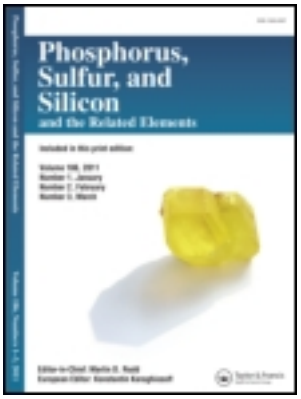

Phosphorus, Sulfur, and Silicon and the Related Elements

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Succinct and Facile Synthesis of Innovative Thiopyrimidines With Antimicrobial and Antitubercular Investigation

Prashant T. Mistry [a], Nimesh R. Kamdar [a], Dhaval D. Haveliwala [a] & Saurabh K. Patel [a]

[a] Department of Chemistry, Veer Narmad South Gujarat University, Surat, 395 007, Gujarat, India

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SUCCINCT AND FACILE SYNTHESIS OF INNOVATIVE THIOPYRIMIDINES WITH ANTIMICROBIAL AND ANTITUBERCULAR INVESTIGATION

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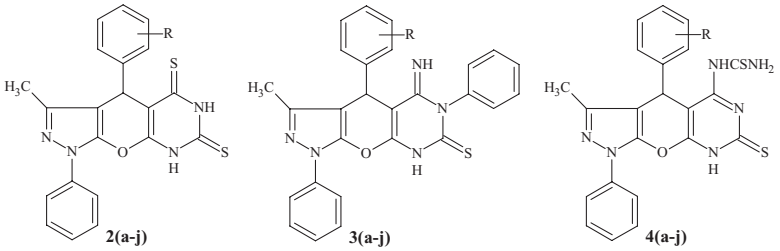
Department of Chemistry, Veer Narmad South Gujarat University, Surat 395 007, Gujarat, India

GRAPHICAL ABSTRACT



Abstract *To develop a series of bioactive heterocycles in minimum number of steps, 3-methyl-4-(substituted phenyl)-1-phenyl-4,8-dihydropyrazolo[4′,3′:5,6]pyrano[2,3-d]pyrimidine-5,7(1H,6H)-dithione* ***2(a–j)****, 4-(4-substituted phenyl)-5-imino-3-methyl-1,6-diphenyl-4,5,6,8-tetrahydropyrazolo[4′,3′:5,6]pyrano[2,3-d]pyrimidine-7(1H)-thione* ***3(a–j),*** *and N-[4-(substituted phenyl)-3-methyl-1-phenyl-7-thioxo-1,4,7,8-hexahydropyrazolo[4′,3′:5,6]pyrano[2,3-d]pyrimidine-5-yl]thiourea* ***4(a–j)*** *have been synthesized from amino nitrile functionality* ***1(a–j).*** *The structures of the compounds were elucidated by IR, ^{1}H NMR, elemental analysis, and some representative ^{13}C NMR and mass spectra. All the title compounds were screened for antimicrobial and antitubercular activities, while some representative compounds were tested for antioxidant activity. Out of synthesized compounds, compounds* ***1j*** *(4-CH_3),* ***2d*** *(4-F),* ***4c*** *(4-OH), and* ***4i*** *(3-Br) exhibited maximum inhibition against Mycobacterium Tuberculosis H_{37}Rv. Compound* ***3c (4-OH)*** *revealed elevated efficacy against all tested bacterial strain, while compounds* ***1i (3-Br)****,* ***2c (4-OH)****, and* ***3h (3-NO_2)*** *were found efficacious against Candida albicans as compared to standard drugs.*

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Address correspondence to Saurabh K. Patel, Department of Chemistry, Veer Narmad South Gujarat University, Surat 395-007, Gujarat, India. E-mail: saurabh@vnsgu.ac.in

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Keywords Thiopyrimidines; pyrimidine dithione; antimicrobial activity; antitubercular activity; antioxidant activity

INTRODUCTION

According to World Health Organization (WHO), the antimicrobial resistance is a serious matter that contributes to health and economic losses throughout the world.[1] The current antimicrobial therapy needs crucial attention and continuing research to develop new class of antimicrobial agents.[2] Sulfur-based compounds constitute a major branch of organic chemistry, among which thiopyrimidine compounds in particular possess significant medicinal importance. Thiopyrimidines are privileged heterocycles due to their synthetic versatility and extensive variety of pharmacological activities such as antimicrobial,[3–5] radioprotective,[6] antiproliferative,[7] antiinflammatory,[8,9] antitumor,[10] antiplatelet,[11] anti-lung cancer,[12] antispasmodic,[13] and molluscicidal activity.[14] Thiopyrimidine derivatives exhibited moderate antiviral activity against hepatitis-A virus and herpes simplex virus type-1.[15] Moreover, there has been considerable interest in the chemistry of 4*H*-pyran, which are a core structure in various pharmaceuticals as it reveals diverse pharmacological significance such as antimicrobial,[16–18] antitubercular,[19,20] anticancer,[21] anticonvulsant,[22] vasorelaxant,[23] antihypertensive,[24] antileishmanial,[25] and antirheumatic[26] activities.

It is expected that the two or more pharmacophores if allied together would create different molecular templates with remarkable biological properties. Despite the enormous pharmacological effects of fused pyrazole and thiopyrimidine derivatives, no systematic study has been so far undertaken to focus the synthesis of a heterocycles incorporating both of these bioactive scaffold with their biological properties. In view of our recent success on pyran-based heterocycles with interesting antimicrobial and antituberculosis activities,[27–30] we designed and synthesized novel thiopyrimidine derivatives using common sulfur reagent and evaluated for their in vitro antimicrobial and antituberculosis activities.

RESULT AND DISCUSSION

Chemistry

The key precursors, *o*-aminonitrile of pyranopyrazole **1(a–j)** were prepared by the reported method of Jin et al. in presence of hexadecyltrimethyl ammonium bromide in aqueous media.[31] Structural elucidation of the synthesized compounds was performed by IR, ^{1}H NMR, elemental analysis, and some representative ^{13}C NMR and mass spectra. In IR spectrum of the starting molecules **1(a–j)**, sharp absorption bands of -NH_2 and -C≡N groups were observed in the region of 3445–3330 cm^{-1} and 2208–2174 cm^{-1}, respectively. The C-O-C ether linkage was found at 1145–1070 cm^{-1}. The ^{1}H NMR spectra exhibited one singlet at 1.90–1.78 δ ppm attributed to the -CH_3 protons of fused pyrazole ring. In ^{1}H NMR spectra, common singlet signals appeared in the region of 5.24–4.68 δ ppm and 7.15–6.92 δ ppm corresponds to -CH and -NH_2 of pyran ring, and multiplet at 7.80–6.90 δ ppm corresponds to aromatic protons.

