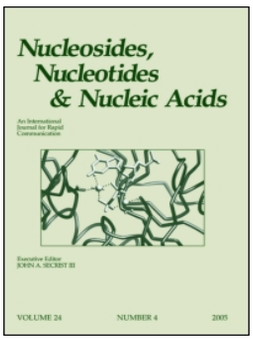

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Pyrimidine non-nucleoside analogs: A direct synthesis of a novel class of *N*-substituted amino and *N*-sulfonamide derivatives of pyrimidines

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ABSTRACT

A convenient method for the regioselective synthesis of pyrimidine non-nucleoside analogs was developed. This study reports a novel and efficient method for the synthesis of a new type of *N*-substituted amino methylsulfanylpyrimidines and the corresponding pyrazolo[3,4-*d*]pyrimidines. This series of compounds was designed through the reaction of dimethyl *N*-cyanodithioiminocarbonate with 2-cyano-*N*′-(thiophen-2-yl-, furan-2-yl- and pyridin-4-ylmethylene)acetohydrazide and *N*′-(2-cyanoacetyl)arylsulfonohydrazides. The scope and limitation of the method are demonstrated. The antibacterial and antifungal activities of the synthesized compounds were also evaluated.

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N-substituted amino methylsulfanylpyrimidines; dimethyl *N*-cyanodithioiminocarbonate; *N*′-(2-cyanoacetyl)arylsulfonohydrazides; antibacterial and antifungal activities; 2-cyano-*N*′-(thiophen-2-yl-, furan-2-yl- and pyridin-4-ylmethylene)acetohydrazide; pyrazolo[3,4-*d*]pyrimidines, purine analogs

Introduction

Pyrimidines and purine bases play key roles in biological systems, since all DNA bases are pyrimidine and purine derivatives, and many modern pharmaceutical agents contain pyrimidine and purine fragments. Several examples of biologically important pyrimidine and purine derivatives are identified, such as the signal transduction inhibitor imatinib (gleevec) which is highlighted as one of the most significant new pyrimidine derivatives to have been identified in the last few years.[1] Besides their importance in exhibiting optimal cytotoxic effect against the cancer cell lines, many derivatives are endowed with antiproliferative effects when evaluated against a panel of tumor cell lines.[2] It is worth noting that sulfonamide derivatives bearing a pyrimidine or purine moieties are attractive molecular targets which possess many types of biological activities,[3] including anticancer activity.[4] Consequently, many benzenesulfonamide derivatives, bearing pyrimidine or purine moieties, has been designed and synthesized as antimetabolic agents.[5] We have recently reported different successful approaches

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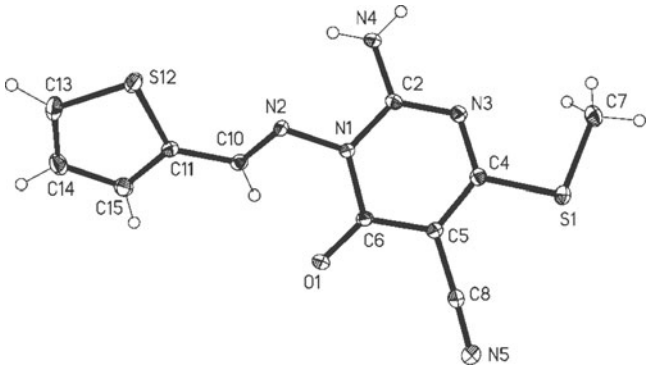


Figure 1. Molecular structure of compound **5a**.

for the synthesis of modified nucleoside analogs.[6–13] Derivatives of these ring systems are interesting as antimetabolites in biochemical reactions.[14–19] In continuation of our research program and among the strategies addressed to the synthesis of the pyrimidine and purine nucleoside analogs, the present study focuses on the novel synthesis of methylsulfanylpyrimidine non-nucleoside analogs and their corresponding pyrazolo[3,4-*d*]pyrimidines by the reaction of dimethyl *N*-cyanodithioiminocarbonate with substituted hydrazides.

