[3,4-*d*][1,2,4] triazolo[3,4-*e*]pyrimidines

conversion of compounds **10**-**13** into **14**-**17** seems to be compatible with literature reported[27] that 3-amino-4-imino-pyrazolo[3,4-*d*]pyrimidines undergo Dimroth rearrangement via base-catalyzed tandem ring opening and ring closure as shown in Figure 1 to give the corresponding 4-hydrazino-pyrazolo[3,4-*d*]pyrimidines **14**-**17**. The structures of the products **10**-**13** and **14**-**17** were elucidated on the basis of the elemental analyses and spectral data. For example, ^{1}H NMR spectrum of **12** showed two singlet signals at δ 2.38 and 8.17 assigned to methyl and vinyl-H, respectively. It also featured two exchangeable singlet signals at 5.67 and 7.57 for the respective NH_2 and NH. The multiplet signal at 7.30-8-06 is assigned to aromatic protons.

The structures of compounds **14**-**17** were confirmed chemically. For example, the reaction of each of the compounds **14**-**17** with aromatic aldehydes in ethanol in the presence of acetic acid as a catalyst yielded the corresponding aldehyde *N*-aryl- and *N*-hetero-hydrazones **18**-**21** (Scheme 3). The structures of the latter products were confirmed by elemental and spectral analyses. For example, ^{1}H NMR spectrum of **19B** showed four doublet signals at 7.03, 7.40, 7.50, and 7.53 for the aromatic protons of two para-substituted aryl groups and mutiplet signal 7.60-8-06 assigned to phenyl protons, four characteristic singlet signals at δ 2.37 for CH_3, at 3.83 for CH_3O, at 8.43 for CH, and at 8.47 for CH, and one exchangeable singlet signal at δ 12.03 for NH.

Oxidation of each of the compounds **19**-**21** with ferric chloride in ethanol resulted in the formation of the corresponding 1,3,6-triarylpyrazolo[3,4-*d*][1,2,4] triazolo[3,4-*e*]pyrimidines **22**-**24** (Scheme 3). The formation of compounds **22**-**24** is assumed to be via oxidation of compounds **18**-**21** that affords the corresponding nitrilimines followed by in situ 1,5-electrocyclization. The formation of the latter seems to result via oxidation of **19**-**21** to yield the corresponding nitrilimines that underwent in situ 1,5-electrocyclization and gave **22**-**24**. This suggested pathway is compatible with literature reports on oxidation of aldehyde *N*-hetarylhydrazones and cyclization of *N*-hetaryl nitrilimines.[28]

When the latter compounds **22**-**24** were heated at reflux in ethanol in the presence of sodium acetate as a base catalyst, they underwent Dimroth rearrangement and gave the 7*H*-pyrazolo[4,3-*e*][1,2,4]triazolo[1,5-*c*] pyrimidine derivatives **25**-**27** (Figure 2). The structures of the latter products were confirmed by their alternate synthesis. Thus, reaction of each of compounds **10**-**13** with the appropriate acyl chloride yielded products that proved identical in all respects (mp, IR, Ms) with those obtained above from **22**-**24** (Scheme 4).

Treatment of hydrazine **14**-**17** in the refluxing ethanol with the appropriate ketone in the presence of few drops of acetic acid gave the corresponding hydrazones **28**-**31** (Scheme 5). The structures of isolated products were identified by their elemental and spectroscopic (IR, ^{1}H NMR, ^{13}C NMR, and MS) analyses (see Section 4). For example, the ^{1}H NMR spectrum of **29A** revealed three singlet signals at δ 2.51 (3H, CH_3), 3.81 (s, CH_3O), and 8.60 (1H, CH) and multiplet signal at δ 6.99-8.10 (13H) revealed to aromatic protons.

The reactions of the 3-amino-4-imino-pyrazolo[3,4-*d*] pyrimidines **11**-**13** with the nitrilimines (generated in

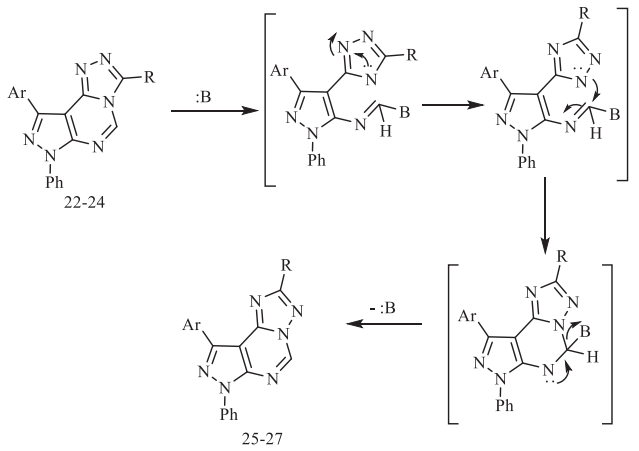
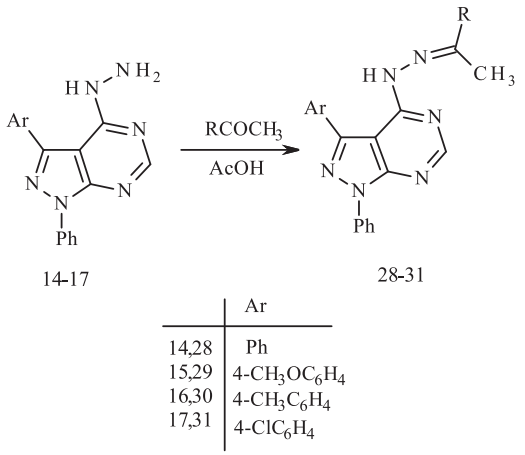


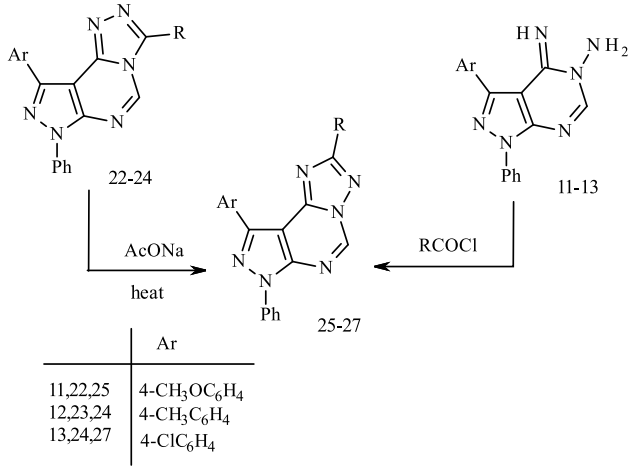
FIGURE 2 Mechanism of base-catalyzed rearrangement of **22**-**24** into **25**-**27**



	Ar
14,28	Ph
15,29	4-$CH_3OC_6H_4$
16,30	4-$CH_3C_6H_4$
17,31	4-ClC_6H_4

R: A, 2-Pyridinyl; B,3-Pyridinyl; C,4-Pyridinyl; D,2-Thienyl; E, Ph; F, 2-Fluorenyl; G,2-Naphthalenyl

SCHEME 5 Synthesis of hydrazone derivatives **28**-**31**



	Ar
11,22,25	4-$CH_3OC_6H_4$
12,23,24	4-$CH_3C_6H_4$
13,24,27	4-ClC_6H_4

R: A,Ph; B, 4-$CH_3C_6H_4$; C, 4-$CH_3OC_6H_4$; D, 4-ClC_6H_4

SCHEME 4 Synthesis of 7*H*-pyrazolo[4,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidine derivatives **25**-**27**

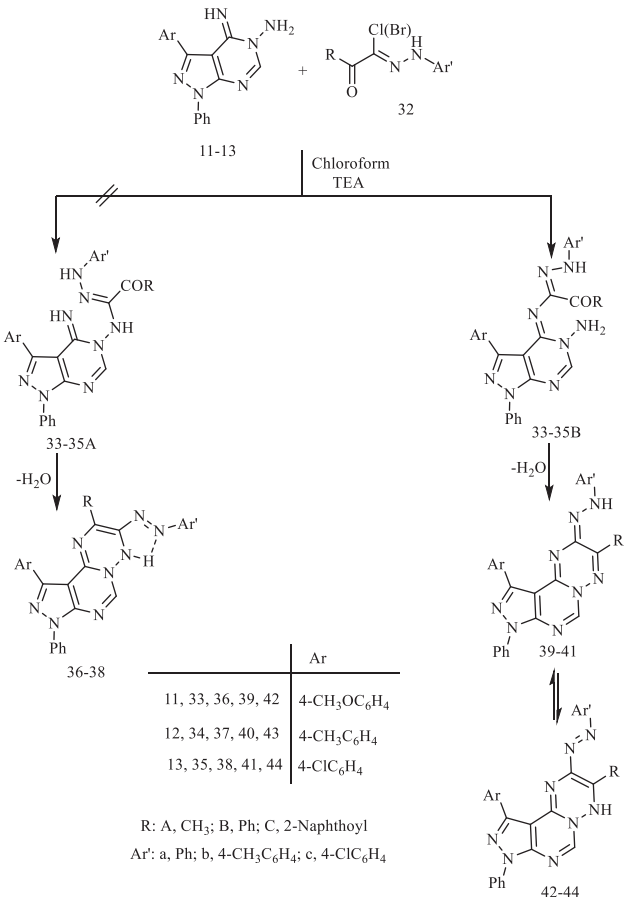
situ by base-catalyzed dehydrohalogenation of the hydrazonoyl halides **32**) were next examined (Scheme 6). In our hands, reaction of **11**-**13** with each of the α-ketohydrazonoyl halides **32** in refluxing chloroform in the presence of triethylamine yielded, in each case, one isolated product pyrazolopyrimidotriazine derivatives **42**-**44**. The IR spectra of the isolated products revealed the absence of the carbonyl absorption bands, thus excluding the two possible nucleophilic substitution structures **33**-**35A** and **33**-**35B**. The results of elemental analyses of the products were found to be consistent with the two isomeric structures **36**-**38** and **39**-**41** and its tautomeric structure **42**-**44** (Scheme 6). Since the imino nitrogen is known to be more basic and in turn more nucleophilic than that of the amino group[29,30] (this reaction seem to follow the same mechanism reported for the reactions of 2-aminopyridine with α-oxohydrazonoyl halides and α-haloketones and esters) (Scheme 7),[31,32] the intermediate **33**-**35A** is not expected to be formed, and accordingly, structure **36**-**38** was discarded. Furthermore, the electronic absorption spectrum of the isolated products excludes the hydrazone structure **39**-**41** since they revealed a characteristic absorption maxima at 361 (logε 4.43) and 400 (logε 4.40) nm assignable to an arylazo chromophore.[33,34] Accordingly, the products obtained from the reaction of **11**-**13** with **32** were assigned structure **42**-**44**. Also, the structures of products were identified, on the basis of their elemental analysis and spectral (IR, NMR, and MS) data (Section 4).

3 | ANTIMICROBIAL SCREENING

The antibacterial and antifungal activities of new synthesized compounds were studied by the disk diffusion method. The antibacterial activities were done on the following pathogenic organisms: the Gram-positive bacteria *Staphylococcus aureus* and *Bacillus subtilis*, the Gram-negative bacteria *Escherichia coli* and *Pseudomonas aeruginosa*. Moreover, antifungal activities against *Aspergillus flavus* and *Candida albicans* were studied. The synthesized compounds were used at the concentration of 20 mg/mL using dimethyl sulfoxide (DMSO) as a solvent. The Ampicillin 10 μL/disk was used as a standard antibacterial agent and the Amphotericin B 20 μg/mL as standard antifungal agent. The results presented in Table 1 suggest that the most potent compounds **5**, **28D**, **29B**, and **31D** exhibited antimicrobial activity.

In vitro susceptibility tests were performed to evaluate minimum inhibitory concentration (MIC)

measured by a broth dilution method.[35–37] MIC values were determined for the highly efficient antibacterial compounds using the most sensitive microorganisms. Results illustrated in Table 2 indicate that compound **28D** achieved the lowest MIC values (high efficient derivative) against the sensitive bacterial strain *B. subtilis* and *P. aeruginosa* with MIC values 40 and 60 μg/mL, respectively.



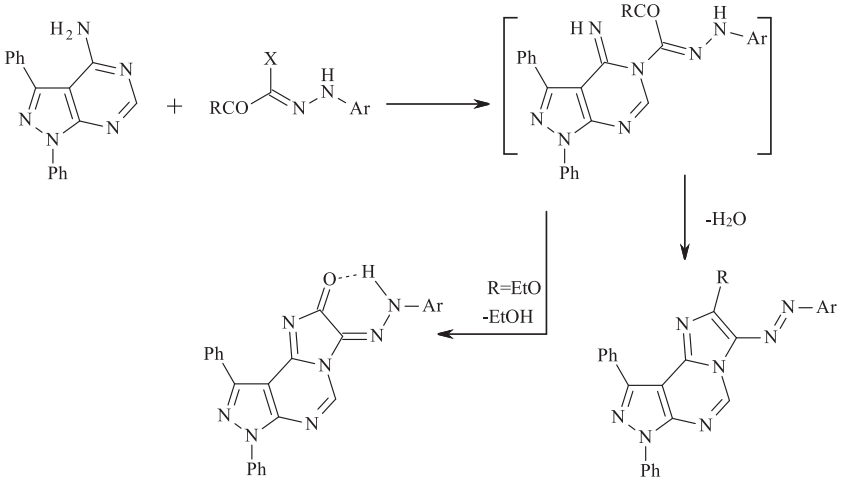
SCHEME 6 Reaction of the 3-amino-4-imino-pyrazolo[3,4-*d*] pyrimidines with α-ketohydrazonoyl halides

4 | EXPERIMENTAL

Melting points were determined on a Stuart melting point apparatus and are uncorrected. The IR spectra were measured as KBr pellets on a FTIR Bruker-Vector 22 spectrophotometer. The ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ or [D_6] DMSO on a Varian Mercury VXR 300 spectrometer (300 MHz for ^{1}H NMR and 75 MHz for ^{13}C NMR) using TMS as internal standard. Mass spectra were measured on a Shimadzu GCMS-Q-1000 EX mass spectrometer at 70 eV. The elemental analyses were carried out at the Microanalytical Center, Cairo University using Automated analyzer CHNS, Vario EL III, Elementar, Germany. The in vitro antimicrobial testing was performed at Microanalytical Center, Cairo University. The agar disk diffusion method and a panel of standard strains (*S. aureus* ATCC 6588, *B. subtilis* CMGB 215, *E. coli* ATCC 11775, *P. aeuroginosa* ATCC 15442, *A. flavus* Link, and *C. albicans* ATCC 7102) were employed. Compounds **2**, **6**, **10**, and **14** were prepared using the reported procedures.[26]