The entire compounds **2**(**a–j**), **3**(**a–j**), and **4**(**a–j**) were synthesized by the reaction of precursor **1**(**a–j**) with carbon disulphide, phenyl isothiocyanate, and ammonium thiocyanate under different reaction conditions, respectively.[30,32,33] The structure of compounds **2**(**a–j**)

were elucidated by IR spectra which showed 2-NH band in the region of 3417–3398 cm^{-1} and 3338–3322 cm^{-1} and 2>C=S band at around 1338–1306 cm^{-1} and 1276–1256 cm^{-1} with the agreement of two singlets at 8.44–8.41 δ ppm and 8.39–8.35 δ ppm accounted for 2-NH protons in ^{1}H NMR spectra, respectively. This was further substantiated by the ^{13}C NMR spectrum of **2c** (**4-OH**), showed a signals at 174.70 and 197.66 δ ppm due to two >C=S of pyrimidine dithione with the agreement of molecular ion peak at *m/z* 420 which confirmed its molecular weight by mass spectrum (MS). The structure of compounds **3**(**a–j**) were elucidated by IR spectra which showed 2-NH band in the region of 3318–3294 cm^{-1} and 3217–3194 cm^{-1} and >C=S band at around 1255–1236 cm^{-1} with the agreement of two singlets at 10.16–10.12 δ ppm and 8.43–8.39 δ ppm accounted for 2-NH protons in ^{1}H NMR spectra, respectively. This was further substantiated by the ^{13}C NMR spectrum of **3j** (**4-CH_3**), showed a signal at 172.51 δ ppm due to >C=S of thiopyrimidine with the agreement of molecular ion peak at *m/z* 477 which confirmed its molecular weight by MS. The structure of compounds **4**(**a–j**) were elucidated by IR spectra which showed -NH_2 band in the region of 3375–3354 cm^{-1} and 3346–3327 cm^{-1}, 2-NH bands at around 3082–3062 cm^{-1} and 3204–3190 cm^{-1}, and 2 >C=S band at 1358–1336 cm^{-1} and 1247–1225 cm^{-1} with the agreement of singlet at around 5.43–5.40 δ ppm accounted for -NH_2 protons in ^{1}H NMR spectra. This was further substantiated by the ^{13}C NMR spectrum of **4d** (**4-F**), showed a signal at 176.31 and 178.54 δ ppm due to two >C=S of thiopyrimidine with the agreement of molecular ion peak at *m/z* 464 which confirmed its molecular weight by MS. In general, ^{1}H NMR spectra showed singlet at around 4.94–4.75 δ ppm which confirme -CH (methine) proton.

Biological Activity

The newly synthesized compounds were tested for their in vitro antibacterial and antifungal activity (minimum inhibitory concentrations (MICs), μg mL^{-1}) by broth dilution method as described by A. Rattan[34] against two Gram-positive bacteria (*Staphylococcus aureus* MTCC 96 and *Streptococcus pyogenes* MTCC 442), two Gram-negative bacteria (*Escherichia coli* MTCC 443 and *Pseudomonas aeruginosa* MTCC 1688), and three fungi (*Candida albicans* MTCC 227, *Aspergillus niger* MTCC 282, and *Aspergillus clavatus* MTCC 1323) organisms. Ampicillin and griseofulvin were used as standard drugs for antimicrobial activity. For in vitro antitubercular activity, primary screening of the compounds has been conducted at 62.5 μg mL^{-1} for *Mycobacterium Tuberculosis $H_{37}Rv$* strain using Lowenstein–Jensen medium method.[34] The antitubercular activity data were compared with that of standard drug rifampicin. Some randomly selected, compounds were screened for their in vitro antioxidant activity (free radical scavenging activity) at different concentrations (10 μg, 50 μg, and 100 μg) using 1,1-diphenyl-2-picryl hydrazyl method.[35] Butylated hydroxyl anisole (BHA) was used as standard antioxidant agent. The antimicrobial, antitubercular, and antioxidant activity data of the newly synthesized compounds were compared with standard drugs as well as with corresponding precursors **1**(**a–j**). Additional details are provided in the online Supplementary Materials (Tables S1 and S2 and Figure S1).

Antibacterial Activity

Among the synthesized compounds, **1c** (4 OH, pyran with free amino cyano group), **1i** (3-Br), and **1j** (4-CH_3) exhibited MIC of 100 μg mL^{-1}, 100 μg mL^{-1}, and 150 μg mL^{-1} for *S. aureus* as compared to ampicillin 250 μg mL^{-1} and MIC of these compounds was

decreased when converted into **2c** (4-OH, pyrimidine dithione), **2i** (3-Br), **2j** (4-CH_3), **3i** (3-Br, pyrimidine thione), **3j** (4-CH_3), **4c** (4-OH, pyrimidine thione with thiourea linkage), **4i** (3-Br), and **4j** (4-CH_3). MIC remains same when compound **1c** (4-OH) converted into **3c** (4-OH). The compounds **1i** (3-Br, pyran with free amino cyano group) and **3c** (4-OH, pyrimidine thione) demonstrated good MIC with 100 μg mL^{-1} for *S. pyogenes* as compared to ampicillin but compound **1i** (3-Br) converted to compounds **2i** (3-Br, pyrimidine dithione), **3i** (3-Br, pyrimidine thione), and **4i** (3-Br, pyrimidine thione with thiourea linkage), MIC was slightly decreased. Compound **1c** (4-OH) exhibited MIC of 200 μg mL^{-1} for *S. pyogenes* when converted to **3c** (4-OH, pyrimidine thione), MIC was significantly improved. The compounds **1j** (4-CH_3) and **3c** (4-OH, pyrimidine thione) showed maximum MIC with 62.5 μg mL^{-1} for *E. coli* as compared to standard drug but compound **1j** (4-CH_3) converted to compounds **2j**, **3j**, and **4j** MIC were slightly decreased. The compounds **1h** (3-NO_2, pyran with free amino cyano group), **1j** (4-CH_3, pyran with free amino cyano group), **2d** (4-F, pyrimidine dithione), **3c** (4-OH, pyrimidine thione), and **4i** (3-Br, pyrimidine thione with thiourea linkage) showed equal MIC of 100 μg mL^{-1} for *P. aeruginosa* as compared to standard drug ampicillin but compounds **1h** (3-NO_2) and **1j** converted to **2h** (3-NO_2), **2j** (4-CH_3), **3h** (3-NO_2), **3j** (4-CH_3), **4h** (3-NO_2), and **4j** (4-CH_3), MIC of these compound were slightly reduced. In case of *P. aeruginosa*, MIC of compounds **1c** (4-OH), **1d** (4-F), and **1i** (3-Br) were found to be equal or enhanced when converted to **2c** (4-OH), **2d** (4-F), **2i** (3-Br), **3c** (4-OH), **3d** (4-F), **3i** (3-Br), **4d** (4-F), and **4i** (3-Br), while the remaining compounds showed moderate to poor activity than standard drugs (Table S1).