Results and discussion

Chemistry

It has been found that cyanamide reacts with carbon disulfide and methyl iodide in the presence of alkali to produce the *S*,*S*-dimethyl *N*-cyanodithioiminocarbonate **1**. When compound **1** was treated with 2-cyano-*N*′-(thiophen-2-yl-, furan-2-yl- and pyridin-4-ylmethylene)acetohydrazide **2a-c** at room temperature and in presence of pulverized potassium hydroxide-1,4-dioxane, the corresponding (1)*N*-heterylmethyleneamino-4-methylsulfanylpyrimidines **5** was obtained. The compounds **5** displayed spectroscopic data (IR, ^{1}H NMR, ^{13}C NMR and MS) and elemental analysis result consistent with the proposed structures. In order to prove unambiguously the structure of the compound **5a**, its crystal structure was measured. The X-ray analysis confirms the presence of the (1)*N*-(thiophene-2-ylmethyleneamino)pyrimidine-6-one form **5a** in the solid state (Figs. 1 and 2).

The synthesis of **5** from the reaction of **1** with **2** is assumed to proceed via Michael addition of active methylene of **2** to the double bond in **1**, the formed adducts then cyclized smoothly via CH_3SH elimination and additionally to the cyano group. Compounds **5** were treated with hydrazine in refluxing DMF to be converted into the corresponding pyrazolo[3,4-*d*] pyrimidin-4(3*H*)-ones **6**. The elemental analysis and spectral data were compatible with the suggested individual structure of compounds **6** (Chart 1). In order to investigate the scope of this reaction and to establish whether the reaction of dimethyl *N*-cyanodithioiminocarbonate with

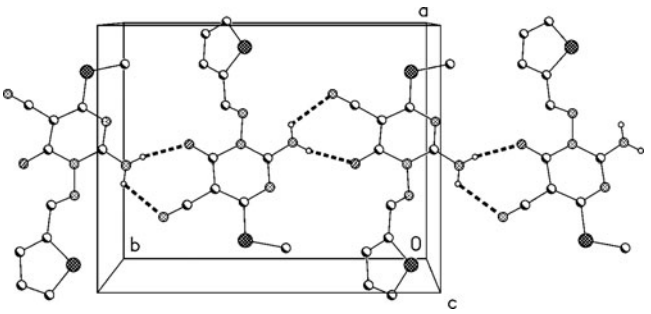


Figure 2. Packing diagram of **5a**, viewed perpendicular to (100). Thick dashed bonds represent classical H-bonds. Atom names correspond to the asymmetric unit.