4.1 | 5-Amino-3-aryl-1-phenyl-1*H*-pyrazole-4-carbonitrile derivatives (3-5)

Malonitrile (1.3 g, 20.0 mmol) was added to ethanol sodium ethoxide solution (prepared from sodium metal [0.46 g, 20.0 mmol] and absolute ethanol [20 mL]). The mixture was stirred for 10 minutes, and hydrazonoyl chloride **1b-d** (20.0 mmol) was added. The mixture was



SCHEME 7 Reaction of 2-aminopyridine with α-oxohydrazonoyl halides and α-haloketones and esters

TABLE 1 In vitro antibacterial and antifungal activities of some new synthesized compounds (inhibition zone in millimeters)

Compounds		Antimicrobial Activity											
		Bacterial Species (G^+)				Bacterial Species (G^-)				Fungi			
		Bacillus subtilis		Staphylococcus aureus		Escherichia coli		Pseudomonas aeruginosa		Aspergillus flavus		Candida albicans	
		IZ	RA%	IZ	RA%	IZ	RA%	IZ	RA%	IZ	RA%	IZ	RA%
Control: DMSO		**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**
Standard	Ampicillin (Antibacterial agent)	18	100	18	100	22	100	17	100				
	Amphotericin B (Antifungal agent)									15	100	18	100
3		15	83.3	9	50	0.0	0.0	12	70.6	20	133.3	17	94.4
4		14	77.7	10	55.6	9	40.9	12	70.6	14	93.3	12	66.7
5		15	83.3	11	61.1	11	50	13	76.5	13	86.7	10	55.6
17		15	83.3	13	72.2	11	50	15	88.2	0.0	0.0	11	61.1
28A		0.0	0.0	9	50	9	40.9	0.0	0.0	0.0	0.0	0.0	0.0
28B		0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
28D		22	122.2	22	122.2	19	86.3	22	129.4	0.0	0.0	13	72.2
29A		0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
29B		17	94.4	14	77.7	13	59.5	17	100	0.0	0.0	12	66.6
29D		0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
30A		0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
30B		13	72.2	11	61.1	11	50	14	82.3	0.0	0.0	9	50
30D		0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
31A		0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
31D		17	94.4	13	72.2	11	50	16	94.1	0.0	0.0	10	55.5

Note. G^-, Gram negative; G^+, Gram positive; R.A., relative activity.

TABLE 2 MIC of compounds **5, 28D, 29B, 31D** against the sensitive microorganism

	MIC, μg/mL			
	G^+	G^-		Fungi
Compound	Bacillus subtilis	Pseudomonas aeruginosa	Escherichia coli	Candida albicans
5	182	232	--	420
28D	40	60	--	420
29B	134	142	--	600
31D	88	102	--	840

Abbreviation: MIC, minimum inhibitory concentration.

stirred for further 15 minutes at room temperature and then left overnight. Solids that precipitated were collected, washed with water, and then crystallized from suitable solvent.

4.1.1 | 5-Amino-3-(4-methoxyphenyl)-1-phenyl-1*H*-pyrazole-4-carbonitrile (3)

Yield (81%); White crystals; mp 163°C-165°C (EtOH); IR (ν_{max}, cm^{-1}) ν 3430 and 3320 (NH_2) and 2238 (CN); ^1H NMR (300 MHz, DMSO-d_6) δ 3.81 (s, 3H, CH_3O), 6.75 (s, 2H, NH_2) and 7.04-7.85 (m, 9H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 55.2, 71.1, 114.2, 115.7, 123.7, 124.2, 127.6, 127.8, 129.4, 137.4, 150.1, 152.8, 159.9; MS (EI, 70 eV) *m/z* (%): 290 (M^+, 100). Anal. Calcd. for $C_{17}H_{14}N_4O$ (290): C, 70.33; H, 4.86; N, 19.30. Found: C, 70.30; H, 4.79; N, 19.27.

4.1.2 | 5-Amino-1-phenyl-3-(*p*-tolyl)-1*H*-pyrazole-4-carbonitrile (4)

Yield (85%); White crystals; mp 148°C-150°C (EtOH); IR (ν_{max}, cm^{-1}) ν 3444 and 3300 (NH_2) and 2222 (CN); ^1H NMR (300 MHz, DMSO-d_6) δ 2.35 (s, 3H, CH_3), 6.9 (s, 2H, NH_2) and 7.28-7.78 (m, 9H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 20.7, 71.3, 113.4, 115.6, 124.2, 125.8, 127.9, 129.0, 137.4, 138.6, 144.2, 150.3, 152.8; MS (EI, 70 eV) *m/z* (%): 274 (M^+, 100). Anal. Calcd. for $C_{17}H_{14}N_4$ (274.12): C, 74.43; H, 5.14; N, 20.42. Found: C, 74.32; H, 5.06; N, 20.51.

4.1.3 | 5-Amino-3-(4-chlorophenyl)-1-phenyl-1*H*-pyrazole-4-carbonitrile (5)

Yield (88%); White crystals; mp 174°C-176°C (CH_3CN); IR (ν_{max}, cm^{-1}) ν 3436 and 3309 (NH_2) and 2230 (CN); MS (EI, 70 eV) *m/z* (%): 294 (M^+, 100). Anal. Calcd. for $C_{16}H_{11}ClN_4$ (294.07): C, 65.20; H, 3.76; Cl, 12.03; N, 19.01. Found: C, 65.13; H, 3.78; Cl, 12.11; N, 18.91.

4.2 | Ethyl-*N*-(3-aryl-4-cyano-1-phenyl-1*H*-pyrazol-5-yl)formimidate derivatives (7-9)

The appropriate 5-amino-3-aryl-1-phenyl-1*H*-pyrazole-4-carbonitrile derivatives **3**-**5** (50.0 mmol) were dissolved in acetic anhydride (50 mL). To the resulting solution, triethyl orthoformate (7.40 g, 50.0 mmol) was added, the mixture was refluxed for 5 hours, and the excess acetic anhydride was distilled off under reduced pressure. The solid that precipitated on cooling was filtered, and the crude product was crystallized from the suitable solvent to give **7**-**9**.

4.2.1 | Ethyl-*N*-(4-cyano-3-(4-methoxyphenyl)-1-phenyl-1*H*-pyrazol-5-yl)formimidate (7)

Yield (76%); White crystals; mp 127°C-128°C (CH_3CN); IR (ν_{max}, cm^{-1}) ν 2220 (CN); ^1H NMR (300 MHz, DMSO-d_6) δ 1.27 (t, J = 7 Hz, 3H, $\underline{CH_3}CH_2$), 3.80 (s, 3H, CH_3O), 4.30 (q, J = 7 Hz, 2H, $\underline{CH_2}CH_3$), 7.07-7.91 (m, 9H) and 8.59 (s, 1H, CH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 13.7, 55.2, 64.0, 79.10, 114.36, 115.10, 123.02, 123.69, 127.46, 127.82, 128.91, 137.63, 150.55, 151.70, 160.25, 162.19; MS (EI, 70 eV) *m/z* (%): 346 (M^+, 100). Anal. Calcd. for $C_{20}H_{18}N_4O_2$ (346.14): C, 69.35; H, 5.24; N, 16.17. Found: C, 69.28; H, 5.21; N, 16.20.

4.2.2 | Ethyl-*N*-(4-cyano-1-phenyl-3-(*p*-tolyl)-1*H*-pyrazol-5-yl)formimidate (8)

Yield (80%); White crystals; mp 126°C-128°C (EtOH); IR (ν_{max}, cm^{-1}) ν 2214 (CN); ^1H NMR (300 MHz, DMSO-d_6) δ 1.29 (t, J = 7 Hz, 3H, $\underline{CH_3}CH_2$), 2.30 (s, 3H, CH_3), 4.27 (q, J = 7 Hz, 2H, $\underline{CH_2}CH_3$), 7.00-7.86 (m, 9H) and 8.63 (s,

1H, CH); MS (EI, 70 eV) *m/z* (%): 330 (M^+, 4.1), 77 (100). Anal. Calcd. for $C_{20}H_{18}N_4O$ (330.15): C, 72.71; H, 5.49; N, 16.96. Found: C, 72.62; H, 5.52; N, 16.99.

4.2.3 | Ethyl-*N*-(3-(4-chlorophenyl)-4-cyano-1-phenyl-1*H*-pyrazol-5-yl) formimidate (9)

Yield (78%); White crystals; mp 136°C-138°C (Dioxane); IR (ν_{max}, cm^{-1}) ν 2235 (CN); ^1H NMR (300 MHz, DMSO-d_6) δ 1.27 (t, J = 7 Hz, 3H, CH_3), 4.28 (q, J = 7 Hz, 2H, CH_2), 7.43-7.97 (m, 9H) and 8.61 (s, 1H, CH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 13.74, 64.11, 114.66, 123.80, 127.65, 128.09, 128.98, 129.12, 129.33, 134.28, 137.45, 149.41, 152.05, 160.00, 162.49; MS (EI, 70 eV) *m/z* (%): 350 (M^+, 100). Anal. Calcd. for $C_{19}H_{15}ClN_4O$ (350.09): C, 65.05; H, 4.31; Cl, 10.11; N, 15.97. Found: C, 65.12; H, 4.26; Cl, 10.04; N, 15.92.

4.3 | 3-Aryl-4-imino-1-phenyl-1,4-dihydro-5*H*-pyrazolo[3,4-*d*]pyrimidin-5-amine derivatives (11-13)

A mixture of the appropriate ethyl-*N*-(3-aryl-4-cyano-1-phenyl-1*H*-pyrazol-5-yl)formimidate **7-9** (50 mmol) and hydrazine hydrate (5.0 g, 100 mmol) was stirred for 6 hours in ethanol (200 mL) at room temperature. The solid that was separated and filtered, dried, and crystallized from the suitable solvent gave **11-13**.

4.3.1 | 4-Imino-3-(4-methoxyphenyl)-1-phenyl-1,4-dihydro-5*H*-pyrazolo[3,4-*d*] pyrimidin-5-amine (11)

Yield (82%); Yellow crystals; mp 192°C-194°C (Dioxane); IR (ν_{max}, cm^{-1}) ν 3350, 3343, 3316 (NH, NH_2); ^1H NMR (300 MHz, DMSO-d_6) δ, 3.81 (s, 3H, CH_3O), 5.67 (s, 2H, NH_2), 7.49 (s, 1H, NH), 7.03-8.06 (m, 9H) and 8.17 (s, 1H, CH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 55.11, 102.28, 113.62, 121.76, 124.57, 126.64, 128.97, 130.14, 138.25, 138.25, 147.24, 149.10, 151.32, 159.66; MS (EI, 70 eV) *m/z* (%): 332 (M^+, 17.8), 80 (100). Anal. Calcd. for $C_{18}H_{16}N_6O$ (332.14): C, 65.05; H, 4.85; N, 25.29. Found: C, 64.97; H, 4.86; N, 25.32.

4.3.2 | 4-Imino-1-phenyl-3-(*p*-tolyl)-1,4-dihydro-5*H*-pyrazolo[3,4-*d*]pyrimidin-5-amine (12)

Yield (86%); Yellow crystals; mp 194°C-196°C (Dioxane); IR (ν_{max}, cm^{-1}) ν 3347, 3335, 3310 (NH, NH_2); ^1H NMR (300 MHz, DMSO-d_6) δ 2.38 (s, 3H, CH_3), 5.67 (s, 2H, NH_2), 7.30-8.06 (m, 9H), 7.57 (s, 1H, NH) and 8.17 (s, 1H, CH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 20.85, 111.65, 117.31, 121.78, 126.69, 128.60, 128.80, 128.97, 129.32, 138.20, 147.40, 148.91, 151.28, 159.53; MS (EI, 70 eV) *m/z* (%): 316 (M^+, 100). Anal. Calcd. for $C_{18}H_{16}N_6$ (316.14): C, 68.34; H, 5.10; N, 26.56. Found: C, 68.29; H, 5.03; N, 26.58.

4.3.3 | 3-(4-Chlorophenyl)-4-imino-1-phenyl-1,4-dihydro-5*H*-pyrazolo[3,4-*d*] pyrimidin-5-amine (13)

Yield (91%); Yellow crystals; mp 188°C-190°C (DMF); IR (ν_{max}, cm^{-1}) ν 3354, 3348, 3321 (NH, NH_2);MS (EI, 70 eV) *m/z* (%): 336 (M^+, 100). Anal. Calcd. for $C_{17}H_{13}ClN_6$ (336.09): C, 60.63; H, 3.89; Cl, 10.53; N, 24.95. Found: C, 60.58; H, 3.84; Cl, 10.58; N, 24.99.

4.4 | 4-Hydrazinyl-3-aryl-1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine derivatives (15-17)

To a solution of 3-aryl-4-imino-1-phenyl-1,4-dihydro-5*H*-pyrazolo[3,4-*d*]pyrimidin-5-amine derivatives **11-13** (20.0 mmol) in ethanol (50 mL), hydrazine hydrate (5 mL) was added, and the reaction mixture was refluxed for 6 hours. The solid that precipitated was filtered and crystallized from dioxane to give corresponding 4-hydrazinyl-3-aryl-1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine **15-17**.

4.4.1 | 4-Hydrazinyl-3-(4-methoxyphenyl)-1-phenyl-1*H*-pyrazolo [3,4-*d*]pyrimidine (15)

Yield (86%); Pale yellow crystals; mp 194°C-196°C; IR (ν_{max}, cm^{-1}) ν 3429, 3316, and 3281 (NH, NH_2); ^1H NMR (300 MHz, DMSO-d_6) δ 3.85 (s, 3H, CH_3O), 4.38 (s, 2H, NH_2), 7.08-8.14 (m, 9H), 7.54 (s, 1H, NH) and 8.20 (s, 1H, CH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 50.3, 104.5, 112.4, 118.9, 124.6, 125.9, 127.8, 129.2, 135.8, 139.1, 144.5, 153.2, 161.6, 165.3; MS (EI, 70 eV) *m/z* (%): 332 (M^+, 100). Anal. Calcd. for $C_{18}H_{16}N_6O$ (332.14): C, 65.05; H, 4.85; N, 25.29. Found: C, 64.90; H, 4.80; N, 25.25.