Antifungal Activity

The results revealed that compounds **1b** (4-OCH_3, pyran with free amino cyano group), **1d** (4-F), and **1i** (3-Br) demonstrated superior antifungal activity for *C. albicans* as compared to greseofulvin. MIC were slightly reduced when converted to **2b** (4-OCH_3, pyrimidine dithione), **2d** (4-F), **2i** (3-Br), **3b** (4-OCH_3, pyrimidine thione), **3d** (4-F), **3i** (3-Br), **4b** (4-OCH_3, pyrimidine thione with thiourea linkage), **4d** (4-F), and **4i** (3-Br). MIC of compounds **1a** (-H), **1c** (4-OH), **1e** (2-Cl), and **1h** (3-NO_2), were enhanced when converted to **2c** (4-OH), **3e** (2-Cl), **3h** (3-NO_2), and **4a** (-H). All the remaining compounds showed, moderate to poor antifungal activity for all three fungal species compared to that of standards (Table S1).

Antitubercular Activity

The synthesized compounds were tested against *M. Tuberculosis $H_{37}Rv$*. Among the synthesized compounds, **1j** (4-CH_3, pyran with free amino cyano group) was revealed highest inhibition for *M. Tuberculosis $H_{37}Rv$*. When compound **1j** converted to compounds **2j**, **3j**, and **4j**, activity were slightly decreased. Inhibition activity was improved when compounds **1b** (4-OCH_3), **1c** (4-OH), and **1i** (3-Br) were converted to **2b** (pyrimidine dithione), **2c** (4-OH), **2i** (3-Br), **3b** (4-OCH_3, pyrimidine thione), **3c** (4-OH), **3i** (3-Br), **4b** (4-OCH_3, pyrimidine thione with thiourea linkage), **4c** (4-OH), and **4i** (3-Br), while all the remaining compounds revealed, moderate to poor efficacy.

Antioxidant Activity

One of the compound, **2g** (4-Cl) revealed good antioxidant activity of 42.06% and 68.25% at 50 μg and 100 μg concentrations as compared to standard BHA (39.80% and 59.16%), respectively, while the compound **4g** (4-Cl) was found to be inactive at all concentrations. Pyrimidine dithione nucleus showed comparatively better activity than the thiopyrimidine derivative (Table S2).

CONCLUSION

Thiopyrimidines have been successfully synthesized and evaluated for their antimicrobial and antitubercular activities, while some representative compounds have been tested for antioxidant activity. It is obvious from the biological screening result that the several thiopyrimidines were interestingly found to be active compared to their corresponding precursors. Among the synthesized compounds, compound **3c** (4-OH) revealed elevated efficacy against all tested bacterial strain, while compounds **1i** (3-Br), **2c** (4-OH), and **3h** (3-NO_2) were found efficacious against *C. albicans* as compared to standard drugs. Antitubercular activity of compounds **1j** (4-CH_3), **2d** (4-F), **4c** (4-OH), and **4i** (3-Br) exhibited remarkable inhibition against *M. Tuberculosis* $H_{37}Rv$ compared to that of rifampicin. Although a generalization could not be made, the screened compound **2g** (4-Cl) showed very good antioxidant property. From the present study, it is concluded that the introduction of thione (>C=S) group in pyrimidine nucleus play vital role in enhancing the antimicrobial activity. Some of the synthesized compounds may be helpful for the development of novel alternative thearapeutic agents and open the possibility of finding new clinically effective rich source of bioactive candidates.

EXPERIMENTAL

Melting points were taken in open capillary tubes and are uncorrected. The progress of the reactions were monitored by thin layer chromatography using silica gel as adsorbent [Mobile phase: toluene:ethyl acetate (7.5:2.5)] and visualization was accomplished by Ultra violet light or iodine vapor. IR spectra were recorded on Thermo Scientific Nicolec iS 10 and Shimadzu spectrophotometer using KBr pallets. The ^{1}H NMR and representative ^{13}C NMR spectra were recorded on a Bruker Avance II 400 spectrometer using tetramethylsilane as the internal standard in $CDCl_3$ or dimethyl sulfoxide as solvent. Elemental analysis was carried out on Carlo Erba 1108 analyzer. Mass spectra of some representative compounds were recorded on Waters Q-Tof Micro (TOF MS ES+) mass spectrometer.

General Preparation of 3-Methyl-4-(substituted phenyl)-1-phenyl-4,8-dihydropyrazolo[4′,3′:5,6]pyrano[2,3-*d*]pyrimidine-5,7(1*H*,6*H*)-dithione 2(a–j)

A mixture of 6-amino-4-(substituted phenyl)-5-cyano-3-methyl-1-phenyl-1,4-dihydropyrano[2,3-*c*]pyrazole **1(a–j)** (2.0 mmol) and carbon disulphide (3.0 mmol) in pyridine (10 mL) was refluxed for 7–8 h. After completion of reaction, the reaction mixture was left to cool to room temperature, poured into crushed ice, and neutralized with dilute hydrochloric acid (1:1). The crude product was separated by filtration, washed with

water, dried, and recrystallized from methanol to give 3-methyl-4-(substituted phenyl)-1-phenyl-4,8-dihydropyrazolo[4′,3′:5,6]pyrano[2,3-*d*]pyrimidine-5,7(1*H*,6*H*)-dithione **2(a–j)**.