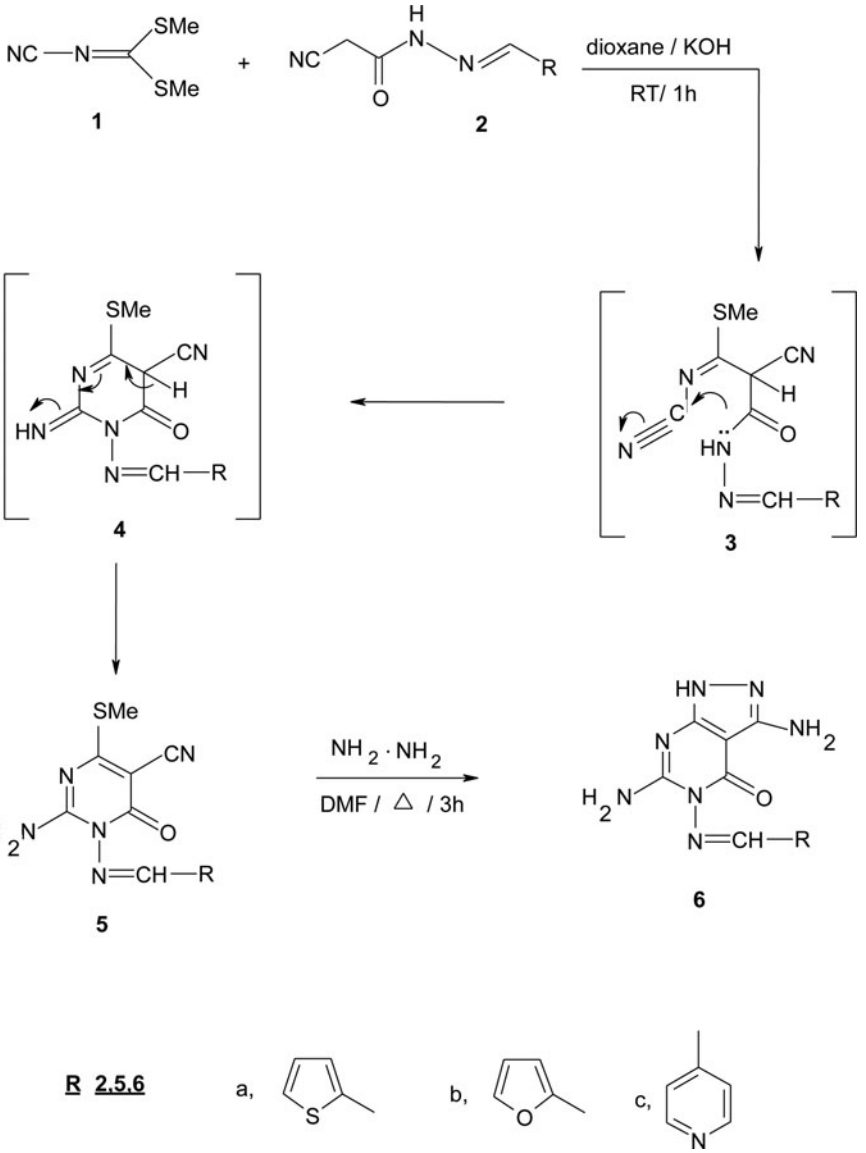
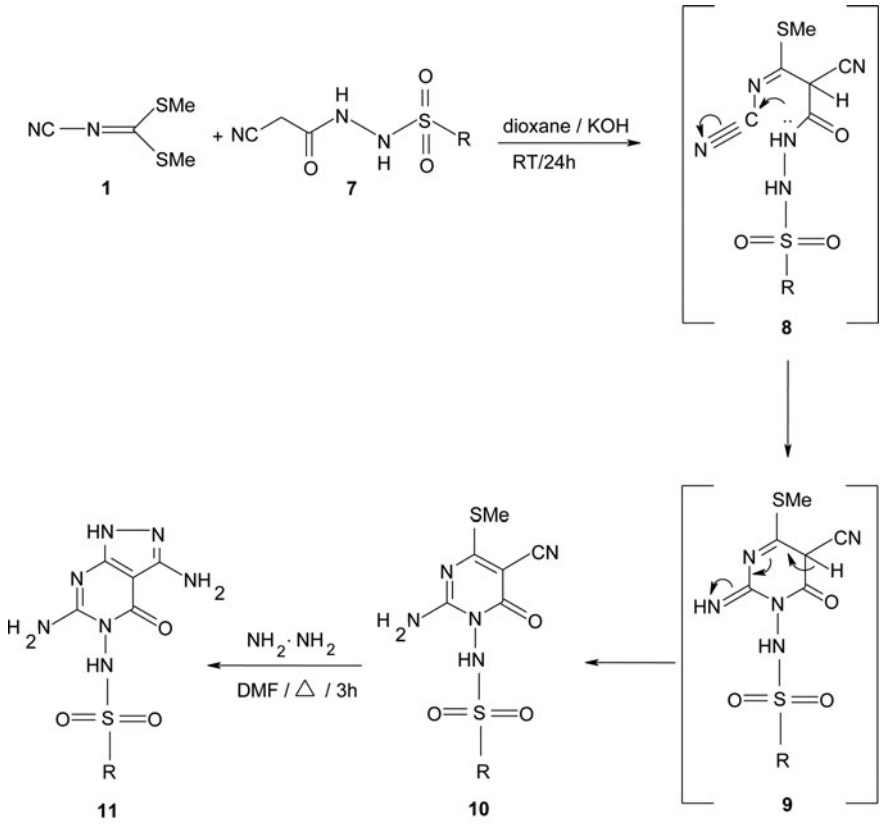