4.4.2 | 4-Hydrazinyl-1-phenyl-3-(*p*-tolyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine (16)

Yield (83%); Yellow crystals; mp 194°C-196°C; IR (ν_{max}, cm^{-1}) ν 3428, 3331, and 3276 (NH, NH_2); ^1H NMR

(300 MHz, DMSO-d_6) δ 2.38 (s, 3H, CH_3), 4.34 (s, 2H, NH_2), 7.02-8.11 (m, 9H), 7.57 (s, 1H, NH) and 8.23 (s, 1H, CH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 21.0, 104.3, 112.5, 118.7, 124.5, 125.2, 128.6, 129.0, 135.3, 140.5, 144.8, 153.4, 161.1, 164.7; MS (EI, 70 eV) *m/z* (%): 316 (M^+, 100). Anal. Calcd. for $C_{18}H_{16}N_6$ (316.14): C, 68.34; H, 5.10; N, 26.56. Found: C, 68.22; H, 5.99; N, 26.50.

4.4.3 | 3-(4-Chlorophenyl)-4-hydrazinyl-1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine (17)

Yield (87%); Yellow crystals; mp 194°C-196°C; IR (ν_{max}, cm^{-1}) ν 3420, 3325, and 3269 (NH, NH_2); MS (EI, 70 eV) *m/z* (%): 336 (M^+, 100). Anal. Calcd. for $C_{17}H_{13}ClN_6$ (336.09): C, 60.63; H, 3.89; Cl, 10.53; N, 24.95. Found: C, 60.53; H, 3.87; Cl, 10.50; N, 24.90.

4.5 | 3-Aryl-4-(2-benzylidenehydrazinyl)-1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine derivatives (18-21)

Refluxing of mixture of the appropriate hydrazinyl compound **14**-**17** (5.0 mmol), the appropriate aldehyde (5.0 mmol) and a few drops of acetic acid in ethanol (30 mL) for 6 hours. The reaction mixture was cooled, and the precipitate that separated was collected and crystallized from the suitable solvent to give the corresponding benzylidene hydrazinyl derivatives **18**-**21**.

4.5.1 | 4-(2-((1*H*-Indol-3-yl)methylene) hydrazinyl)-1,3-diphenyl-1*H*-pyrazolo[3,4-*d*] pyrimidine (18H)

Yield (75%); Yellow crystals; mp 222°C-224°C (Dioxane); ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.21-8.12 (m, 14H), 8.47 (s, 1H, CH), 8.54 (s, 1H, CH), 8.67 (s, 1H, CH-Indol), 11.41 (s, 1H, NH) and 11.63 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 100.9, 111.7, 112.5, 120.4, 122.1, 122.2, 124.5, 126.6, 127.8, 128.1, 128.5, 129.0, 129.1, 131.5, 132.2, 137.1, 138.2, 144.4, 146.8, 148.2, 150.2, 151.5; MS (EI, 70 eV) *m/z* (%): 429 (M^+, 29.3), 286 (100) . Anal. Calcd. for $C_{26}H_{19}N_7$ (429.17): C, 72.71; H, 4.46; N, 22.83. Found: C, 72.76; H, 4.42; N, 22.80.

4.5.2 | 4-(2-Benzylidenehydrazinyl)-3-(4-methoxyphenyl)-1-phenyl-1*H*-pyrazolo [3,4-*d*]pyrimidine (19A)

Yield (83%); White crystals; mp 180°C-182°C (DMF); ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.83 (s, 3H, CH_3O), 7.04-8.11 (m, 14H), 8.45 (s, 1H, CH), 8.48 (s, 1H, CH) and 11.95 (s, 1H, NH) ; ^{13}C NMR (75 MHz, DMSO-d_6) δ 55.10, 100.52, 113.22, 120.63, 121.38, 122.11, 124.56, 126.57, 127.90, 128.95, 129.87, 130.63, 135.19, 138.21, 146.94, 147.65, 150.45, 153.69, 159.64; MS (EI, 70 eV) *m/z* (%): 420 (M^+, 49.9), 317 (100). Anal. Calcd. for $C_{25}H_{20}N_6O$ (420.17): C, 71.41; H, 4.79; N, 19.99. Found: C, 71.32; H, 4.81; N, 19.90.

4.5.3 | 3-(4-Methoxyphenyl)-4-(2-(4-methylbenzylidene)hydrazinyl)-1-phenyl-1*H*-pyrazolo[3,4-*d*]-pyrimidine (19B)

Yield (80%); Yellow crystals; mp 212°C-214°C (DMF); ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.37 (s, 3H, CH_3), 3.83 (s, 3H, CH_3O), 7.03 (d, 2H), 7.40 (d, 2H), 7.50 (d, 2H), 7.53 (d, 2H), 7.60-8.10 (m, 5H), 8.43 (s, 1H, CH), 8.47 (s, 1H, CH) and 12.03 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 20.9, 55.2, 100.6, 113.3, 121.4, 122.2, 124.6, 126.6, 126.8, 127.9, 128.7, 129.0, 129.2, 130.6, 132.5, 138.2, 146.9, 147.8, 153.8, 159.7; MS (EI, 70 eV) *m/z* (%): 434 (M^+, 50.3), 317 (100) . Anal. Calcd. for $C_{26}H_{22}N_6O$ (434.19): C, 71.87; H, 5.10; N, 19.34. Found: C, 71.70; H, 5.20; N, 19.41.

4.5.4 | 4-(2-(4-Methoxybenzylidene) hydrazinyl)-3-(4-methoxyphenyl)-1-phenyl-1*H*-pyrazolo[3,4-*d*]-pyrimidine (19C)

Yield (79%); Yellow crystals; mp 197°C-198°C (DMF); ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.81 (s, 3H, CH_3O), 3.83 (s, 3H, CH_3O), 7.00 (d, 2H), 7.23 (d, 2H), 7.40 (d, 2H), 7.50 (d, 2H), 7.61-8.11 (m, 5H), 8.42 (s, 1H, CH), 8.48 (s, 1H, CH) and 11.95 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 55.1, 55.2, 100.5, 113.2, 114.0, 120.6, 122.1, 124.6, 126.7, 127.8, 128.2, 128.9, 129.5, 130.6, 138.2, 146.8, 147.6, 150.3, 159.6; MS (EI, 70 eV) *m/z* (%): 450 (M^+, 39.1), 317 (100). Anal. Calcd. for $C_{26}H_{22}N_6O_2$ (450.18): C, 69.32; H, 4.92; N, 18.66. Found: C, 69.20; H, 5.01; N, 18.75.

4.5.5 | 4-(2-(4-Chlorobenzylidene) hydrazinyl)-3-(4-methoxyphenyl)-1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine (19D)

Yield (83%); Yellow crystals; mp 206°C-208°C (DMF); MS (EI, 70 eV) *m/z* (%): 454 (M^+, 41.3), 317 (100) . Anal. Calcd. for $C_{25}H_{19}ClN_6O$ (454.13): C, 66.01; H, 4.21; Cl, 7.79; N, 18.47. Found: C, 65.95; H, 4.27; Cl, 7.84; N, 18.51.

4.5.6 | 3-(4-Methoxyphenyl)-4-(2-(4-nitrobenzylidene)hydrazinyl)-1-phenyl-1*H*-pyrazolo[3,4-*d*] pyrimidine (19E)

Yield (79%); Yellow crystals; mp 240°C-242°C (DMF); ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.76 (s, 3H, CH_3O), 7.03-8.09 (m, 13H), 8.46 (s, 1H, CH), 8.56 (s, 1H, CH) and 11.85 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 55.2, 101.6, 113.7, 120.8, 122.3, 126.8, 127.0, 127.6, 129.7, 130.9, 133.1, 138.5, 144.5, 146.1, 146.8, 150.8, 153.7, 161.3, 161.9; MS (EI, 70 eV) *m/z* (%): 465 (M^+, 59.8), 317 (100) . Anal. Calcd. for $C_{25}H_{19}N_7O_3$ (465.15): C, 64.51; H, 4.11; N, 21.06. Found: C, 64.43; H, 4.28; N, 21.20.

4.5.7 | 3-(4-Methoxyphenyl)-1-phenyl-4-(2-(pyridin-4-ylmethylene)hydrazinyl)-1*H*-pyrazolo[3,4-*d*]-pyrimidine (19F)

Yield (75%); Yellow crystals; mp 242°C-244°C (DMF); ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.83 (s, 3H, CH_3O), 7.10-8.20 (m, 13H), 8.40 (s, 1H, CH), 8.51 (s, 1H, CH) and 11.80 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 55.5, 114.1, 120.8, 123.1, 126.0, 126.5, 127.4, 129.5, 130.8, 133.5, 138.8, 143.7, 146.8, 148.8, 153.5, 153.6, 161.9, 165.6; MS (EI, 70 eV) *m/z* (%): 421 (M^+, 53.9), 343 (100) . Anal. Calcd. for $C_{24}H_{19}N_7O$ (421.17): C, 68.40; H, 4.54; N, 23.26. Found: C, 68.31; H, 4.51; N, 23.29.

4.5.8 | 3-(4-Methoxyphenyl)-1-phenyl-4-(2-(thiophen-2-ylmethylene)hydrazinyl)-1*H*-pyrazolo[3,4-*d*]-pyrimidine (19G)

Yield (78%); Yellow crystals; mp 218°C-220°C (DMF); ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.79 (s, 3H, CH_3O), 7.03-8.17 (m, 12H), 8.42 (s, 1H, CH), 8.50 (s, 1H, CH) and 11.64 (s, 1H, NH); MS (EI, 70 eV) *m/z* (%): 426 (M^+, 47.6), 317 (100) . Anal. Calcd. for $C_{23}H_{18}N_6OS$ (426.13): C, 64.77; H, 4.25; N, 19.71; S, 7.52. Found: C, 64.60; H, 4.23; N, 19.68; S, 7.58.

4.5.9 | 4-(2-((1*H*-Indol-3-yl)methylene) hydrazinyl)-3-(4-methoxyphenyl)-1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine (19H)

Yield (73%); Yellow crystals; mp 216°C-218°C (Dioxane); IR (ν_{max}, cm^{-1}) ν 3331 (NH) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.85 (s, 3H, CH_3O), 7.05-8.11 (m, 13H), 8.49 (s, 1H, CH), 8.54 (s, 1H, CH), 8.70 (s, 1H, CH-Indol), 11.40 (s, 1H, NH) and 11.63 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 55.1, 100.7, 111.7, 112.5, 113.2, 120.4, 122.1, 122.5, 124.5, 126.7, 128.5, 128.9, 130.5, 131.4, 137.1, 138.3, 144.5, 146.7, 148.0, 150.8, 151.4, 159.8; MS (EI, 70 eV) *m/z* (%): 459 (M^+, 13.21), 317 (100) . Anal. Calcd. for $C_{27}H_{21}N_7O$ (459.18): C, 70.57; H, 4.61; N, 21.34. Found: C, 70.50; H, 4.63; N, 21.38.

4.5.10 | 4-(2-Benzylidenehydrazinyl)-1-phenyl-3-(*p*-tolyl)-1*H*-pyrazolo[3,4-*d*] pyrimidine (20A)

Yield (78%); Yellow crystals; mp 194°C-196°C (DMF); IR (ν_{max}, cm^{-1}) ν 3336 (NH) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.37 (s, 3H, CH_3), 7.28-8.11 (m, 14H), 8.37 (s, 1H, CH), 8.45 (s, 1H, CH) and 12.01 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 20.7, 100.6, 120.7, 121.4, 122.4, 126.3, 127.9, 128.5, 128.9, 129.1, 129.3, 133.6, 137.6, 138.2, 145.1, 147.7, 150.5, 153.8, 154.9; MS (EI, 70 eV) *m/z* (%): 404 (M^+, 51.8), 77 (100). Anal. Calcd. for $C_{25}H_{20}N_6$ (404.17): C, 74.24; H, 4.98; N, 20.78. Found: C, 74.13; H, 4.88; N, 20.75.

4.5.11 | 4-(2-(4-Methylbenzylidene) hydrazinyl)-1-phenyl-3-(*p*-tolyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine (20B)

Yield (76%); Yellow crystals; mp 189°C-190°C (CH_3CN); MS (EI, 70 eV) *m/z* (%): 418 (M^+, 44.5), 300 (100) . Anal. Calcd. for $C_{26}H_{22}N_6$ (418.19): C, 74.62; H, 5.30; N, 20.08. Found: C, 74.59; H, 5.24; N, 20.17.

4.5.12 | 4-(2-(4-Methoxybenzylidene) hydrazinyl)-1-phenyl-3-(*p*-tolyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine (20C)

Yield (75%); Yellow crystals; mp 188°C-190°C (CH_3CN); ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.38 (s, 3H, CH_3), 3.81 (s, 3H, CH_3O), 7.00-8.09 (m, 13H), 8.34 (s, 1H, CH), 8.38 (s, 1H, CH) and 12.00 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 20.9, 55.2, 100.7, 114.0, 120.6, 122.2, 126.9, 127.8, 128.4, 128.9, 129.1, 129.3, 129.5, 137.9, 138.2, 147.0, 147.7, 150.4, 153.5, 160.8; MS (EI, 70 eV) *m/z* (%): 434 (M^+, 38.3), 301 (100). Anal. Calcd. for $C_{26}H_{22}N_6O$ (434.19): C, 71.87; H, 5.10; N, 19.34. Found: C, 71.72; H, 5.19; N, 19.39.

4.5.13 | 4-(2-(4-Chlorobenzylidene) hydrazinyl)-1-phenyl-3-(*p*-tolyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine (20D)

Yield (77%); Yellow crystals; mp 208°C-210°C (DMF); MS (EI, 70 eV) *m/z* (%): 438 (M^+, 41.5), 300 (100). Anal.

Calcd. for $C_{25}H_{19}ClN_6$ (438.14): C, 68.41; H, 4.36; Cl, 8.08; N, 19.15. Found: C, 68.29; H, 4.40; Cl, 8.10; N, 19.19.