3-Methyl-1,4-diphenyl-4,8-dihydropyrazolo[4′,3′:5,6]pyrano[2,3-*d*]-pyrimidine-5,7(1*H*,6*H*) dithione (2a). Reddish yellow; 59%; mp: 207 °C–209 °C; (methanol) IR (KBr) υ (cm^{-1}): 3417, 3322 (2-NH), 3078, 2969, 2852 (C-H str.), 1320, 1266 (2>C=S), 1167, 1047 (C-O-C); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.43 (s, 1H, -NH), 8.37 (s, 1H, -NH), 7.93–6.96 (m, 10H, Ar-H), 4.82 (s, 1H, -CH), 2.24 (s, 3H, -CH_3); Anal. Calcd for $C_{21}H_{16}N_4OS_2$: C 62.35, H 3.99, N 13.85; Found: C 62.31, H 4.03, N 13.88.

3-Methyl-4-(4-methoxyphenyl)-1-phenyl-4,8-dihydropyrazolo[4′,3′:5,6]-pyrano[2,3-*d*]pyrimidine-5,7(1*H*,6*H*)-dithione (2b). Turmeric yellow; 66%; mp: 252 °C–255 °C; (methanol) IR (KBr) υ (cm^{-1}): 3410, 3330 (2-NH), 3085, 2962, 2845 (C-H str.), 1315, 1262 (2>C=S), 1180, 1035 (C-O-C); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.43 (s, 1H, -NH), 8.35 (s, 1H, -NH), 7.91–6.98 (m, 9H, Ar-H), 4.77 (s, 1H, -CH), 3.69 (s, 3H, -OCH_3), 2.20 (s, 3H, -CH_3); Anal. Calcd for $C_{22}H_{18}N_4O_2S_2$: C, 60.81; H, 4.18; N, 12.89. Found: C, 60.85; H, 4.20; N, 12.84.

3-Methyl-4-(4-hydroxyphenyl)-1-phenyl-4,8-dihydropyrazolo[4′,3′:5,6]-pyrano[2,3-*d*]pyrimidine-5,7(1*H*,6*H*)-dithione (2c). Turmeric yellow; 53%; mp: >280 °C; (methanol) IR (KBr) υ (cm^{-1}): 3398, 3335 (2-NH), 3266 (-OH), 3076, 2968, 2838 (C-H str.), 1322, 1276 (2>C=S), 1187, 1024 (C-O-C); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.43 (s, 1H, -NH), 8.35 (s, 1H, -NH), 7.92–6.97 (m, 9H, Ar-H), 5.21 (s, 1H, -OH), 4.78 (s, 1H, -CH), 2.23 (s, 3H, -CH_3); ^{13}C NMR (400 MHz, $CDCl_3$) δ (ppm): 15.2 (CH_3), 37.0 (CH), 100.9 (C), 111.1 (C), 118.2 (CH), 121.8 (CH), 124.8 (CH), 128.4 (CH), 129.4 (CH), 138.0 (C), 142.3 (C), 143.6 (C), 151.5 (C-CH_3), 154.1 (C-OH), 166.5 (C), 174.7, 197.7 (2>C=S); MS (*m/z*): 420 (M^+); Anal. Calcd for $C_{21}H_{16}N_4O_2S_2$: C, 59.98; H, 3.84; N, 13.32; Found: C, 59.97; H, 3.86; N, 13.33.

3-Methyl-1–4-(4-fluorophenyl)-phenyl-4,8-dihydropyrazolo[4′,3′:5,6]-pyrano[2,3-*d*]pyrimidine-5,7(1*H*,6*H*)-dithione (2d). Greenish yellow; 61%; mp: 269 °C–273 °C; (methanol) IR (KBr) υ (cm^{-1}): 3412, 3334 (2-NH), 3080, 2956, 2852 (C-H str.), 1321, 1265 (2>C=S), 1185, 1042 (C-O-C), 752 (C-F); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.44 (s, 1H, -NH), 8.37 (s, 1H, -NH), 7.90–7.05 (m, 9H, Ar-H), 4.77 (s, 1H, -CH), 2.23 (s, 3H, -CH_3); Anal. Calcd for $C_{21}H_{15}N_4OFS_2$: C, 59.70; H, 3.58; N, 13.26; Found: C, 59.72; H, 3.54; N, 13.25.

3-Methyl-4-(2-chlorophenyl)-1-phenyl-4,8-dihydropyrazolo[4′,3′:5,6]-pyrano[2,3-*d*]pyrimidine-5,7(1*H*,6*H*)-dithione (2e). Turmeric yellow; 55%; mp: 239 °C–242 °C; (methanol) IR (KBr) υ (cm^{-1}): 3402, 3324 (2-NH), 3076, 2968, 2856 (C-H str.), 1330, 1256 (2>C=S), 1196, 1045 (C-O-C), 756 (C-Cl); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.43 (s, 1H, -NH), 8.38 (s, 1H, -NH), 7.92–7.04 (m, 9H, Ar-H), 4.79 (s, 1H, -CH), 2.21 (s, 3H, -CH_3); Anal. Calcd for $C_{21}H_{15}N_4OClS_2$: C, 57.46; H, 3.44; N, 12.76; Found: C, 57.42; H, 3.48; N, 12.75.

3-Methyl-4-(3-chlorophenyl)-1-phenyl-4,8-dihydropyrazolo[4′,3′:5,6]-pyrano[2,3-*d*]pyrimidine-5,7(1*H*,6*H*)-dithione (2f). Light brown; 62%; mp: 260 °C–264 °C; (methanol) IR (KBr) υ (cm^{-1}): 3416, 3332 (2-NH), 3080, 2962, 2854 (C-H str.), 1338, 1260 (2>C=S), 1186, 1035 (C-O-C), 752 (C-Cl); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.42 (s, 1H, -NH), 8.35 (s, 1H, -NH), 7.90–7.00 (m, 9H, Ar-H), 4.75 (s, 1H, -CH), 2.19 (s, 3H, -CH_3); Anal. Calcd for $C_{21}H_{15}N_4OClS_2$: C, 57.46; H, 3.44; N, 12.76; Found: C, 57.43; H, 3.49; N, 12.78.

3-Methyl-4-(4-chlorophenyl)-1-phenyl-4,8-dihydropyrazolo[4′,3′:5,6]-pyrano[2,3-*d*]pyrimidine-5,7(1*H*,6*H*)-dithione (2g). Turmeric yellow; 65%; mp: 249 °C–251 °C; (methanol) IR (KBr) υ (cm^{-1}): 3414, 3338 (2-NH), 3094, 2954, 2842 (C-H str.), 1306, 1267 (2>C=S), 1177, 1028 (C-O-C), 755 (C-Cl); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.43 (s, 1H, -NH), 8.36 (s, 1H, -NH), 7.95–6.98 (m, 9H, Ar-H), 4.77 (s, 1H, -CH), 2.23 (s, 3H, $-CH_3$); Anal. Calcd for $C_{21}H_{15}N_4OClS_2$: C, 57.46; H, 3.44; N, 12.76; Found: C, 57.41; H, 3.47; N, 12.77.