Chart 1. Synthesized derivatives **5a-c** and **6a-c.**



7.10.11	R
a	C_6H_4Br
b	C_6H_4Cl

Chart 2. Synthesized derivatives **10a,b** and **11a,b.**

substituted cyanohydrazides could be extended to provide a general approach to (1)*N*-substituted amino methylthiopyrimidines, we studied the reaction of dimethyl *N*-cyanodithioiminocarbonate **1** with other functionalized cyanohydrazides. Thus, it has been found that cyanoacetohydrazide reacts with 4-bromobenzene-1-sulfonyl chloride and 4-chlorobenzene-1-sulfonyl chloride in ethanol to obtain the corresponding *N*′-(2-cyanoacetyl)arylsulfonohydrazides **7a,b** in good yields. Then, the syntheses of *N*-(4-methylthio-6-oxopyrimidin-1-yl)arylsulfonamides **10** was carried out by the reaction of **7** with **1** in dioxane in the presence of a catalytic amount of potassium hydroxide. The structure of **10** was characterized by spectroscopic techniques including IR, ^{1}H NMR and ^{13}C NMR and elemental analysis. In order to prove unambiguously the structure of compound **10a**, its crystal structure was measured (Chart 2). The X-ray analysis proves the presence of the pyrimidone form **10a** in the solid state (Figs. 3 and 4). The synthetic route to target compounds **10** from **1** and **7** is assumed to proceed via addition of the active methylene group

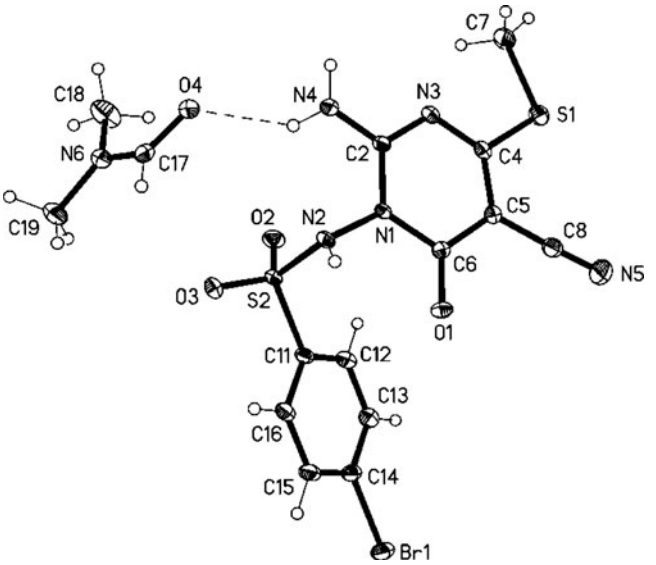


Figure 3. Molecular structure of compound **10a**.

of **7** to the double bond of **1** to give intermediate Michael adducts. The latter loses elements of CH_3SH to yield the intermediate **8**. Cyclization of **8** led to the novel *N*-(4-methylthio-6-oxopyrimidin-1-yl)arylsulfonamides **10**. Compounds **10** is allowed to react with hydrazine in refluxing DMF to give the corresponding analogs **11**. The individual structure of compounds **11** was established on the basis of elemental analysis and spectral data.

Antibacterial activity

An approach to screen the antimicrobial activity of compounds (**5a, 5b, 5c, 6a, 10a and 10b**) was examined against the bacterial strains *Bacillus subtilis, Echerichia coli, Pseudomonas aeruginosa, Staphylococcus aureus* and the fungal strains, *Asperigillusflavus and Candida albicans*. Compound **10a** has exhibited various degree