4.5.14 | 4-(2-(4-Nitrobenzylidene) hydrazinyl)-1-phenyl-3-(*p*-tolyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine (20E)

Yield (82%); Yellow crystals; mp 260°C-262°C (DMF); ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.30 (s, 3H, CH_3), 7.00-8.05 (m, 13H), 8.52 (s, 1H, CH), 8.60 (s, 1H, CH) and 11.95 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 21.5, 103.8, 114.0, 118.9, 120.3, 124.5, 125.6, 128.8, 129.0, 129.3, 130.1, 132.4, 138.1, 140.3, 143.2, 146.5, 151.0, 153.6, 161.2; MS (EI, 70 eV) *m/z* (%): 449 (M^+, 66.8), 300 (100). Anal. Calcd. for $C_{25}H_{19}N_7O_2$ (449.16): C, 66.81; H, 4.26; N, 21.81. Found: C, 66.72; H, 4.28; N, 21.89.

4.5.15 | 1-Phenyl-4-(2-(pyridin-4-ylmethylene)hydrazinyl)-3-(*p*-tolyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine (20F)

Yield (80%); Yellow crystals; mp 248°C-250°C (DMF); ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.35 (s, 3H, CH_3), 7.08-8.19 (m, 13H), 8.43 (s, 1H, CH), 8.56 (s, 1H, CH) and 11.82 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 22.0, 113.9, 117.8, 120.5, 120.8, 123.4, 125.1, 128.5, 129.7, 130.6, 131.6, 136.1, 141.3, 143.2, 149.8, 153.6, 164.5, 166.2; MS (EI, 70 eV) *m/z* (%): 405 (M^+, 47.8), 327 (100). Anal. Calcd. for $C_{24}H_{19}N_7$ (405.17): C, 71.09; H, 4.72; N, 24.18. Found: C, 70.90; H, 4.75; N, 24.25.

4.5.16 | 1-Phenyl-4-(2-(thiophen-2-ylmethylene)hydrazinyl)-3-(*p*-tolyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine (20G)

Yield (81%); Yellow crystals; mp 199°C-200°C (DMF); MS (EI, 70 eV) *m/z* (%): 410 (M^+, 69.8), 300 (100). Anal. Calcd. for $C_{23}H_{18}N_6S$ (410.13): C, 67.30; H, 4.42; N, 20.47; S, 7.81. Found: C, 67.21; H, 4.45; N, 20.49; S, 7.79.

4.5.17 | 4-(2-((1*H*-Indol-3-yl)methylene) hydrazinyl)-1-phenyl-3-(*p*-tolyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine (20H)

Yield (82%); Yellow crystals; mp 238°C-240°C (CH_3CN); IR (ν_{max}, cm^{-1}) ν 3340 (NH) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.39 (s, 3H, CH_3), 7.22-8.11 (m, 13H), 8.38 (s, 1H, CH), 8.52 (s, 1H, CH), 8.68 (s, 1H, CH-Indole), 11.39 (s, 1H, NH) and 11.63 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 20.9, 100.8, 111.6, 112.5, 120.4, 122.2, 123.0, 124.5, 126.8, 128.3, 129.0, 129.4, 130.7, 131.4, 137.8, 138.2, 144.4, 146.9, 148.1, 150.1, 151.5, 159.2; MS (EI, 70 eV) *m/z* (%): 443 (M^+, 13.96), 300 (100). Anal. Calcd. for $C_{27}H_{21}N_7$ (443.19): C, 73.12; H, 4.77; N, 22.11. Found: C, 73.19; H, 4.72; N, 22.14.

4.5.18 | 4-(2-Benzylidenehydrazinyl)-3-(4-chlorophenyl)-1-phenyl-1*H*-pyrazolo [3,4-*d*]pyrimidine (21A)

Yield (75%); Yellow crystals; mp 202°C-204°C (CH_3CN); MS (EI, 70 eV) *m/z* (%): 424 (M^+, 61.6), 77 (100). Anal. Calcd. for $C_{24}H_{17}ClN_6$ (424.12): C, 67.84; H, 4.03; Cl, 8.34; N, 19.78. Found: C, 67.76; H, 4.12; Cl, 8.10; N, 19.73.

4.5.19 | 3-(4-Chlorophenyl)-4-(2-(4-methylbenzylidene)hydrazinyl)-1-phenyl-1*H*-pyrazolo[3,4-*d*] pyrimidine (21B)

Yield (82%); Yellow crystals; mp 203°C-204°C (DMF); ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.35 (s, 3H, CH_3), 7.25-8.08 (m, 13H), 8.43 (s, 1H, CH), 8.50 (s, 1H, CH) and 12.00 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 21.0, 100.6, 120.7, 121.5, 122.2, 126.3, 127.0, 127.9, 129.0, 129.1, 130.8, 132.4, 133.3, 138.0, 139.8, 145.8, 147.9, 150.6, 154.1; MS (EI, 70 eV) *m/z* (%): 438 (M^+, 47.6), 77 (100). Anal. Calcd. for $C_{25}H_{19}ClN_6$ (438.14): C, 68.41; H, 4.36; Cl, 8.08; N, 19.15. Found: C, 68.23; H, 4.38; Cl, 8.10; N, 19.01.

4.5.20 | 3-(4-Chlorophenyl)-4-(2-(4-methoxybenzylidene)hydrazinyl)-1-phenyl-1*H*-pyrazolo[3,4-*d*] pyrimidine (21C)

Yield (79%); Yellow crystals; mp 184°C-185°C (CH_3CN); ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.80 (s, 3H, CH_3O), 6.98-8.07 (m, 13H), 8.51 (s, 1H, CH), 8.58 (s, 1H, CH) and 11.92 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 55.2, 100.9, 114.0, 121.4, 122.1, 126.5, 126.9, 127.8, 129.5, 130.8, 133.2, 138.1, 145.7, 146.8, 147.8, 150.5, 153.7, 160.3, 161.6; MS (EI, 70 eV) *m/z* (%): 454 (M^+, 41.5), 77 (100) . Anal. Calcd. for $C_{25}H_{19}ClN_6O$ (454.13): C, 66.01; H, 4.21; Cl, 7.79; N, 18.47. Found: C, 65.91; H, 4.25; Cl, 7.74; N, 18.49.

4.5.21 | 4-(2-(4-Chlorobenzylidene) hydrazinyl)-3-(4-chlorophenyl)-1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine (21D)

Yield (74%); Yellow crystals; mp 226°C-228°C (DMF); MS (EI, 70 eV) *m/z* (%): 458 (M^+, 36.5), 77 (100). Anal. Calcd. for $C_{24}H_{16}Cl_2N_6$ (458.08): C, 62.76; H, 3.51; Cl, 15.44; N, 18.30. Found: C, 62.68; H, 3.56; Cl, 15.42; N, 18.39.

4.5.22 | 3-(4-Chlorophenyl)-4-(2-(4-nitrobenzylidene)hydrazinyl)-1-phenyl-1*H*-pyrazolo[3,4-*d*] pyrimidine (21E)

Yield (74%); Yellow crystals; mp 270°C-272°C (DMF); MS (EI, 70 eV) *m/z* (%): 469 (M^+, 47.9), 77 (100). Anal. Calcd. for $C_{24}H_{16}ClN_7O_2$ (469.11): C, 61.35; H, 3.43; Cl, 7.54; N, 20.87. Found: C, 61.19; H, 3.46; Cl, 7.59; N, 20.90.

4.5.23 | 3-(4-Chlorophenyl)-1-phenyl-4-(2-(pyridin-4-ylmethylene)hydrazinyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine (21F)

Yield (74%); Yellow crystals; mp 298°C-300°C; MS (EI, 70 eV) *m/z* (%): 425 (M^+, 50.0), 347 (100). Anal. Calcd. for $C_{23}H_{16}ClN_7$ (425.12): C, 64.87; H, 3.79; Cl, 8.32; N, 23.02. Found: C, 64.78; H, 3.81; Cl, 8.38; N, 23.00.

4.5.24 | 3-(4-Chlorophenyl)-1-phenyl-4-(2-(thiophen-2-ylmethylene)hydrazinyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine (21G)

Yield (76%); Yellow crystals; mp 218°C-220°C (DMF); MS (EI, 70 eV) *m/z* (%): 430 (M^+, 54.7), 77 (100). Anal. Calcd. for $C_{22}H_{15}ClN_6S$ (430.08): C, 61.32; H, 3.51; Cl, 8.23; N, 19.50; S, 7.44. Found: C, 61.19; H, 3.56; Cl, 8.29; N, 19.49; S, 7.47.

4.5.25 | 4-(2-((1*H*-Indol-3-yl)methylene) hydrazinyl)-3-(4-chlorophenyl)-1-phenyl-1*H*-pyrazolo[3,4-*d*]-pyrimidine (21H)

Yield (79%); Yellow crystals; mp 222°C-224°C (DMF); IR (ν_{max}, cm^{-1}) ν 3329 (NH) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 7.21-8.10 (m, 13H), 8.52 (s, 1H, CH), 8.56 (s, 1H, CH), 8.71 (s, 1H, CH-Indol), 11.42 (s, 1H, NH) and 11.64 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 101.0, 111.7, 112.5, 120.4, 122.3, 124.5, 127.0, 127.8, 129.0, 130.8, 131.1, 131.5, 133.2, 137.1, 138.1, 144.2, 144.2, 145.6, 148.3, 150.3, 151.8, 158.8; MS (EI, 70 eV) *m/z* (%): 463 (M^+, 17.8), 320 (100). Anal. Calcd. for $C_{26}H_{18}ClN_7$ (463.13): C, 67.31; H, 3.91; Cl, 7.64; N, 21.13. Found: C, 67.40; H, 3.87; Cl, 7.62; N, 21.10.

4.6 | 7-Phenyl-7*H*-pyrazolo[4,3-*e*][1,2,4] triazolo[4,3-*c*]pyrimidine derivatives (22-24)

To a solution of the appropriate hydrazone **19**-**21** (1.0 mmol) in ethanol (25 mL), a solution of ferric chloride (2 M, 2.0 mL) was added, and the mixture was stirred at room temperature for 12 hours. The reaction mixture was poured on cold water (50 mL); the solid was collected, washed with water, and finally crystallized from the suitable solvent to give **22**-**24**.

4.6.1 | 9-(4-Methoxyphenyl)-7-phenyl-3-(*p*-tolyl)-7*H*-pyrazolo[4,3-*e*][1,2,4]triazolo [4,3-*c*]pyrimidine (22B)

Yield (80%); Yellow crystals; mp 210°C-212°C (DMF); ^1H NMR (300 MHz, DMSO-d_6) δ 2.30 (s, 3H, CH_3), 3.85 (s, 3H, CH_3O), 7.13-8.77 (m, 13H) and 9.25 (s, 1H, CH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 20.99, 55.20, 98.23, 114.10, 122.32, 122.70, 123.54, 127.48, 128.65, 128.81, 129.23, 129.78, 137.96, 138.54, 140.48, 144.76, 145.24, 145.56, 147.08, 160.06; MS (EI, 70 eV) *m/z* (%): 432 (M^+, 100). Anal. Calcd. for $C_{26}H_{20}N_6O$ (432.17): C, 72.21; H, 4.66; N, 19.43. Found: C, 72.06; H, 4.64; N, 19.48.

4.6.2 | 9-(4-Methoxyphenyl)-7-phenyl-3-(pyridin-4-yl)-7*H*-pyrazolo[4,3-*e*][1,2,4] triazolo[4,3-*c*]pyrimidine (22F)

Yield (75%); Yellow crystals; mp 252°C-254°C (DMF); ^1H NMR (300 MHz, DMSO-d_6) δ 3.82 (s, 3H, CH_3O), 7.02-8.81 (m, 13H) and 9.31(s, 1H, CH); MS (EI, 70 eV) *m/z* (%): 419 (M^+, 100). Anal. Calcd. for $C_{24}H_{17}N_7O$ (419.15): C, 68.72; H, 4.09; N, 23.38. Found: C, 68.62; H, 4.14; N, 23.40.

4.6.3 | 7-Phenyl-3,9-di-*p*-tolyl-7*H*-pyrazolo[4,3-*e*][1,2,4]triazolo[4,3-*c*] pyrimidine (23B)

Yield (82%); Yellow crystals; mp 208°C-210°C (CH_3CN); ^1H NMR (300 MHz, DMSO-d_6) δ 2.29 (s, 3H, CH_3), 2.37 (s, 3H, CH_3), 7.25-8.71 (m, 13H) and 9.26 (s, 1H, CH); MS (EI, 70 eV) *m/z* (%): 416 (M^+, 100). Anal. Calcd. for $C_{26}H_{20}N_6$ (416.17): C, 74.98; H, 4.84; N, 20.18. Found: C, 74.82; H, 4.86; N, 20.16.

4.6.4 | 3-(4-Chlorophenyl)-7-phenyl-9-(*p*-tolyl)-7*H*-pyrazolo[4,3-*e*][1,2,4]triazolo[4,3-*c*]pyrimidine (23D)

Yield (79%); Yellow crystals; mp 218°C-220°C (CH_3CN); ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.50 (s, 3H, CH_3), 7.04-8.77 (m, 13H) and 9.31 (s, 1H, CH); Anal. Calcd. for $C_{25}H_{17}ClN_6$ (436.12): C, 68.73; H, 3.92; Cl, 8.11; N, 19.24. Found: C, 68.61; H, 3.89; Cl, 8.15; N, 19.27.

4.6.5 | 7-Phenyl-3-(pyridin-4-yl)-9-(*p*-tolyl)-7*H*-pyrazolo[4,3-*e*][1,2,4]triazolo[4,3-*c*]pyrimidine (23F)

Yield (78%); Yellow crystals; mp 280°C-282°C (DMF); ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.30 (s, 3H, CH_3), 7.24-8.39 (m, 13H) and 9.29(s, 1H, CH); MS (EI, 70 eV) *m/z* (%): 403 (M^+, 48.3), 64 (100). Anal. Calcd. for $C_{24}H_{17}N_7$ (403.15): C, 71.45; H, 4.25; N, 24.30. Found: C, 71.30; H, 4.26; N, 24.33.