3-Methyl-4-(3-nitrophenyl)-1-phenyl-4,8-dihydropyrazolo[4′,3′:5,6]-pyrano[2,3-*d*]pyrimidine-5,7(1*H*,6*H*)-dithione (2h). Dark brown; 53%; mp: 273 °C–277 °C; (methanol) IR (KBr) υ (cm^{-1}): 3398, 3322 (2-NH), 3076, 2968, 2840 (C-H str.), 1540, 1363 ($-NO_2$ asym, sym), 1327, 1258 (2>C=S), 1188, 1034 (C-O-C); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.41 (s, 1H, -NH), 8.35 (s, 1H, -NH), 7.92–6.97 (m, 9H, Ar-H), 4.78 (s, 1H, -CH), 2.21 (s, 3H, $-CH_3$); Anal. Calcd for $C_{21}H_{15}N_5O_3S_2$: C, 56.11; H, 3.36; N, 15.58; Found: C, 56.15; H, 3.364; N, 15.57.

3-Methyl-4-(3-bromophenyl)-1-phenyl-4,8-dihydropyrazolo[4′,3′:5,6]-pyrano[2,3-*d*]pyrimidine-5,7(1*H*,6*H*)-dithione (2i). Orange; 58%; mp: >280 °C; (methanol) IR (KBr) υ (cm^{-1}): 3408, 3335 (2-NH), 3086, 2959, 2852 (C-H str.), 1315, 1266 (2>C=S), 1181, 1035 (C-O-C), 755 (C-Br); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.43 (s, 1H, -NH), 8.35 (s, 1H, -NH), 7.95–7.06 (m, 9H, Ar-H), 4.78 (s, 1H, -CH), 2.23 (s, 3H, $-CH_3$); Anal. Calcd for $C_{21}H_{15}N_4OBrS_2$: C, 52.18; H, 3.13; N, 11.59; Found: C, 52.15; H, 3.14; N, 11.57.

3-Methyl-4-(4-methylphenyl)-1-phenyl-4,8-dihydropyrazolo[4′,3′:5,6]-pyrano[2,3-*d*]pyrimidine-5,7(1*H*,6*H*)-dithione (2j). Dark yellow; 54%; mp: 254 °C–258 °C; (methanol) IR (KBr) υ (cm^{-1}): 3416, 3329 (2-NH), 3090, 2963, 2847 (C-H str.), 1309, 1265 (2>C=S), 1177, 1045 (C-O-C); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.41 (s, 1H, -NH), 8.39 (s, 1H, -NH), 7.94–6.97 (m, 9H, Ar-H), 4.76 (s, 1H, -CH), 2.21 (s, 3H, $-CH_3$), 2.00 (s, 3H, $-CH_3$); Anal. Calcd for $C_{22}H_{18}N_4OS_2$: C, 63.13; H, 4.33; N, 13.39; Found: C, 63.15; H, 4.35; N, 13.41.

General Preparation of 4-(4-Substituted phenyl)-5-imino-3-methyl-1,6-diphenyl-4,5,6,8-tetrahydropyrazolo[4′,3′:5,6]pyrano[2,3-*d*] pyrimidine-7(1*H*)-thione 3(a–j)

A mixture of 6-amino-4-(substituted phenyl)-5-cyano-3-methyl-1-phenyl-1,4-dihydropyrano[2,3-*c*]pyrazole **1(a–j)** (2.0 mmol) and phenyl isothiocyanate (2.0 mmol) in pyridine (10 mL) was refluxed for 14–16 h. After completion of reaction, the reaction mixture was left to cool to room temperature, poured into crushed ice and neutralized with dilute hydrochloric acid (1:1). The crude product was separated by filtration, washed with water, dried, and recrystallized from ethanol to give 4-(4-substituted phenyl)-5-imino-3-methyl-1,6-diphenyl-4,5,6,8-tetrahydropyrazolo[4',3':5,6]pyrano[2,3-*d*]pyrimidine-7(1*H*)-thione **3(a-j)**.

5-Imino-3-Methyl-1,4,6-triphenyl-4,5,6,8-tetrahydropyrazolo[4′,3′:5,6]-pyrano[2,3-*d*]pyrimidine-7(1*H*)-thione (3a). Beige; 66%; mp: 227 °C–230 °C; (ethanol) IR (KBr) υ (cm^{-1}): 3310, 3205 (2-NH), 3070, 2995, 2935 (C-H str.), 1655 (-C=N), 1245 (>C=S), 1155, 1062 (C-O-C); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 10.14 (s, 1H, -NH), 8.41 (s, 1H, -NH), 7.77–7.15 (m, 15H, Ar-H), 4.90 (s, 1H, -CH), 2.36 (s, 3H, $-CH_3$); Anal. Calcd for $C_{27}H_{21}N_5OS$: C 69.96, H 4.57, N 15.11; Found: C 69.99, H 4.55, N 15.07.

4-(4-Methoxyphenyl)-5-imino-3-methyl-1,6-diphenyl-4,5,6,8-tetrahydropyrazolo[4′,3′:5,6]pyrano[2,3-*d*]pyrimidine-7(1*H*)-thione (3b). Light yellow; 51%; mp: 241 °C–244 °C; (ethanol) IR (KBr) υ (cm^{-1}): 3318, 3196 (2-NH), 3061, 3008, 2922 (C-H str.), 1666 (-C=N), 1236 (>C=S), 1222, 1029 (-OCH_3), 1167, 1051 (C-O-C); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 10.12 (s, 1H, -NH), 8.42 (s, 1H, -NH), 7.75–7.19 (m, 14H, Ar-H), 4.88 (s, 1H, -CH), 3.67 (s, 3H, -OCH_3), 2.37 (s, 3H, -CH_3); Anal. Calcd for $C_{28}H_{23}N_5O_2S$: C 68.13, H 4.70, N 14.19; Found: C 68.09, H 4.66, N 14.23.