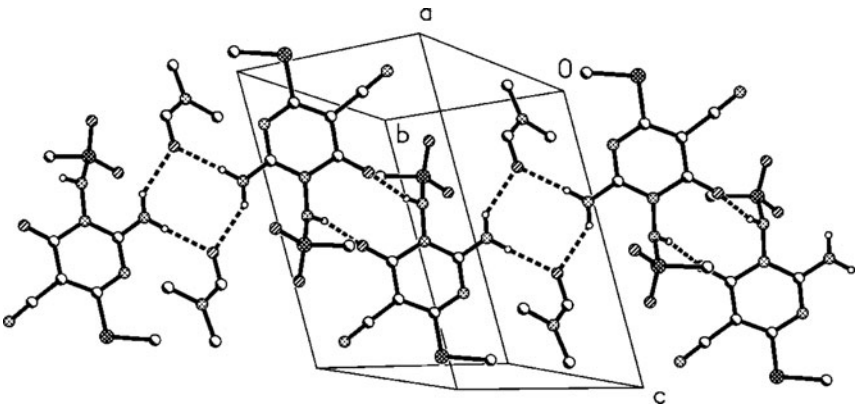


Figure 4. Packing diagram of **10a**, viewed perpendicular to (100). Thick dashed bonds represent classical H-bonds. Atom names correspond to the asymmetric unit.

Table 1. Antibacterial and antifungal data of the synthesized compounds **5a-c, 6a, 10a,b**.

	Inhibition zone diameter (mm / mg Sample)					
Sample	*Bacillus subtilis* (G+)	*Escherichia coli* (G−)	*Pseudomonasaeruginosa* (G−)	*Staphylococcusaureus* (G+)	*Aspergillusflavus* (Fungus)	*Candida albicans* (Fungus)
Control: DMSO	0.0	0.0	0.0	0.0	0.0	0.0
Standard Ampicillin Antibacterial agent	20	22	17	18	—	—
Amphotericin B Antifungal agent	—	—	—	—	17	19
5a	0.0	0.0	0.0	0.0	0.0	9
5b	0.0	0.0	0.0	0.0	0.0	0.0
5c	0.0	0.0	0.0	0.0	0.0	0.0
6a	10	0.0	0.0	0.0	0.0	0.0
10a	15	15	13	15	0.0	15
10b	0.0	0.0	0.0	0.0	0.0	0.0

of inhibitory activity on the four pathogenic bacterial strains. It was observed that this compound has an effect against gram positive and gram negative bacteria. The bacterial zones of inhibition (mm) values are summarized in Table 1.

Antifungal activity

Compounds **5a and 10a** are moderately active compared with the reference drug (amphotericin) against *C. albicans*. The fungal zones of inhibition (mm) values are summarized in Table 1.

Conclusion

In conclusion, searching for novel antimetabolic agents, we have achieved the synthesis of interesting alkythiopyrimidine non-nucleoside analogs and their corresponding pyrazolo[3,4-*d*]pyrimidines by the reaction of dimethyl *N*-cyanodithioiminocarbonate with 2-cyano-*N*′-(thiophen-2-yl-, furan-2-yl- and pyridin-4-ylmethylene)acetohydrazide and *N*-cyanoacetoarylsulfonylhydrazides. The compounds obtained seem promising as high potential intermediates for synthesizing other antimetabolic agents and for biological screening.

Experimental

Chemistry

The melting points were determined on a Gallenkamp melting point apparatus and were uncorrected. ^{1}H NMR spectra were recorded on a Jeol-600 spectrometer operating at 600 MHz and 500 MHz for ^{1}H and ^{13}C nuclei, respectively, in DMSO-d_6 with $Si(CH_3)_4$ as internal standard at National Research Center, Cairo, Egypt. Shifts were given in ppm and the abbreviations were as follows: s (singlet), d (doublet), t (triplet),

and m (multiplet). The mass spectra were run in the Cairo University. The reactions were monitored by thin-layer chromatography (TLC) using aluminum sheets coated with silica gel F254 (Merck). Spots were detected by their absorption under a short-wavelength UV lamp. The reagents and solvents were purchased in commercially available grade purity.

General procedure for the synthesis of 5a-c

Dimethyl *N*-cyanodithioiminocarbonate **1** (0.01 mol) was added to a stirred solution of the 1-cyanoacetyl-4-aryl methylidenesemicarbazide **3** (0.01 mol) in dry dioxane (30 mL) containing potassium hydroxide (0.01 mol) at room temperature. The mixture was stirred magnetically for 1 h, then the precipitated product was filtered off and recrystalized from the appropriate solvent to give the desired compound.