4.6.6 | 9-(4-Chlorophenyl)-7-phenyl-3-(*p*-tolyl)-7*H*-pyrazolo[4,3-*e*][1,2,4]triazolo[4,3-*c*]pyrimidine (24B)

Yield (78%); Yellow crystals; mp 232°C-234°C (DMF); ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.31 (s, 3H, CH_3), 7.45-8.85 (m, 13H) and 9.29 (s, 1H, CH); MS (EI, 70 eV) *m/z* (%): 438 (M^+, 100). Anal. Calcd. for $C_{25}H_{17}ClN_6$ (436.12): C, 68.73; H, 3.92; Cl, 8.11; N, 19.24. Found: C, 68.60; H, 3.91; Cl, 8.16; N, 19.27.

4.6.7 | 3,9-Bis(4-chlorophenyl)-7-phenyl-7*H*-pyrazolo[4,3-*e*][1,2,4]triazolo[4,3-*c*]pyrimidine (24D)

Yield (82%); Yellow crystals; mp 220°C-222°C (DMF); ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.34-8.51 (m, 13H) and 9.28 (s, 1H, CH); MS (EI, 70 eV) *m/z* (%): 456 (M^+, 52.5), 321 (100). Anal. Calcd. for $C_{24}H_{14}Cl_2N_6$ (456.07): C, 63.03; H, 3.09; Cl, 15.50; N, 18.38. Found: C, 62.92; H, 3.12; Cl, 15.54; N, 18.40.

4.6.8 | 9-(4-Chlorophenyl)-7-phenyl-3-(pyridin-4-yl)-7*H*-pyrazolo[4,3-*e*][1,2,4]triazolo[4,3-*c*]pyrimidine (24F)

Yield (77%); Yellow crystals; mp 246°C-248°C (DMF); ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.34-8.85 (m, 13H) and 9.28 (s, 1H, CH); MS (EI, 70 eV) *m/z* (%): 423 (M^+, 51.4), 64 (100). Anal. Calcd. for $C_{23}H_{14}ClN_7$ (423.10): C, 65.17; H, 3.33; Cl, 8.36; N, 23.13. Found: C, 65.02; H, 3.32; Cl, 8.39; N, 23.16.

4.7 | 7*H*-Pyrazolo[4,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidine derivatives (25-27)

Method A: To a solution of the appropriate **22**-**24** (2.0 mmol) in ethanol (30 mL), sodium acetate (0.16 g, 2.0 mmol) was added, and the mixture was refluxed for 8 hours and then cooled. The precipitated solid was filtered, washed with water, and finally crystallized from DMF to give the respective product **25**-**27**.

Method B: Refluxing of equal moles of compound **11**-**13** (5.0 mmol) and acid chloride (5.0 mmol) in pyridine (10 mL) for 4 hours, then cooled and poured into cooled HCl (10%) with stirring. The solid that precipitated was collected, washed with cold water, and finally crystallized from DMF to give **25**-**27**.

4.7.1 | 9-(4-Methoxyphenyl)-2,7-diphenyl-7*H*-pyrazolo[4,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidine (25A)

Yield (81%); Yellow crystals; mp 220°C-222°C; MS (EI, 70 eV) *m/z* (%): 418 (M^+, 100) . Anal. Calcd. for $C_{25}H_{18}N_6O$ (418.15): C, 71.76; H, 4.34; N, 20.08. Found: C, 71.68; H, 4.28; N, 20.04.

4.7.2 | 9-(4-Methoxyphenyl)-7-phenyl-2-(*p*-tolyl)-7*H*-pyrazolo[4,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidine (25B)

Yield (80%); Yellow crystals; mp 260°C-262°C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.50 (s, 3H, CH_3), 3.89 (s, 3H, CH_3O), 7.20-8.80 (m, 13H) and 9.72 (s, 1H, CH); MS (EI, 70 eV) *m/z* (%): 432 (M^+, 100). Anal. Calcd. for $C_{26}H_{20}N_6O$ (432.17): C, 72.21; H, 4.66; N, 19.43. Found: C, 72.09; H, 4.60; N, 19.39.

4.7.3 | 2,9-Bis(4-methoxyphenyl)-7-phenyl-7*H*-pyrazolo[4,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidine (25C)

Yield (79%); Yellow crystals; mp 250°C-252°C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.87 (s, 3H, CH_3O), 3.89 (s, 3H, CH_3O), 7.14-8.80 (m, 13H) and 9.69 (s, 1H, CH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 55.1, 55.5, 103.8, 116.0, 119.8, 123.6, 126.3, 128.9, 129.6, 129.9, 130.5, 131.2, 131.7, 135.3, 140.4, 141.3, 145.8, 149.9, 150.9, 157.8; MS (EI,

70 eV) *m/z* (%): 448 (M^+, 100). Anal. Calcd. for $C_{26}H_{20}N_6O_2$ (448.16): C, 69.63; H, 4.50; N, 18.74. Found: C, 69.54; H, 4.55; N, 18.79.

4.7.4 | 2-(4-Chlorophenyl)-9-(4-methoxyphenyl)-7-phenyl-7*H*-pyrazolo[4,3-*e*][1,2,4]triazolo[1,5-*c*]-pyrimidine (25D)

Yield (80%); Yellow crystals; mp 262°C-264°C; MS (EI, 70 eV) *m/z* (%): 452 (M^+, 100). Anal. Calcd. for $C_{25}H_{17}ClN_6O$ (452.12): C, 66.30; H, 3.78; Cl, 7.83; N, 18.56. Found: C, 66.19; H, 3.71; Cl, 7.79; N, 18.50.

4.7.5 | 2,7-Diphenyl-9-(*p*-tolyl)-7*H*-pyrazolo[4,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidine (26A)

Yield (85%); Yellow crystals; mp 190°C-192°C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.50 (s, 3H, CH_3), 7.00-8.91 (m, 14H) and 9.35 (s, 1H, CH); MS (EI, 70 eV) *m/z* (%): 402 (M^+, 100) . Anal. Calcd. for $C_{25}H_{18}N_6$ (402.16): C, 74.61; H, 4.51; N, 20.88. Found: C, 74.52; H, 4.48; N, 20.85.

4.7.6 | 7-Phenyl-2,9-di-*p*-tolyl-7*H*-pyrazolo[4,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidine (26B)

Yield (83%); Yellow crystals; mp 264°C-266°C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.30 (s, 3H, CH_3), 2.33 (s, 3H, CH_3), 7.28-8.54 (m, 13H) and 9.43 (s, 1H, CH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 20.6, 21.5, 104.5, 115.3, 120.8, 124.5, 126.1, 128.5, 129.3, 129.7, 130.1, 130.8, 131.5, 134.6, 140.8, 141.7, 145.0, 149.9, 150.2, 158.3; MS (EI, 70 eV) *m/z* (%): 416 (M^+, 100). Anal. Calcd. for $C_{26}H_{20}N_6$ (416.17): C, 74.98; H, 4.84; N, 20.18. Found: C, 74.92; H, 4.78; N, 20.10.

4.7.7 | 2-(4-Methoxyphenyl)-7-phenyl-9-(*p*-tolyl)-7*H*-pyrazolo[4,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidine (26C)

Yield (82%); Yellow crystals; mp 255°C-257°C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.32 (s, 3H, CH_3), 3.82 (s, 3H, CH_3O), 7.09-8.64 (m, 13H) and 9.64 (s, 1H, CH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 22.6, 55.4, 103.1, 116.5, 119.4, 123.3, 126.8, 128.4, 129.9, 130.5, 130.9, 131.5, 131.9, 135.1, 140.0, 141.3, 145.6, 149.4, 150.2, 158.4; MS (EI, 70 eV) *m/z* (%): 432 (M^+, 100). Anal. Calcd. for $C_{26}H_{20}N_6O$ (432.17): C, 72.21; H, 4.66; N, 19.43. Found: C, 72.12; H, 4.60; N, 19.47.

4.7.8 | 2-(4-Chlorophenyl)-7-phenyl-9-(*p*-tolyl)-7*H*-pyrazolo[4,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidine (26D)

Yield (85%); Yellow crystals; mp 280°C-282°C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.42 (s, 3H, CH_3), 7.40-8.66 (m, 13H) and 9.70 (s, 1H, CH); MS (EI, 70 eV) *m/z* (%): 436 (M^+, 100). Anal. Calcd. for $C_{25}H_{17}ClN_6$ (436.12): C, 68.73; H, 3.92; Cl, 8.11; N, 19.24. Found: C, 68.63; H, 3.88; Cl, 8.08; N, 19.19.

4.7.9 | 9-(4-Chlorophenyl)-2,7-diphenyl-7*H*-pyrazolo[4,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidine (27A)

Yield (79%); Yellow crystals; mp 272°C-274°C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.37-8.81 (m, 14H) and 9.31 (s, 1H, CH); MS (EI, 70 eV) *m/z* (%): 422 (M^+, 100). Anal. Calcd. for $C_{24}H_{15}ClN_6$ (422.10): C, 68.17; H, 3.58; Cl, 8.38; N, 19.87. Found: C, 68.09; H, 3.60; Cl, 8.30; N, 19.85.

4.7.10 | 9-(4-Chlorophenyl)-7-phenyl-2-(*p*-tolyl)-7*H*-pyrazolo[4,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidine (27B)

Yield (85%); Yellow crystals; mp 268°C-270°C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.37 (s, 3H, CH_3), 7.43-8.87 (m, 13H) and 9.30 (s, 1H, CH); MS (EI, 70 eV) *m/z* (%): 436 (M^+, 100). Anal. Calcd. for $C_{25}H_{17}ClN_6$ (436.12): C, 68.73; H, 3.92; Cl, 8.11; N, 19.24. Found: C, 68.60; H, 3.95; Cl, 8.05; N, 19.30.

4.7.11 | 9-(4-Chlorophenyl)-2-(4-methoxyphenyl)-7-phenyl-7*H*-pyrazolo[4,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidine (27C)

Yield (84%); Yellow crystals; mp 260°C-262°C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.80 (s, 3H, CH_3O), 7.15-8.58 (m, 13H) and 9.60 (s, 1H, CH); MS (EI, 70 eV) *m/z* (%): 452 (M^+, 100). Anal. Calcd. for $C_{25}H_{17}ClN_6O$ (452.12): C, 66.30; H, 3.78; Cl, 7.83; N, 18.56. Found: C, 66.21; H, 3.81; Cl, 7.78; N, 18.52.

4.7.12 | 2,9-Bis(4-chlorophenyl)-7-phenyl-7*H*-pyrazolo[4,3-*e*][1,2,4]triazolo[1,5-*c*] pyrimidine (27D)

Yield (77%); Yellow crystals; mp 288°C-290°C; MS (EI, 70 eV) *m/z* (%): 456 (M^+, 26.7), 64 (100). Anal. Calcd. for $C_{24}H_{14}Cl_2N_6$ (456.07): C, 63.03; H, 3.09; Cl, 15.50; N, 18.38. Found: C, 62.95; H, 3.00; Cl, 15.47; N, 18.30.

4.8 | 1-Phenyl-4-(2-(1-(aryl)ethylidene) hydrazinyl)-1H-pyrazolo[3,4-*d*]pyrimidine derivatives (28-31)

A mixture of hydrazine **14**-**17** (5.0 mmol) and the appropriate ketone (5.0 mmol) were refluxed in absolute ethanol (30 mL) for 6 hours in the presence of few drops of acetic acid. The reaction mixture was cooled; the precipitate that separated was collected and crystallized from the suitable solvent to give the corresponding hydrazone derivatives **28**-**31**.

4.8.1 | 1,3-Diphenyl-4-(2-(1-(pyridin-2-yl) ethylidene)hydrazinyl)-1*H*-pyrazolo[3,4-*d*] pyrimidine (28A)

Yield (81%); Yellow crystals; mp 179°C-180°C (EtOH); IR (ν_{max}, cm^{-1}) ν 3354 (NH) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 2.49 (s, 3H, CH_3), 7.34-8.10 (m, 14H), 8.60 (s, 1H, CH), and 11.96 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 18.6, 101.5, 121.2, 122.2, 123.8, 126.9, 127.7, 128.6, 129.0, 129.3, 132.0, 135.9, 138.2, 147.1, 147.2, 147.8, 148.5, 150.6, 155.9, 159.8; MS (EI, 70 eV) *m/z* (%): 405 (M^+, 11.97), 327 (100). Anal. Calcd. for $C_{24}H_{19}N_7$ (405.17): C, 71.09; H, 4.72; N, 24.18. Found: C, 71.13; H, 4.69; N, 24.15.

4.8.2 | 1,3-Diphenyl-4-(2-(1-(pyridin-3-yl) ethylidene)hydrazinyl)-1*H*-pyrazolo[3,4-*d*] pyrimidine (28B)

Yield (82%); Yellow crystals; mp 234°C-236°C (DMF); IR (ν_{max}, cm^{-1}) ν 3351 (NH) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 2.47 (s, 3H, CH_3), 7.30-8.42 (m, 14H), 8.62 (s, 1H, CH), and 11.86 (s, 1H, NH); MS (EI, 70 eV) *m/z* (%): 405 (M^+, 21.84), 77 (100). Anal. Calcd. for $C_{24}H_{19}N_7$ (405.17): C, 71.09; H, 4.72; N, 24.18. Found: C, 70.96; H, 4.61; N, 24.20.

4.8.3 | 1,3-Diphenyl-4-(2-(1-(pyridin-4-yl) ethylidene)hydrazinyl)-1*H*-pyrazolo[3,4-*d*] pyrimidine (28C)

Yield (81%); Yellow crystals; mp 266°C-268°C (DMF); IR (ν_{max}, cm^{-1}) ν 3359 (NH) cm^{-1}; MS (EI, 70 eV) *m/z* (%): 405 (M^+, 57.0), 390 (100). Anal. Calcd. for $C_{24}H_{19}N_7$ (405.17): C, 71.09; H, 4.72; N, 24.18. Found: C, 70.94; H, 4.76; N, 24.11.

4.8.4 | 1,3-Diphenyl-4-(2-(1-(thiophen-2-yl)ethylidene)hydrazinyl)-1*H*-pyrazolo [3,4-*d*]pyrimidine (28D)

Yield (82%); Yellow crystals; mp 167°C-168°C (Ethanol); IR (ν_{max}, cm^{-1}) ν 3362 (NH) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 2.49 (s, 3H, CH_3), 7.12-8.23 (m, 13H), 8.43 (s, 1H, CH), and 11.40 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 15.4, 101.4, 120.6, 121.1, 122.1, 126.3, 127.0, 127.6, 128.3, 129.0, 129.4, 132.5, 138.6, 144.9, 145.5, 147.0, 148.0, 150.4, 154.7; MS (EI, 70 eV) *m/z* (%): 410 (M^+, 59.48), 395 (100). Anal. Calcd. for $C_{23}H_{18}N_6S$ (410.13): C, 67.30; H, 4.42; N, 20.47; S, 7.81. Found: C, 67.25; H, 4.46; N, 20.41; S, 7.86.