4-(4-Hydroxyphenyl)-5-imino-3-methyl-1,6-diphenyl-4,5,6,8-tetrahydropyrazolo[4′,3′:5,6]pyrano[2,3-*d*]pyrimidine-7(1*H*)-thione (3c). Dark brown; 69%; mp: >280 °C; (ethanol) IR (KBr) υ (cm^{-1}): 3302, 3217 (2-NH), 3221 (-OH), 3079, 2988, 2941 (C-H str.), 1648 (-C=N), 1253 (>C=S), 1146, 1067 (C-O-C); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 10.15 (s, 1H, -NH), 8.40 (s, 1H, -NH), 7.76–7.13 (m, 14H, Ar-H), 5.25 (s, 1H, -OH), 4.91 (s, 1H, -CH), 2.34 (s, 3H, -CH_3); ^{13}C NMR (400MHz, $CDCl_3$) δ (ppm): 15.3 (CH_3), 36.2 (CH), 92.0 (C), 98.4 (C), 117.1 (CH), 122.5 (CH), 123.8 (CH), 126.1 (CH), 127.3 (CH), 128.8 (CH), 129.6 (CH), 139.0 (C), 140.8 (C), 143.4 (C), 147.7 (C-CH_3), 148.9 (C), 151.9 (C), 155.0 (C-OH), 172.2 (>C=S); Anal. Calcd for $C_{27}H_{21}N_5O_2S$: C, 67.62; H, 4.41; N, 14.60; Found: C, 67.64; H, 4.43; N, 14.64.

4-(4-Fluorophenyl)-5-imino-3-methyl-1,6-diphenyl-4,5,6,8-tetrahydro-pyrazolo[4′,3′:5,6]pyrano[2,3-*d*]pyrimidine-7(1*H*)-thione (3d). Cream; 71%; mp: 218 °C–220 °C; (ethanol) IR (KBr) υ (cm^{-1}): 3312, 3211 (2-NH), 3064, 2998, 2934 (C-H str.), 1659 (-C=N), 1240 (>C=S), 1154, 1057 (C-O-C), 746 (C-F); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 10.14 (s, 1H, -NH), 8.42 (s, 1H, -NH), 7.71–7.20 (m, 14H, Ar-H), 4.94 (s, 1H, -CH), 2.33 (s, 3H, -CH_3); Anal. Calcd for $C_{27}H_{20}N_5OFS$: C, 67.34; H, 4.19; N, 14.54; Found: C, 67.38; H, 4.22; N, 14.58.

4-(2-Chlorophenyl)-5-imino-3-methyl-1,6-diphenyl-4,5,6,8-tetrahydro-pyrazolo[4′,3′:5,6]pyrano[2,3-*d*]pyrimidine-7(1*H*)-thione (3e). Light brown; 54%; mp: 159 °C–162 °C; (ethanol) IR (KBr) υ (cm^{-1}): 3299, 3214 (2-NH), 3070, 2990, 2930 (C-H str.), 1651 (-C=N), 1250 (>C=S), 1159, 1061 (C-O-C), 757 (C-Cl); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 10.16 (s, 1H, -NH), 8.40 (s, 1H, -NH), 7.75–7.19 (m, 14H, Ar-H), 4.91 (s, 1H, -CH), 2.35 (s, 3H, -CH_3); Anal. Calcd for $C_{27}H_{20}N_5OClS$: C, 65.12; H, 4.05; N, 14.06; Found: C, 65.10; H, 4.02; N, 14.03.

4-(3-Chlorophenyl)-5-imino-3-methyl-1,6-diphenyl-4,5,6,8-tetrahydro-pyrazolo[4′,3′:5,6]pyrano[2,3-*d*]pyrimidine-7(1*H*)-thione (3f). Light brown; 64%; mp: 207 °C–210 °C; (ethanol) IR (KBr) υ (cm^{-1}): 3318, 3202 (2-NH), 3080, 3010, 2927 (C-H str.), 1656 (-C=N), 1244 (>C=S), 1148, 1072 (C-O-C), 751 (C-Cl); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 10.13 (s, 1H, -NH), 8.42 (s, 1H, -NH), 7.78–7.16 (m, 14H, Ar-H), 4.89 (s, 1H, -CH), 2.35 (s, 3H, -CH_3); Anal. Calcd for $C_{27}H_{20}N_5OClS$: C, 65.12; H, 4.05; N, 14.06; Found: C, 65.10; H, 4.07; N, 14.03.

4-(4-Chlorophenyl)-5-imino-3-methyl-1,6-diphenyl-4,5,6,8-tetrahydro-pyrazolo[4′,3′:5,6]pyrano[2,3-*d*]pyrimidine-7(1*H*)-thione (3g). Beige; 57%; mp: 234 °C–237 °C; (ethanol) IR (KBr) υ (cm^{-1}): 3305, 3194 (2-NH), 3067, 2989, 2944 (C-H str.), 1661 (-C=N), 1239 (>C=S), 1151, 1058 (C-O-C), 756 (C-Cl); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 10.15 (s, 1H, -NH), 8.43 (s, 1H, -NH), 7.77–7.11 (m, 14H, Ar-H), 4.91 (s, 1H, -CH), 2.34 (s, 3H, -CH_3); Anal. Calcd for $C_{27}H_{20}N_5OClS$: C, 65.12; H, 4.05; N, 14.06; Found: C, 65.15; H, 4.03; N, 14.08.

4-(3-Nitrophenyl)-5-imino-3-methyl-1,6-diphenyl-4,5,6,8-tetrahydro-pyrazolo[4′,3′:5,6]pyrano[2,3-*d*]pyrimidine-7(1*H*)-thione (3h). Turmeric yellow; 53%; mp: 209 °C–213 °C; (ethanol) IR (KBr) υ (cm^{-1}): 3294, 3212 (2-NH), 3070,

2996, 2930 (C-H str.), 1648 (-C=N), 1552, 1350 (-NO_2 asym, sym), 1255 (>C=S), 1160, 1062 (C-O-C); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 10.13 (s, 1H, -NH), 8.39 (s, 1H, -NH), 7.79–7.16 (m, 14H, Ar-H), 4.92 (s, 1H, -CH), 2.35 (s, 3H, -CH_3); Anal. Calcd for $C_{27}H_{20}N_6O_3S$: C, 63.77; H, 3.96; N, 16.53; Found: C, 63.79; H, 3.93; N, 16.55.