2-Amino-4-(methylthio)-6-oxo-1-(thiophen-2-ylmethyleneamino)-1,6-dihydropyrimidine-5-carbonitrile (5a). Colorless crystals; (DMF), yield (73.3%), mp 260°C; IR (KBr, cm^{-1}) υ 3436 and 3283 (NH_2), 2210 (CN) and 1651 (C=O). ^{1}H NMR (600 MHz, DMSO-d_6): δ 2.49 (s, 3H, SCH_3), 7.6 (s, br, 2H, NH_2), 7.23–7.97 (m, 3H, C_4H_3), 9.1 (s, ^{1}H, CH). ^{13}C NMR: (DMSO) δ11.7 (SCH_3), 82.0 (C-5), 115.9 (CN), 127.1 (C-2′), (C-3′), 133 (C-4′), 134.9 (C-1′), 152.2 (CH=N), 158.0 (C-2), 164.1 (C=O), 171.9 (C-4). MS: $m/z = 291$. Anal. Calcd. For $C_{11}H_9N_5OS_2$(291.02): C, 45.35; H, 3.11; N, 24.04; S, 22.01. Found: C, 45.33; H, 3.11; N, 24.01; S, 22.01.

2-Amino-1-(furan-2-ylmethyleneamino)-4-(methylthio)-6-oxo-1,6-dihydropyrimidine-5-carbonitrile (5b). Buff solid; (DMF), yield (90.8%), mp 268°C; IR (KBr, cm^{-1}) υ 3433 and 3279 (NH_2), 2210 (CN) and 1656 (C=O). ^{1}H NMR (600 MHz, DMSO-d_6): δ 2.52 (s, 3H, SCH_3), 6.7 (s, br, 2H, NH_2), 7.3–8.05 (d, t, d, 3H, C_4H_3), 8.5 (s, 1H, CH). ^{13}C NMR: (DMSO) δ12.8 (SCH_3), 82.0 (C-5), 116.1 (CN), 118.0 (C-2′), (C-3′), 122.0 (C-4′), 147.0 (C-1′), 154.2 (CH=N), 157.0 (C-2), 159.1(C=O), 172.5 (C-4). MS: $m/z = 275$. Anal. Calcd. for $C_{11}H_9N_5O_2S$ (275.29): C, 47.99; H, 3.30; N, 25.44; S, 11.65. Found: C, 47.95; H, 3.30; N, 25.41; S, 11.61.

2-Amino-4-(methylthio)-6-oxo-1-(pyridin-4-ylmethyleneamino)-1,6-dihydropyrimidine-5-carbonitrile (5c). White solid; (DMF), yield (50%), mp 258–260°C; IR (KBr, cm^{-1}) υ 3734 and 3447 (NH_2), 2211 (CN) and 1679 (C=O). ^{1}H NMR (600 MHz, DMSO-d_6): δ 2.51 (s, 3H, SCH_3), 7.9 (s, br, 2H, NH_2), 8.71–8.76 (m, 4H, C_5H_4), 9.10 (s, 1H, CH). ^{13}C NMR: (DMSO) δ 12.0 (SCH_3), 80.0 (C-5), 115.1 (CN), 120.1 (C-2′), C-6′), 139.0 (C-3′), (C-5′), 150.0 (C-1′), 156.0 (CH=N), 157.0 (C-2), 168.0 (C=O), 172.5 (C-4). MS: $m/z = 286$. Anal. Calcd. for $C_{12}H_{10}N_6OS$ (275.29): C, 50.34; H, 3.52; N, 29.35; S, 11.20. Found: 50.32; H, 3.52; N, 29.31; S, 11.20.

General procedure for the synthesis of 6a-c

A mixture of **5a-c** (0.01 mol) and hydrazine hydrate (0.02 mol) was heated in (30 mL) DMF for 3 h. After cooling of the reaction, the precipitated final product was filtered off.