4.8.5 | 1,3-Diphenyl-4-(2-(1-phenylethylidene)hydrazinyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine (28E)

Yield (79%); Yellow crystals; mp 161°C-162°C (Ethanol); IR (ν_{max}, cm^{-1}) ν 3354 (NH) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 2.50 (s, 3H, CH_3), 7.41-8.12 (m, 15H), 8.47 (s, 1H, CH), and 11.82 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 18.5, 101.4, 120.5, 122.1, 1267, 126.9, 127.6, 128.0, 128.5, 128.9, 129.1, 132.1, 138.2, 138.4, 146.3, 147.1, 147.8, 150.5, 158.5; MS (EI, 70 eV) *m/z* (%): 404 (M^+, 8.05), 59 (100). Anal. Calcd. for $C_{25}H_{20}N_6$ (404.17): C, 74.24; H, 4.98; N, 20.78. Found: C, 74.30; H, 4.95; N, 20.73.

4.8.6 | 4-(2-(1-(9*H*-Fluoren-1-yl) ethylidene)hydrazinyl)-1,3-diphenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine (28F)

Yield (83%); Yellow crystals; mp 228°C-230°C (Dioxane); IR (ν_{max}, cm^{-1}) ν 3364 (NH) cm^{-1}; MS (EI, 70 eV) *m/z* (%): 492 (M^+, 100). Anal. Calcd. for $C_{32}H_{24}N_6$ (492.21): C, 78.03; H, 4.91; N, 17.06. Found: C, 78.11; H, 4.88; N, 17.00.

4.8.7 | 4-(2-(1-(Naphthalen-1-yl) ethylidene)hydrazinyl)-1,3-diphenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine (28G)

Yield (85%); Yellow crystals; mp 216°C-218°C (DMF); IR (ν_{max}, cm^{-1}) ν 3360 (NH) cm^{-1}; MS (EI, 70 eV) *m/z* (%): 454 (M^+, 33.68), 439 (100). Anal. Calcd. for $C_{29}H_{22}N_6$ (454.19): C, 76.63; H, 4.88; N, 18.49. Found: C, 76.69; H, 4.85; N, 18.44.

4.8.8 | 3-(4-Methoxyphenyl)-1-phenyl-4-(2-(1-(pyridin-2-yl)ethyl-idene) hydrazinyl)-1*H*-pyrazolo[3,4-*d*] pyrimidine (29A)

Yield (80%); Yellow crystals; mp 175°C-176°C (CH_3CN); IR (ν_{max}, cm^{-1}) ν 3357 (NH) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.51 (s, 3H, CH_3), 3.81 (s, 3H, CH_3O), 6.99-8.10 (m, 13H), 8.60 (s, 1H, CH), and 11.92 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 13.5, 55.1, 101.1, 113.1, 120.6, 121.1, 122.0, 123.7, 124.5, 126.8, 128.9, 130.6, 135.9, 138.2, 147.0, 147.1, 147.6, 148.5, 150.5, 155.9, 159.6; MS (EI, 70 eV) *m/z* (%): 435 (M^+,17.27), 357 (100). Anal. Calcd. for $C_{25}H_{21}N_7O$ (435.18): C, 68.95; H, 4.86; N, 22.51. Found: C, 68.90; H, 4.89; N, 22.49.

4.8.9 | 3-(4-Methoxyphenyl)-1-phenyl-4-(2-(1-(pyridin-3-yl)ethyl-idene) hydrazinyl)-1*H*-pyrazolo[3,4-*d*] pyrimidine (29B)

Yield (84%); Yellow crystals; mp 218°C-220°C (DMF); IR (ν_{max}, cm^{-1}) ν 3351 (NH) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.50 (s, 3H, CH_3), 3.76 (s, 3H, CH_3O), 7.20-8.29 (m, 13H), 8.54 (s, 1H, CH), and 11.90 (s, 1H, NH); MS (EI, 70 eV) *m/z* (%): 435 (M^+, 30.13), 420 (100). Anal. Calcd. for $C_{25}H_{21}N_7O$ (435.18): C, 68.95; H, 4.86; N, 22.51. Found: C, 68.81; H, 4.80; N, 22.55.

4.8.10 | 3-(4-Methoxyphenyl)-1-phenyl-4-(2-(1-(pyridin-4-yl)ethy-lidene) hydrazinyl)-1*H*-pyrazolo[3,4-*d*] pyrimidine (29C)

Yield (78%); Yellow crystals; mp 248°C-250°C (DMF); IR (ν_{max}, cm^{-1}) ν 3362 (NH) cm^{-1}; MS (EI, 70 eV) *m/z* (%): 435 (M^+, 61.1), 420 (100). Anal. Calcd. for $C_{25}H_{21}N_7O$ (435.18): C, 68.95; H, 4.86; N, 22.51. Found: C, 68.85; H, 4.84; N, 22.47.

4.8.11 | 3-(4-Methoxyphenyl)-1-phenyl-4-(2-(1-(thiophen-2-yl)ethyli-dene) hydrazinyl)-1*H*-pyrazolo[3,4-*d*] pyrimidine (29D)

Yield (83%); Yellow crystals; mp 191°C-192°C (Dioxane); IR (ν_{max}, cm^{-1}) ν 3358 (NH) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.50 (s, 3H, CH_3), 3.82 (s, 3H, CH_3O), 7.00-8.10 (m, 12H), 8.41 (s, 1H, CH), and 11.50 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 15.6, 55.2, 101.1, 113.2, 120.8, 122.1, 124.6, 125.6, 126.9, 127.6, 128.4, 130.6, 138.2,144.1, 145.8, 146.9, 147.9,150.3, 154.7, 159.7; MS (EI, 70 eV) *m/z* (%): 440 (M^+, 47.11), 77 (100). Anal. Calcd. for $C_{24}H_{20}N_6OS$ (440.14): C, 65.44; H, 4.58; N, 19.08; S, 7.28. Found: C, 65.39; H, 4.56; N, 19.04; S, 7.24.

4.8.12 | 3-(4-Methoxyphenyl)-1-phenyl-4-(2-(1-phenylethylidene)-hydrazinyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine (29E)

Yield (84%); Yellow crystals; mp 179°C-180°C (Dioxane); IR (ν_{max}, cm^{-1}) ν 3340 (NH) cm^{-1}; MS (EI, 70 eV) *m/z* (%): 434 (M^+, 29.61), 419 (100). Anal. Calcd. for $C_{26}H_{22}N_6O$ (434.19): C, 71.87; H, 5.10; N, 19.34. Found: C, 71.91; H, 5.13; N, 19.30.

4.8.13 | 4-(2-(1-(9*H*-Fluoren-1-yl) ethylidene)hydrazinyl)-3-(4-methoxyphenyl)-1-phenyl-1*H*-pyrazolo-[3,4-*d*]pyrimidine (29F)

Yield (74%); Yellow crystals; mp 191°C-192°C (Dioxane); IR (ν_{max}, cm^{-1}) ν 3358 (NH) cm^{-1}; MS (EI, 70 eV) *m/z* (%): 522 (M^+, 24.91), 165 (100). Anal. Calcd. for $C_{33}H_{26}N_6O$ (522.22): C, 75.84; H, 5.01; N, 16.08. Found: C, 75.90; H, 4.98; N, 16.02.

4.8.14 | 1-Phenyl-4-(2-(1-(pyridin-2-yl) ethylidene)hydrazinyl)-3-(*p*-tolyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine (30A)

Yield (85%); Yellow crystals; mp 193°C-194°C (EtOH); IR (ν_{max}, cm^{-1}) ν 3353 (NH) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.36 (s, 3H, CH_3), 2.52 (s, 3H, CH_3), 7.25-8.30 (m, 13H), 8.58 (s, 1H, CH), and 11.96 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 18.5, 20.9, 101.3, 120.4, 121.1, 122.1, 123.7, 126.9, 128.3, 129.0, 129.1, 129.2, 135.8, 137.9, 147.1, 147.7, 148.7, 150.6, 155.7, 159.6, 169.7; MS (EI, 70 eV) *m/z* (%): 419 (M^+,11.89), 341 (100). Anal.

Calcd. for $C_{25}H_{21}N_7$ (419.19): C, 71.58; H, 5.05; N, 23.37. Found: C, 71.62; H, 5.00; N, 23.39.

4.8.15 | 1-Phenyl-4-(2-(1-(pyridin-3-yl) ethylidene)hydrazinyl)-3-(*p*-tolyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine (30B)

Yield (79%); Yellow crystals; mp 252°C-254°C (DMF); IR (ν_{max}, cm^{-1}) ν 3349 (NH) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 2.38 (s, 3H, CH_3), 2.48 (s, 3H, CH_3), 7.27-8.37 (m, 13H), 8.59 (s, 1H, CH), and 11.97 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 14.4, 20.9, 101.3, 120.8, 122.2, 123.2, 127.0, 128.4, 129.1, 129.3, 133.8, 133.9, 138.1,138.2, 147.1,147.2, 147.9, 148.1, 149.8, 150.6, 156.6; MS (EI, 70 eV) *m/z* (%): 419 (M^+, 22.3), 404 (100). Anal. Calcd. for $C_{25}H_{21}N_7$ (419.19): C, 71.58; H, 5.05; N, 23.37. Found: C, 71.41; H, 5.12; N, 23.30.

4.8.16 | 1-Phenyl-4-(2-(1-(pyridin-4-yl) ethylidene)hydrazinyl)-3-(*p*-tolyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine (30C)

Yield (77%); Yellow crystals; mp 236°C-238°C (DMF); IR (ν_{max}, cm^{-1}) ν 3358 (NH) cm^{-1}; MS (EI, 70 eV) *m/z* (%): 419 (M^+, 52.7), 404 (100). Anal. Calcd. for $C_{25}H_{21}N_7$ (419.19): C, 71.58; H, 5.05; N, 23.37. Found: C, 71.45; H, 5.15; N, 23.42.

4.8.17 | 1-Phenyl-4-(2-(1-(thiophen-2-yl) ethylidene)hydrazinyl)-3-(*p*-tolyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine (30D)

Yield (84%); Yellow crystals; mp 193°C-194°C (Dioxane); IR (ν_{max}, cm^{-1}) ν 3335 (NH) cm^{-1}; MS (EI, 70 eV) *m/z* (%): 424 (M^+, 47.87), 409 (100). Anal. Calcd. for $C_{24}H_{20}N_6S$ (424.15): C, 67.90; H, 4.75; N, 19.80; S, 7.55. Found: C, 67.94; H, 4.72; N, 19.83; S, 7.50.

4.8.18 | 1-Phenyl-4-(2-(1-phenylethylidene)hydrazinyl)-3-(*p*-tolyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine (30E)

Yield (83%); Yellow crystals; mp 189°C-190°C (Dioxane); IR (ν_{max}, cm^{-1}) ν 3320 (NH) cm^{-1}; MS (EI, 70 eV) *m/z* (%): 418 (M^+, 27.70), 403 (100). Anal. Calcd. for $C_{26}H_{22}N_6$ (418.19): C, 74.62; H, 5.30; N, 20.08. Found: C, 74.69; H, 5.32; N, 20.02.

4.8.19 | 4-(2-(1-(9*H*-Fluoren-1-yl) ethylidene)hydrazinyl)-1-phenyl-3-(*p*-tolyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine (30F)

Yield (75%); Yellow crystals; mp 242°C-244°C (DMF); IR (ν_{max}, cm^{-1}) ν 3329 (NH) cm^{-1}; MS (EI, 70 eV) *m/z* (%): 506 (M^+, 29.80), 165 (100). Anal. Calcd. for $C_{33}H_{26}N_6$ (506.22): C, 78.24; H, 5.17; N, 16.59. Found: C, 78.30; H, 5.15; N, 16.57.

4.8.20 | 3-(4-Chlorophenyl)-1-phenyl-4-(2-(1-(pyridin-2-yl)ethylidene)-hydrazinyl)-1*H*-pyrazolo[3,4-*d*] pyrimidine (31A)

Yield (83%); Yellow crystals; mp 216°C-218°C (Dioxane); IR (ν_{max}, cm^{-1}) ν 3338 (NH) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 2.45 (s, 3H, CH_3), 7.32-8.05 (m, 13H), 8.52 (s, 1H, CH), and 11.86 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 13.5, 101.4, 120.7, 121.1, 122.0, 123.6, 126.9, 127.6, 128.8, 130.7, 130.8, 133.2, 135.7, 138.0, 145.8, 147.6, 148.4, 150.6, 155.7, 159.7; MS (EI, 70 eV) *m/z* (%): 439 (M^+,12.59), 361 (100). Anal. Calcd. for $C_{24}H_{18}ClN_7$ (439.13): C, 65.53; H, 4.12; Cl, 8.06; N, 22.29. Found: C, 65.60; H, 4.15; Cl, 8.02; N, 22.25.

4.8.21 | 3-(4-Chlorophenyl)-1-phenyl-4-(2-(1-(pyridin-3-yl)ethylidene)-hydrazinyl)-1*H*-pyrazolo[3,4-*d*] pyrimidine (31B)

Yield (80%); Yellow crystals; mp 262°C-264°C (DMF); IR (ν_{max}, cm^{-1}) ν 3342 (NH) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 2.49 (s, 3H, CH_3), 7.40-8.49 (m, 13H), 8.60 (s, 1H, CH), and 11.95 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 14.5, 101.4, 122.2, 123.2, 127.1, 127.8, 129.1, 130.9, 131.0,133.4, 133.8, 133.9, 138.1, 145.9, 146.9, 147.9, 148.1, 149.7, 150.7, 156.7; MS (EI, 70 eV) *m/z* (%): 439 (M^+, 21.31), 77 (100). Anal. Calcd. for $C_{24}H_{18}ClN_7$ (439.13): C, 65.53; H, 4.12; Cl, 8.06; N, 22.29. Found: C, 65.40; H, 4.20; Cl, 8.04; N, 22.31.