4-(3-Bromophenyl)-5-imino-3-methyl-1,6-diphenyl-4,5,6,8-tetrahydro-pyrazolo[4′,3′:5,6]pyrano[2,3-*d*]pyrimidine-7(1*H*)-thione (3i). Black; 61%; mp: >280 °C; (ethanol) IR (KBr) υ (cm^{-1}): 3318, 3209 (2-NH), 3082, 3008, 2942 (C-H str.), 1654 (-C=N), 1236 (>C=S), 1154, 1068 (C-O-C), 748 (C-Br); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 10.14 (s, 1H, -NH), 8.40 (s, 1H, -NH), 7.75–7.18 (m, 14H, Ar-H), 4.90 (s, 1H, -CH), 2.35 (s, 3H, -CH_3); Anal. Calcd for $C_{27}H_{20}N_5OBrS$: C, 59.78; H, 3.72; N, 12.91; Found: C, 59.75; H, 3.70; N, 12.95.

4-(4-Methylphenyl)-5-imino-3-methyl-1,6-diphenyl-4,5,6,8-tetrahydro-pyrazolo[4′,3′:5,6]pyrano[2,3-*d*]pyrimidine-7(1*H*)-thione (3j). Cream; 74%; mp: 259 °C–262 °C; (ethanol) IR (KBr) υ (cm^{-1}): 3309, 3217 (2-NH), 3065, 2990, 2928 (C-H str.), 1662 (-C=N), 1248 (>C=S), 1164, 1055 (C-O-C); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 10.13 (s, 1H, -NH), 8.39 (s, 1H, -NH), 7.76–7.15 (m, 14H, Ar-H), 4.92 (s, 1H, -CH), 2.37 (s, 3H, -CH_3), 1.96 (s, 3H, -CH_3); ^{13}C NMR (400 MHz, $CDCl_3$) δ (ppm): 15.2 (CH_3), 23.1 (CH_3), 37.0 (CH), 93.0 (C), 98.3 (C), 122.2 (CH), 123.9 (CH), 125.9 (CH), 127.6 (CH), 128.3 (CH), 129.2 (CH), 130.7 (CH), 136.2 (C-CH_3), 139.5 (C), 142.5 (C), 143.8 (C), 145.1 (C), 148.4 (C-CH_3), 149.4 (C), 152.3 (C), 172.5 (>C=S); MS (*m/z*): 477 (M^+); Anal. Calcd for $C_{28}H_{23}N_5OS$: C, 70.42; H, 4.85; N, 14.66; Found: C, 70.39; H, 4.87; N, 14.68.

General Preparation of *N*-[4-(Substituted phenyl)-3-methyl-1-phenyl-7-thioxo-1,4,7,8-hexahydropyrazolo[4′,3′:5,6]pyrano[2,3-*d*] pyrimidine-5-yl]thiourea 4(a–j)

A mixture of 6-amino-4-(substituted phenyl)-5-cyano-3-methyl-1-phenyl-1,4-dihydropyrano[2,3-*c*]pyrazole **1(a–j)** (2.0 mmol) and ammonium thiocyanate (4.0 mmol) in dimethyl formamide (10 mL) was refluxed for 10–11 h. After completion of reaction, the reaction mixture was left to cool to room temperature and poured into crushed ice. The crude product was separated by filtration, washed with water, dried, and recrystallized from ethanol to give *N*-[4-(substituted phenyl)-3-methyl-1-phenyl-7-thioxo-1,4,7,8-hexahydropyrazolo[4',3':5,6]pyrano[2,3-*d*]pyrimidine-5-yl]thiourea **4(a–j)**.

***N*-(3-Methyl-1,4-diphenyl-7-thioxo-1,4,7,8-tetrahydropyrazolo[4′,3′:5,6]-pyrano[2,3-*d*]pyrimidine-5-yl)thiourea (4a).** Light brown; 46%; mp: >280 °C; (ethanol) IR (KBr) υ (cm^{-1}): 3365, 3335 (-NH_2), 3062 (2-NH), 2935, 2880 (C-H str.), 1651 (-C=N), 1348, 1238 (2>C=S), 1141, 1062 (C-O-C); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.89 (s, 2H, 2-NH), 7.82–7.15 (m, 10H, Ar-H), 5.43 (s, 2H, -NH_2), 4.91 (s, 1H, -CH), 2.35 (s, 3H, -CH_3); Anal. Calcd for $C_{22}H_{18}N_6OS_2$: C 59.17, H 4.06, N 18.82; Found: C 59.20, H 4.10, N 18.79.

***N*-[4-(4-Methoxyphenyl)-3-methyl-1-phenyl-7-thioxo-1,4,7,8-tetrahydro-pyrazolo[4′,3′:5,6]pyrano[2,3-*d*]pyrimidine-5-yl]thiourea (4b).** Beige; 53%; mp: 262 °C–266 °C; (ethanol) IR (KBr) υ (cm^{-1}): 3354, 3338 (-NH_2), 3082, 3195 (2-NH), 2944, 2872 (C-H str.), 1658 (-C=N), 1336, 1225 (2>C=S), 1230, 1038 (-OCH_3), 1152, 1055 (C-O-C); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.91 (s, 2H, 2-NH), 7.80–7.19 (m, 9H, Ar-H), 5.43 (s, 2H, -NH_2), 4.92 (s, 1H, -CH), 3.62 (s, 3H, -OCH_3), 2.35 (s, 3H, -CH_3);

Anal. Calcd for $C_{23}H_{20}N_6O_2S_2$: C 57.97, H 4.23, N 17.63; Found: C 58.02, H 4.25, N 17.60.

***N*-[4-(4-Hydroxyphenyl)-3-methyl-1-phenyl-7-thioxo-1,4,7,8-tetrahydropyrazolo[4′,3′:5,6]pyrano[2,3-*d*]pyrimidine-5-yl]thiourea (4c).** Reddish brown; 57%; mp: >280 °C; (ethanol) IR (KBr) υ (cm^{-1}): 3359, 3342 (-NH_2), 3235 (-OH), 3076, 3190, (2-NH), 2932, 2884 (C-H str.), 1650 (-C=N), 1352, 1240 (2>C=S), 1145, 1066 (C-O-C); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.90 (s, 2H, 2-NH), 7.78–7.16 (m, 9H, Ar-H), 5.40 (s, 2H, -NH_2), 5.22 (s, 1H, -OH), 4.89 (s, 1H, -CH), 2.38 (s, 3H, -CH_3); ^{13}C NMR (400 MHz, $CDCl_3$) δ (ppm): 15.4 (CH_3), 37.1 (CH), 92.0 (C), 98.4 (C), 116.3 (CH), 122.1 (CH), 123.7 (CH), 128.6 (CH), 129.4 (CH), 139.3 (C), 142.1 (C), 143.9 (C), 148.1 (C-CH_3), 152.0 (C), 155.1 (C-OH), 157.1 (C-$NHCSNH_2$), 176.4, 179.0 (2>C=S); Anal. Calcd for $C_{22}H_{18}N_6O_2S_2$: C, 57.13; H, 3.92; N, 18.17; Found: C, 57.15; H, 3.96; N, 18.15.