3,6-Diamino-5-(thiophen-2-ylmethyleneamino)-1H-pyrazolo[3,4-d]pyrimidin-4(5H)-one(6a). Yellow solid; (EtOH), yield (50%), mp > 300°C; IR (KBr, cm^{-1}) υ 3451(NH_2). ^{1}H NMR (600 MHz, DMSO-d_6): δ 5.07 (s, br, 2H, NH_2), 5.13 (s, br, 2H, NH_2), 6.87–7.00 (m, 3H, C_4H_3), 8.01 (s, 1H, NH), 9.00 (s, 1H, CH). Anal. Calcd. for $C_{10}H_9N_7OS$ (275.29): C, 43.63; H, 3.30; N, 35.62; S, 11.65. Found: C, 43.61; H, 3.30; N, 35.60; S, 11.64.

3,6-Diamino-5-(furan-2-ylmethyleneamino)-1H-pyrazolo[3,4-d]pyrimidin-4(5H)-one(6b). Buff solid; (EtOH), yield (66.8%), mp > 300°C; IR (KBr, cm^{-1}) υ 3451 (NH_2). ^{1}H NMR (600 MHz, DMSO-d_6): δ 5.09 (s, br, 2H, NH_2), 5.15 (s, 2H, NH_2), 7.00–7.70 (m, 3H, C_4H_3), 9.10 (s, 1H, CH),11.46 (s, br, 1H, NH). Anal. Calcd. for $C_{10}H_9N_7O_2$ (259.22): C, 46.33; H, 3.50; N, 37.82. Found: C, 46.31; H, 3.50; N, 37.81.

3,6-Diamino-5-(pyridin-4-ylmethyleneamino)-1H-pyrazolo[3,4-d]pyrimidin-4(5H)-one (6c). Yellow solid; (EtOH), yield (42.36%), mp > 340°C; IR (KBr, cm^{-1}) υ 3433 (NH_2). ^{1}H NMR (600 MHz, DMSO-d_6): δ 5.10 (s, br, 2H, NH_2), 6.21 (s, br, 2H, NH_2), 7.00–7.90 (m, 4H, C_5H_4), 8.30 (s, 1H, CH), 10.22 (s, 1H, NH). MS: m/z = 270. Anal. Calcd. for $C_{11}H_{10}N_8O$ (270.25): C, 48.89; H, 3.73; N, 41.46. Found: C, 48.87; H, 3.71; N, 41.46.

General procedure for the synthesis of 10a,b

To a stirred solution of *N*-cyanoacetoarylsulfonylhydrazides (0.01 mol) in dry dioxane (30 mL) containing potassium hydroxide was added dimethyl *N*-cyanodithioiminocarbonate **1** (0.01 mol). The mixture was stirred magnetically at room temperature for 30 min, then the precipitated solid was collected by filtration and recrystallized from DMF.

N-(2-amino-5-cyano-4-(methylthio)-6-oxopyrimidin-1(6H)-yl)-4-bromobenzenesulfonamide (10a). Yellow crystals; (DMF), yield (40%), mp 210 °C; ^{1}H NMR (600 MHz, DMSO-d_6): δ 2.51 (s, 3H, SCH_3), 7.9 (s, br, 2H, NH_2), 8.71–8.76 (m, 4H, C_6H_4), 9.1 (s, 1H, NH). ^{13}C NMR: (DMSO) δ 11.5 (SCH_3), 81.1 (C-5), 115.8 (CN), 122.0 (C-4′), 127.1 (C-2′), (C-6′), 128 (C-3′), (C-5′), 148.0 (C-2), 158.0 (C=O), 168.9 (C-4). Anal. Calcd. for $C_{12}H_{10}BrN_5O_3S_2$(416.27): C, 34.62; H, 2.42; Br, 19.20; N, 16.82; S, 15.418. Found: C, 34.60; H, 2.42; Br, 19.20; N, 16.82; S, 15.41.

N-(2-amino-5-cyano-4-(methylthio)-6-oxopyrimidin-1(6H)-yl)-4-chlorobenzenesulfonamide (10b). Buff solid; (DMF), yield (20%), mp 220°C; ^{1}H NMR (600 MHz, DMSO-d_6): δ 2.46 (s, 3H, SCH_3), 7.25 (s, br, 2H, NH_2), 7.31–7.62 (m, 4H, C_6H_4), 7.87 (s, br, 1H, NH). Anal. Calcd. for $C_{12}H_{10}Cl\,N_5O_3S_2$(371.82): C, 38.76; H, 2.71; Cl, 9.53; N, 18.84; S, 17.25. Found: C, 38.74; H, 2.71; Cl, 9.52; N, 18.84; S, 17.25.