4.8.22 | 3-(4-Chlorophenyl)-1-phenyl-4-(2-(1-(pyridin-4-yl)ethylid-ene) hydrazinyl)-1*H*-pyrazolo[3,4-*d*] pyrimidine (31C)

Yield (75%); Yellow crystals; mp 256°C-258°C (DMF); IR (ν_{max}, cm^{-1}) ν 3339 (NH) cm^{-1}; MS (EI, 70 eV) *m/z* (%):

439 (M^+, 53.1), 424 (100). Anal. Calcd. for $C_{24}H_{18}ClN_7$ (439.13): C, 65.53; H, 4.12; Cl, 8.06; N, 22.29. Found: C, 65.48; H, 4.10; Cl, 8.00; N, 22.22.

4.8.23 | 3-(4-Chlorophenyl)-1-phenyl-4-(2-(1-(thiophen-2-yl)ethy-lidene) hydrazinyl)-1*H*-pyrazolo[3,4-*d*] pyrimidine (31D)

Yield (80%); Yellow crystals; mp 200°C-202°C (Dioxane); IR (ν_{max}, cm^{-1}) ν 3350 (NH) cm^{-1}; MS (EI, 70 eV) *m/z* (%): 444 (M^+,1.0), 77 (100). Anal. Calcd. for $C_{23}H_{17}ClN_6S$ (444.09): C, 62.09; H, 3.85; Cl, 7.97; N, 18.89; S, 7.21. Found: C, 62.15; H, 3.80; Cl, 7.93; N, 18.87; S, 7.18.

4.8.24 | 3-(4-Chlorophenyl)-1-phenyl-4-(2-(1-phenylethylidene)-hydrazinyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine (31E)

Yield (78%); Yellow crystals; mp 200°C-202°C (Dioxane); IR (ν_{max}, cm^{-1}) ν 3341 (NH) cm^{-1}; MS (EI, 70 eV) *m/z* (%): 438 (M^+, 37.31), 423 (100). Anal. Calcd. for $C_{25}H_{19}ClN_6$ (438.14): C, 68.41; H, 4.36; Cl, 8.08; N, 19.15. Found: C, 68.48; H, 4.32; Cl, 8.03; N, 19.11.

4.8.25 | 4-(2-(1-(9*H*-Fluoren-1-yl) ethylidene)hydrazinyl)-3-(4-chloro-phenyl)-1-phenyl-1*H*-pyrazolo-[3,4-*d*] pyrimidine (31F)

Yield (76%); Yellow crystals; mp 238°C-240°C (DMF); IR (ν_{max}, cm^{-1}) ν 3343 (NH) cm^{-1}; MS (EI, 70 eV) *m/z* (%): 526 (M^+, 13.49), 165 (100). Anal. Calcd. for $C_{32}H_{23}ClN_6$ (526.17): C, 72.93; H, 4.40; Cl, 6.73; N, 15.95. Found: C, 72.99; H, 4.38; Cl, 6.70; N, 15.92.

4.9 | 3-Methyl-8-phenyl-4,8-dihydropyrazolo[3′,4′: 4,5]pyrimido [1,6-*b*][1,2,4]triazine (42-44)

To a mixture of 3-aryl-4-imino-1-phenyl-1,4-dihydro-5*H*-pyrazolo[3,4-*d*]pyrimidin-5-amine derivatives **11-13** (3.0 mmol) and hydrazonoyl halides **32** (3.0 mmol) in chloroform (20 mL), triethylamine (0.6 mL, 6.0 mmol) was added at room temperature. The reaction mixture was refluxed for 6 hours and then cooled; the excess chloroform was removed under reduced pressure, and the residue was treated with ethanol (10 mL). The solid that precipitated was collected and crystallized from DMF to give **42-44**.

4.9.1 | 10-(4-Methoxyphenyl)-3-methyl-8-phenyl-2-(phenyldiazenyl)-4,8-dihydropyrazolo[3′,4′:4,5]pyrimido[1,6-*b*] [1,2,4]triazine (42Aa)

Yield (76%); Red crystals; mp 240°C-242°C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.13 (s, 3H, CH_3), 3.85 (s, 3H, $\underline{CH_3}O$), 6.77-8.04 (m, 14H), 8.42 (s, 1H, CH) and 11.40 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 14.8, 55.6, 112.3, 113.8, 114.9, 120.4, 122.9, 124.5, 125.6, 128.1, 128.9, 129.5, 134.7, 140.0, 142.6, 144.8, 145.1, 148.9, 150.3, 151.3, 159.6; MS (EI, 70 eV) *m/z* (%): 474 (M^+, 100). Anal. Calcd. for $C_{27}H_{22}N_8$ (474.19): C, 68.34; H, 4.67; N, 23.61. Found: C, 68.15; H, 4.69; N, 23.65.

4.9.2 | 10-(4-Methoxyphenyl)-3-methyl-8-phenyl-2-(*p*-tolyldiazenyl)-4,8-dihydropyrazolo[3′,4′:4,5] pyrimido [1,6-*b*][1,2,4]triazine (42Ab)

Yield (71%); Red crystals; mp 242°C-244°C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.17 (s, 3H, CH_3), 2.22 (s, 3H, 4-$\underline{CH_3}C_6H_4$), 3.82 (s, 3H, $\underline{CH_3}O$), 7.15-8.10 (m, 13H), 8.42 (s, 1H, CH) and 11.49 (s, 1H, NH). Anal. Calcd. for $C_{28}H_{24}N_8O$ (488.21): C, 68.84; H, 4.95; N, 22.94. Found: C, 68.67; H, 4.96; N, 22.98.

4.9.3 | 2-((4-Chlorophenyl)diazenyl)-10-(4-methoxyphenyl)-3-methyl-8-phenyl-4,8-dihydropyrazolo [3′,4′:4,5]pyrimido [1,6-*b*][1,2,4]triazine (42Ac)

Yield (70%); Red crystals; mp 255°C-257°C; MS (EI, 70 eV) *m/z* (%): 508 (M^+, 100). Anal. Calcd. for $C_{27}H_{21}ClN_8O$ (508.15): C, 63.72; H, 4.16; Cl, 6.97; N, 22.02. Found: C, 63.60; H, 4.19; Cl, 7.00; N, 22.05.

4.9.4 | 10-(4-Methoxyphenyl)-3,8-diphenyl-2-(phenyldiazenyl)-4,8-dihydropyrazolo[3′,4′:4,5]pyrimido[1,6-*b*] [1,2,4]triazine (42Ba)

Yield (73%); Red crystals; mp 230°C-232°C; MS (EI, 70 eV) *m/z* (%): 536 (M^+, 100). Anal. Calcd. for $C_{32}H_{24}N_8O$ (536.21): C, 71.63; H, 4.51; N, 20.88. Found: C, 71.50; H, 4.53; N, 20.84.

4.9.5 | 10-(4-Methoxyphenyl)-3,8-diphenyl-2-(*p*-tolyldiazenyl)-4,8-dihydropyrazolo[3′,4′:4,5]pyrimido[1,6-*b*][1,2,4]triazine (42Bb)

Yield (72%); Red crystals; mp 242°C-244°C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.17 (s, 3H, CH_3), 3.84 (s, 3H, CH_3O), 6.68-8.02 (m, 18H), 8.49 (s, 1H, CH) and 11.43 (s, 1H, NH); MS (EI, 70 eV) *m/z* (%): 550 (M^+, 100). Anal. Calcd. for $C_{33}H_{26}N_8O$ (550.22): C, 71.98; H, 4.76; N, 20.35. Found: C, 71.81; H, 4.73; N, 20.40.

4.9.6 | 3-Methyl-8-phenyl-2-(phenyldiazenyl)-10-(*p*-tolyl)-4,8-dihydropyrazolo[3′,4′:4,5]pyrimido[1,6-*b*][1,2,4]triazine (43Aa)

Yield (71%); Red crystals; mp 222°C-224°C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.17 (s, 3H, CH_3), 2.46 (s, 3H, CH_3), 6.76-8.44 (m, 14H), 8.48 (s, 1H, CH) and 11.43 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 14.6, 22.3, 109.3, 112.6, 113.4, 119.7, 121.6, 124.1, 125.3, 128.6, 128.7, 129.3, 130.7, 139.8, 142.4, 144.2, 145.3, 148.6, 150.0, 152.3, 159.8; MS (EI, 70 eV) *m/z* (%): 458 (M^+, 92.9), 77 (100). Anal. Calcd. for $C_{27}H_{22}N_8$ (458.20): C, 70.73; H, 4.84; N, 24.44. Found: C, 70.62; H, 4.86; N, 24.49.

4.9.7 | 3-Methyl-8-phenyl-10-(*p*-tolyl)-2-(*p*-tolyldiazenyl)-4,8-dihydropyrazolo[3′,4′:4,5]pyrimido[1,6-*b*][1,2,4]triazine (43Ab)

Yield (72%); Red crystals; mp 246°C-248°C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.15 (s, 3H, CH_3), 2.16 (s, 3H, CH_3), 2.23 (s, 3H, CH_3), 7.10-8.01 (m, 13H), 8.49 (s, 1H, CH) and 11.47 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 14.6, 21.2, 21.4, 108.1, 110.4, 112.5, 117.9, 120.1, 123.2, 125.0, 127.8, 128.1, 129.2, 130.1, 138.7, 141.9, 143.0, 145.3, 149.2, 150.3, 152.2, 159.5; MS (EI, 70 eV) *m/z* (%): 472 (M^+, 100). Anal. Calcd. for $C_{28}H_{24}N_8$ (472.21): C, 71.17; H, 5.12; N, 23.71. Found: C, 71.02; H, 5.16; N, 23.78.

4.9.8 | 2-((4-Chlorophenyl)diazenyl)-3-methyl-8-phenyl-10-(*p*-tolyl)-4,8-dihydropyrazolo[3′,4′:4,5]pyrimido[1,6-*b*][1,2,4]triazine (43Ac)

Yield (73%); Red crystals; mp 252°C-254°C; MS (EI, 70 eV) *m/z* (%): 492 (M^+, 100). Anal. Calcd. for $C_{27}H_{21}ClN_8$ (492.16): C, 65.78; H, 4.29; Cl, 7.19; N, 22.73. Found: C, 65.62; H, 4.31; Cl, 7.20; N, 22.75.

4.9.9 | 3,8-Diphenyl-2-(phenyldiazenyl)-10-(*p*-tolyl)-4,8-dihydropyrazolo[3′,4′:4,5]pyrimido[1,6-*b*][1,2,4]triazine (43Ba)

Yield (74%); Red crystals; mp 236°C-238°C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.42 (s, 3H, CH_3), 6.73-8.01 (m, 19H), 8.53 (s, 1H, CH) and 11.47 (s, 1H, NH); MS (EI, 70 eV) *m/z* (%): 520 (M^+, 100). Anal. Calcd. for $C_{32}H_{24}N_8$ (520.21): C, 73.83; H, 4.65; N, 21.52. Found: C, 73.73; H, 4.69; N, 21.57.

4.9.10 | 3,8-Diphenyl-10-(*p*-tolyl)-2-(*p*-tolyldiazenyl)-4,8-dihydro-pyrazolo[3′,4′:4,5]pyrimido[1,6-*b*][1,2,4]triazine (43Bb)

Yield (76%); Red crystals; mp 232°C-234°C; Anal. Calcd. for $C_{33}H_{26}N_8$ (534.23): C, 74.14; H, 4.90; N, 20.96. Found: C, 74.01; H, 4.92; N, 20.94.

4.9.11 | 3-(Naphthalen-1-yl)-8-phenyl-2-(phenyldiazenyl)-10-(*p*-tolyl)-4,8-dihydropyrazolo[3′,4′:4,5]pyrimido[1,6-*b*][1,2,4]triazine (43Ca)

Yield (75%); Red crystals; mp 248°C-250°C; MS (EI, 70 eV) *m/z* (%): 570 (M^+, 1.0), 64 (100). Anal. Calcd. for $C_{36}H_{26}N_8$ (570.23): C, 75.77; H, 4.59; N, 19.64. Found: C, 75.62; H, 4.53; N, 19.68.

4.9.12 | 10-(4-Chlorophenyl)-3-methyl-8-phenyl-2-(phenyldiazenyl)-4,8-dihydropyrazolo[3′,4′:4,5]pyrimido[1,6-*b*][1,2,4]triazine (44Aa)

Yield (70%); Red crystals; mp 254°C-256°C; MS (EI, 70 eV) *m/z* (%): 478 (M^+, 100). Anal. Calcd. for $C_{26}H_{19}ClN_8$ (478.14): C, 65.20; H, 4.00; Cl, 7.40; N, 23.40. Found: C, 65.04; H, 3.98; Cl, 7.43; N, 23.45.

4.9.13 | 10-(4-Chlorophenyl)-3-methyl-8-phenyl-2-(*p*-tolyldiazenyl)-4,8-dihydropyrazolo[3′,4′:4,5]pyrimido[1,6-*b*][1,2,4]triazine (44Ab)

Yield (75%); Red crystals; mp 270°C-272°C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.13 (s, 3H, CH_3), 2.26 (s, 3H, CH_3),

7.06-7.94 (m, 13H), 8.45 (s, 1H, CH) and 11.43 (s, 1H, NH); MS (EI, 70 eV) *m/z* (%): 492 (M^+, 68.13), 77 (100). Anal. Calcd. for $C_{27}H_{21}ClN_8$ (492.16): C, 65.78; H, 4.29; Cl, 7.19; N, 22.73. Found: C, 65.65; H, 4.34; Cl, 7.17; N, 22.78.

4.9.14 | 10-(4-Chlorophenyl)-2-((4-chlorophenyl)diazenyl)-3-methyl-8-phenyl-4,8-dihydropyrazolo[3′,4′:4,5]pyrimido[1,6-*b*][1,2,4]triazine (44Ac)

Yield (72%); Red crystals; mp 272°C-274°C; MS (EI, 70 eV) *m/z* (%): 512 (M^+, 7.3), 64 (100). Anal. Calcd. for $C_{26}H_{18}Cl_2N_8$ (512.10): C, 60.83; H, 3.53; Cl, 13.81; N, 21.83. Found: C, 60.70; H, 3.56; Cl, 13.89; N, 21.84.

4.9.15 | 10-(4-Chlorophenyl)-3,8-diphenyl-2-(phenyldiazenyl)-4,8-dihydropyrazolo[3′,4′:4,5]pyrimido[1,6-*b*][1,2,4]triazine (44Ba)

Yield (73%); Red crystals; mp 252°C-254°C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 6.82-8.16 (m, 19H), 8.56 (s, 1H, CH) and 11.50 (s, 1H, NH); MS (EI, 70 eV) *m/z* (%): 540 (M^+, 100). Anal. Calcd. for $C_{31}H_{21}ClN_8$ (540.16): C, 68.82; H, 3.91; Cl, 6.55; N, 20.71. Found: C, 68.71; H, 3.89; N, 20.76.

4.9.16 | 10-(4-Chlorophenyl)-3,8-diphenyl-2-(*p*-tolyldiazenyl)-4,8-dihydropyrazolo[3′,4′:4,5]pyrimido[1,6-*b*][1,2,4]triazine (44Bb)

Yield (71%); Red crystals; mp 242°C-244°C; MS (EI, 70 eV) *m/z* (%): 554 (M^+, 100). Anal. Calcd. for $C_{32}H_{23}ClN_8$ (554.17): C, 69.25; H, 4.18; Cl, 6.39; N, 20.19. Found: C, 69.10; H, 4.23; Cl, 6.40; N, 20.16.

4.9.17 | 10-(4-Chlorophenyl)-3-(naphthalen-1-yl)-8-phenyl-2-(phenyldiazenyl)-4,8-dihydropyrazolo[3′,4′:4,5]pyrimido[1,6-*b*][1,2,4]triazine (44Ca)

Yield (70%); Red crystals; mp 280°C-283°C; MS (EI, 70 eV) *m/z* (%): 590 (M^+, 1.0), 64 (100). Anal. Calcd. for $C_{35}H_{23}ClN_8$ (590.17): C, 71.12; H, 3.92; Cl, 6.00; N, 18.96. Found: C, 71.05; H, 3.96; Cl, 6.02; N, 18.94.

4.10 | Antimicrobial activity evaluation

Antimicrobial activity of the tested compounds was determined using a modified Kirby-Bauer disk diffusion method.[38] Briefly, 100 μL of the test bacteria/fungi were grown in 10 mL of fresh media until they reached a count of approximately 10^8 cells/mL for bacteria or 10^5 cells/mL for fungi.[39] One hundred microliters of microbial suspension was spread onto agar plates corresponding to the broth in which they were maintained.

Of the many media available, NCCLS recommends Mueller-Hinton agar because it results in good batch-to-batch reproducibility. Disk diffusion method for filamentous fungi was tested by using approved standard method (M38-A) developed by the (NCCLS, 2002)[40] for evaluating the susceptibilities of filamentous fungi to antifungal agents. Disk diffusion method for yeasts was developed by using approved standard method (M44-P) by the (NCCLS, 2009).[41]

4.11 | MIC evaluation

The MIC values were measured by the broth dilution method.[35,42] Five hundred microliters of a stock solution (10.24 mg/mL) of each tested compound in DMSO was prepared and then diluted with Mueller-Hinton broth to 1024 μg/mL. The strains were grown briefly at 37°C in Mueller-Hinton media. After 5 hours of bacterial growth, the bacterial culture was diluted to obtain a concentration of 5×10^5 cells/mL. Then, 150-μL bacterial suspensions were added to each well of the flat-bottomed 96-well tissue culture plate. Twofold serial dilutions were carried out from the fist well to the tenth well; the final concentrations of the compounds ranged from 1 to 512 μg/mL, and excess media (150 μL) were discarded from the last well. The plates were incubated at 37°C for 24 hours in an electro-heating standing temperature cultivator and were read visually. The MIC of the sample showing no turbidity was recorded as the lowest concentration of compound that inhibited bacterial growth completely. Each assay was run in triplicate.

ORCID

Hamdi M. Hassaneen https://orcid.org/0000-0003-0963-4192

REFERENCES

[1] S. Schenone, O. Bruno, M. Radi, M. Botta, *Mini. Rev. Org. Chem.* **2009**, *6*(3), 220. https://doi.org/10.2174/157019309788922739
[2] E. Al-Afaleq, S. Abubshait, E. I. Al-Afaleq, S. A. Abubshait, *Molecules* **2001**, *6*(7), 621. https://doi.org/10.3390/60700621
[3] A. Salaheldin, A. Oliveira-Campos, L. Rodrigues, *Synth. Commun.* **2009**, *39*(7), 1186. https://doi.org/10.1080/00397910802517814
[4] Kandeel, M.M., Ali, S.M., ElALL, E.K.A.A., Abdelgawad, M.A. and Lamie, P.; ... M. A.-D. P.; 2012, undefined. Synthesis and

Antitumor Activity of Novel Pyrazolo [3, 4-d] Pyrimidines and Related Heterocycles. *Der Pharma Chem.*, **2012**, *4*, 1704–1715.

[5] Fahmi, A. A.; Mekki, S. T.; Albar, H. A.; Shawali, A. S.; Hassaneen, H. M.; Abdelhamid, H. 71. A facile Synthesis of Some Pyrazolo Analogues of Tricyclic Derivatives via Hydrazonoyl Halides https://scholar.google.com/scholar?hl = en&as_sdt = 0% 2C5&q = Fahmi%2C + A. + A.%3B + Mekki%2C + S. + T.%3B + Albar%2C + H. + A.%3B + Shawali%2C + A. + S.%3B + Hassaneen%2C + H. + M.%3B + Abdelhamid%2C + H. + J. + Chem. + Res.%2C + Synop. + 1994%2C + 6&btnG = ().

[6] P. G. Baraldi, H. El-Kashef, A. R. Farghaly, P. Vanelle, F. Fruttarolo, *Tetrahedron* **2004**, *60*(23), 5093.

[7] Mezheritsky, V.V., Minkin, V.I., Minyaeva, L.G., Tyurin, R.G., Krasnikov, V.V., Vorobyev, E.V. and Starikova, Z. A. Two Approaches to a New Heterocyclic System of Pyrazolo [4, 3-*e*] [1, 2, 4] Triazolo [1, 5-*c*] Pyrimidine. *Arkivoc*, **2005**, No. x, 9–17.

[8] A. S. Shawali, *J. Adv. Res.* **2010**, *1*(4), 255.

[9] A. S. Shawali, *Arkivoc* **2012**, *1*, 383.

[10] H. M. Hassaneen, N. M. Abunada, O. A. Miqdad, A. Fares, *Asian J. Chem.* **2012**, *24*(1), 330.

[11] Hassaneen, Hamdi M., Tayseer A. Abdallah, and E. M. A. A Facile Access for Synthesis of Novel Isoquinoline-Based Heterocycles. *Heterocycles*, **2009**, *78* (6), 1507–1522.

[12] A. S. Shawali, C. Párkanyi, *J. Heterocycl. Chem.* **1980**, *17*(5), 833. https://doi.org/10.1002/jhet.5570170501

[13] A. S. Shawali, *Heterocycles* **1983**, *20*(11), 2239.

[14] A. S. Shawali, *Chem. Rev.* **1993**, *93*(8), 2731. https://doi.org/10.1021/cr00024a007

[15] A. S. Shawali, M. A. Abdallah, *Adv. Heterocycl. Chem.* **1995**, *63*, 277.

[16] A. S. Shawali, S. M. Elsheikh, *J. Heterocycl. Chem.* **2001**, *38*(3), 541. https://doi.org/10.1002/jhet.5570380301

[17] A. S. Shawali, M. A. N. Mosselhi, *J. Heterocycl. Chem.* **2003**, *40* (4), 725. https://doi.org/10.1002/jhet.5570400428

[18] A. S. Shawali, M. A. N. Mosselhi, *J. Sulfur Chem.* **2005**, *26*(3), 267. https://doi.org/10.1080/17415990500124586

[19] Shawali, A. S.; Edrees, M. M. Reactions of Nitrilimines with Heterocyclic Amines and Enamines. Convenient Methodology for Synthesis and Annulation of Heterocycles. *Arkivoc*, **2006**, *ix*, 292–365. https://doi.org/10.3998/ark.5550190.0007.910.

[20] A. S. Shawali, S. M. Sherif, *Curr. Org. Chem.* **2007**, *11*(9), 773. https://doi.org/10.2174/138527207780831747

[21] Ahmad Sami Shawali and Thoraya A. Farghaly. Reactions of Hydrazonoyl Halides with Heterocyclic Thiones. Convenient Methodology for Heteroannulation, Synthesis of Spiroheterocycles and Heterocyclic Ring Transformation. *Arkivoc*, **2008**, *i*, 18–64.

[22] S. Shawali, A.; A. Samy, N. Hydrazonoyl Halides: Their Versatile Biological Activities. *Compd. J.*, **2009**, *2* (1), 8–16. https://doi.org/10.2174/1874847300902010008.

[23] Shawali, A. S. Tandem in Situ Generation and 1, 5-Electrocyclization of N-Hetaryl Nitrilimines. A Facile Methodology for Synthesis of Annulated 1, 2, 4-Triazoles and Their Acyclo C-Nucleosides. *Arkivoc*, **2010**, *i*, 33–97.

[24] T. Nagamatsu, T. Fujita, *Chem. Commun.* **1999**, *16*, 1461.

[25] P. Wolkoff, *J. Chem. Soc. Perkin Trans*, No. **1976**, *2*, 8 921. https://doi.org/10.1039/p29760000921

[26] Shawali, A. S., A. A. Fahmi, H. A. Albar, H. M. Hassaneen, and H. A. A. *J. Chem. Res.(S)*, **1994**, *6*, 1040–1049.

[27] A. E. Rashad, O. A. Heikal, A. O. H. El-Nezhawy, F. M. E. Abdel-Megeid, *Heteroat. Chem.* **2005**, *16*(3), 226. https://doi.org/10.1002/hc.20114

[28] Shamroukh, A. H.; Zaki, M. E. A.; Morsy, E. M. H.; Abdel-Motti, F. M.; Abdel-Megeid, F. M. E. Synthesis, Isomerization, and Antimicrobial Evaluation of Some Pyrazolopyranotriazolopyrimidine Derivatives. *Arch. Pharm. (Weinheim).*, **2007**, *340* (7), 345–351. https://doi.org/10.1002/ardp.200700007.

[29] Shawali, A.S., Sherif, S.M., Farghaly, T.A. and Darwish, M. A. Síntesis Selectiva Y Tautomería de Derivados Arilazo de Pirazolo Triazina. *Afinidad Rev. química teórica y Apl.*, **2008**, *65* (536), 314–318.

[30] M. G. Badrey, S. M. Gomha, *Molecules* **2012**, *17*(10), 11538.

[31] Tschitschibabin, A. E. Zur Tautomerie Des α-Amino-Pyridins, III. Mitteil.: Bicyclische Derivate Der Tautomeren Form Des α-Aminopyridins Mit Imidazol-Kern. *Berichte der Dtsch. Chem. Gesellschaft (A B Ser.*, **1924**, *57* (11), 2092–2101. https://doi.org/10.1002/cber.19240571123.

[32] Tschitschibabin, A. E. Zur Tautomerie Des α-Amino-Pyridins, IV. Mitteilung: Eine Darstellungsmethode Des Pyrimidazols Und Seiner Homologen. *Berichte der Dtsch. Chem. Gesellschaft (A B Ser.*, **1925**, *58* (8), 1704–1706. https://doi.org/10.1002/cber.19250580852.

[33] Yao, H. C.; Resnick, P. Azo-Hydrazone Conversion. I. *J. Am. Chem. Soc.*, **1962**, *84* (18), 3514–3517. https://doi.org/10.1021/ja00877a018.

[34] Burawoy, A., A. G. Salem, and A. R. T. 935. *J. Chem. Soc.*, **1952**, 4793–4798.

[35] A. K. Jordão, J. Novais, B. Leal, A. C. Escobar, H. M. dos Santos Júnior, H. C. Castro, V. F. Ferreira, *Eur. J. Med. Chem.* **2013**, *63*, 196.

[36] X. Lei, J. Li, B. Liu, N. Zhang, H. Liu, *Molecules* **2015**, *20*(9), 16375.

[37] Z.-Z. Geng, J.-J. Zhang, J. Lin, M.-Y. Huang, L.-K. An, H.-B. Zhang, P.-H. Sun, W.-C. Ye, W.-M. Chen, *Eur. J. Med. Chem.* **2015**, *100*, 235. https://doi.org/10.1016/J.EJMECH.2015.06.008

[38] A. W. Bauer, W. M. Kirby, J. C. Sherris, M. Turck, *Am. J. Clin. Pathol.* **1966**, *45*(4), 493.

[39] M. A. Pfaller, L. Burmeister, M. S. Bartlett, M. G. Rinaldi, *J. Clin. Microbiol.* **1988**, *26*(8), 1437.

[40] Nccls. *Reference Method for Broth Dilution Antifungal Susceptibility Testing of Yeasts; Approved Standard — Second Edition Serving the World' S Medical Science Community Through Voluntary Consensus*; 2002; Vol. 22.

[41] Rex, J. H.; Johnson, E. M.; Ghannoum, M. A.; Knapp, C. C.; Alexander, B. D.; Motyl, M. R.; Andes, D.; Ostrosky-Zeichner, L.; Brown, S. D.; Pfaller, M. A.; et al. *Method for Antifungal Disk Diffusion Susceptibility Testing of Yeasts: Approved Guideline M44-A*; 2009; Vol. 24.

[42] N. Suresh, H. N. Nagesh, J. Renuka, V. Rajput, R. Sharma, I. A. Khan, C. S. K. V. Gowri, *Eur. J. Med. Chem.* **2014**, *71*, 324. https://doi.org/10.1016/J.EJMECH.2013.10.055

How to cite this article: Hassaneen HM, Saleh FM, Abdallah TA, Mohamed YS, Awad EM. Synthesis, reactions, and antimicrobial activity of some novel pyrazolo[3,4-*d*]pyrimidine, pyrazolo[4,3-*e*][1,2,4] triazolo[1,5-*c*]pyrimidine, and pyrazolo[4,3-*e*][1,2,4] triazolo[3,4-*c*]pyrimidine derivatives. *J Heterocyclic Chem*. 2019;1–21. https://doi.org/10.1002/jhet.3835