General procedure for the synthesis of 11a,b

The mixture of compound **10** (0.01 mol) and hydrazine hydrates (0.02 mol) in (30 mL) DMF was refluxed for 3 h. After allowing the reaction content to be cooled to room temperature, then the crude product was filtered off and recrystallized from the appropriate solvent to afford the desired compound.

4-Bromo-N-(3,6-diamino-4-oxo-1H-pyrazolo[3,4-d]pyrimidin-5(4H)-yl)benzenesulfonamide (11a). Buff solid; (DMF), yield (24.5%), mp > 300°C; IR (KBr) max/cm^{-1} 3432 (NH). ^{1}H NMR (600 MHz, DMSO-d_6): δ 6.2 (s, br, 2H, NH_2), 7.46–7.52 (m, 4H, C_6H_4), 10.19 (s, 1H, NH). Anal. Calcd. for $C_{11}H_{10}BrN_7O_3S$ (400.21): C, 33.01; H, 2.52; Br, 19.97; N, 24.50; S, 8.01. Found: C, 33.01; H, 2.52; Br, 19.95; N, 24.50; S, 8.00.

4-Chloro-N-(3,6-diamino-4-oxo-1H-pyrazolo[3,4-d]pyrimidin-5(4H)-yl)benzenesulfonamide (11b). White solid; (DMF), yield (55%), mp > 300°C; IR (KBr, cm^{-1}) υ 3433 (NH). ^{1}H NMR (600 MHz, DMSO-d_6): δ5.20 (s, br, 2H, NH_2), 6.30 (s, br, 2H, NH_2), 7.46–7.52 (m, 4H, C_6H_4), 8.4 (s, 1H, NH). Anal. Calcd. for $C_{11}H_{10}Cl\,N_7O_3S$ (355.76): C, 37.14; H, 2.83; Cl, 9.97; N, 27.56; S, 9.01. Found: C, 37.12; H, 2.83; Cl, 9.97; N, 27.55; S, 9.00.

Biological evaluation

In vitro *antibacterial screening*

The compounds **5a, 5b, 5c, 6a, 10a, 10b** were evaluated for their *in vitro* antibacterial activity, such as *Bacillus subtilis, Echerichia coli, Pseudomonas aeruginosa, and Staphylococcusaureus* by a modified Kirby-Bauer disc diffusion.[20] The bioassay was performed using Mueller-Hinton agar (Hi-Media) medium that is rigorously tested for composition and pH. 100 µL of the tested bacteria were grown in 10 mL of fresh media until they reached a count of approximately 108 cells/mL.[21] 100 µL of bacterial suspension was spread onto agar plates corresponding to the broth in which they were maintained. Standard discs of **Ampicillin** (antibacterial agent) served as positive controls for antibacterial activity, filter discs impregnated with 10 µL of solvent (DMSO) were used as a negative control. The zone of inhibition (mm) was measured after 24 h incubation at 30°C.[22]

In vitro *antifungal screening*

The compounds **5a, 5b, 5c, 6a, 10a, 10b** were evaluated for their *in vitro* antifungal activity such the fungal strains, *Asperigillusflavus and C. albicans* by a modified Kirby-Bauer disc diffusion.[20] 100 µL of the test fungi were grown in 10 mL of fresh media until they reached a count of approximately 105 cells/mL.[21] 100 µL of fungal suspension was spread onto agar plates corresponding to the broth in which they were maintained. Standard discs of **Amphotericin B** (antifungal agent) served as positive controls for antifungal activity, filter discs impregnated with 10 µL of solvent (DMSO) were used as a negative control. Plates inoculated with filamentous fungi incubated at 30°C for 24–48 hours and, then the diameters of the inhibition zones were measured in millimeters.[23]

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