***N*-[4-(4-Fluorophenyl)-3-methyl-1-phenyl-7-thioxo-1,4,7,8-tetrahydro-pyrazolo[4′,3′:5,6]pyrano[2,3-*d*]pyrimidine-5-yl]thiourea (4d).** Cream; 51%; mp: 271 °C–274 °C; (ethanol) IR (KBr) υ (cm^{-1}): 3368, 3332 (-NH_2), 3072, 3204 (2-NH), 2930, 2878 (C-H str.), 1648 (-C=N), 1344, 1232 (2>C=S), 1138, 1059 (C-O-C), 752 (C-F); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.92 (s, 2H, 2-NH), 7.85–7.20 (m, 9H, Ar-H), 5.40 (s, 2H, -NH_2), 4.93 (s, 1H, -CH), 2.37 (s, 3H, -CH_3); ^{13}C NMR (400 MHz, $CDCl_3$) δ (ppm): 15.5 (CH_3), 37.1 (CH), 92.1 (C), 98.5 (C), 117.0 (CH), 122.5 (CH), 125.6 (CH), 128.6 (CH), 129.3 (CH), 139.2 (C), 143.5 (C), 144.7 (C), 148.2 (C-CH_3), 152.1 (C), 156.8 (C-$NHCSNH_2$), 158.9 (C-F), 176.3, 178.5 (2>C=S); MS (*m/z*): 464 (M^+); Anal. Calcd for $C_{22}H_{17}N_6OFS_2$: C, 56.88; H, 3.69; N, 18.09; Found: C, 56.85; H, 3.67; N, 18.12.

***N*-[4-(2-Chlorophenyl)-3-methyl-1-phenyl-7-thioxo-1,4,7,8-tetrahydro-pyrazolo[4′,3′:5,6]pyrano[2,3-*d*]pyrimidine-5-yl]thiourea (4e).** Greenish white; 49%; mp: >280 °C; (ethanol) IR (KBr) υ (cm^{-1}): 3358, 3346 (-NH_2), 3080, 3196 (2-NH), 2941, 2886 (C-H str.), 1656 (-C=N), 1358, 1244 (2>C=S), 1150, 1072 (C-O-C), 754 (C-Cl); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.91 (s, 2H, 2-NH), 7.77–7.14 (m, 9H, Ar-H), 5.43 (s, 2H, -NH_2), 4.89 (s, 1H, -CH), 2.37 (s, 3H, -CH_3); Anal. Calcd for $C_{22}H_{17}N_6OClS_2$: C, 54.94; H, 3.56; N, 17.47; Found: C, 54.98; H, 3.61; N, 17.51.

***N*-[4-(3-Chlorophenyl)-3-methyl-1-phenyl-7-thioxo-1,4,7,8-tetrahydro-pyrazolo[4′,3′:5,6]pyrano[2,3-*d*]pyrimidine-5-yl]thiourea (4f).** Light brown; 55%; mp: >280 °C; (ethanol) IR (KBr) υ (cm^{-1}): 3365, 3342 (-NH_2), 3069, 3192 (2-NH), 2934, 2878 (C-H str.), 1651 (-C=N), 1350, 1237 (2>C=S), 1135, 1064 (C-O-C), 758 (C-Cl); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.92 (s, 2H, 2-NH), 7.82–7.15 (m, 9H, Ar-H), 5.40 (s, 2H, -NH_2), 4.91 (s, 1H, -CH), 2.37 (s, 3H, -CH_3); Anal. Calcd for $C_{22}H_{17}N_6OClS_2$: C, 54.94; H, 3.56; N, 17.47; Found: C, 54.98; H, 3.59; N, 17.50.

***N*-[4-(4-Chlorophenyl)-3-methyl-1-phenyl-7-thioxo-1,4,7,8-tetrahydro-pyrazolo[4′,3′:5,6]pyrano[2,3-*d*]pyrimidine-5-yl]thiourea (4g).** Dark brown; 64%; mp: 258 °C–261 °C; (ethanol) IR (KBr) υ (cm^{-1}): 3372, 3330 (-NH_2), 3074, 3192 (2-NH), 2929, 2884 (C-H str.), 1646 (-C=N), 1345, 1231 (2>C=S), 1148, 1058 (C-O-C), 752 (C-Cl); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.91 (s, 2H, 2-NH), 7.80–7.17 (m, 9H, Ar-H), 5.42 (s, 2H, -NH_2), 4.91 (s, 1H, -CH), 2.37 (s, 3H, -CH_3); Anal. Calcd for $C_{22}H_{17}N_6OClS_2$: C, 54.94; H, 3.56; N, 17.47; Found: C, 54.99; H, 3.60; N, 17.50.

***N*-[4-(3-Nitrophenyl)-3-methyl-1-phenyl-7-thioxo-1,4,7,8-tetrahydro-pyrazolo[4′,3′:5,6]pyrano[2,3-*d*]pyrimidine-5-yl]thiourea (4h).** Black; 59%; mp: >280 °C; (ethanol) IR (KBr) υ (cm^{-1}): 3360, 3336 (-NH_2), 3062, 3198 (2-NH), 2940, 2876 (C-H str.), 1658 (-C=N), 1545, 1357 (-NO_2 asym, sym), 1343, 1247 (2>C=S), 1140, 1067 (C-O-C); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.92 (s, 2H, 2-NH), 7.72–7.21

(m, 9H, Ar-H), 5.41 (s, 2H, -NH_2), 4.93 (s, 1H, -CH), 2.36 (s, 3H, -CH_3); Anal. Calcd for $C_{22}H_{17}N_7O_3S_2$: C, 53.76; H, 3.49; N, 19.95; Found: C, 53.78; H, 3.47; N, 19.98.

***N*-[4-(3-bromophenyl)-3-methyl-1-phenyl-7-thioxo-1,4,7,8-tetrahydro-pyrazolo[4′,3′:5,6]pyrano[2,3-*d*]pyrimidine-5-yl]thiourea (4i).** Black; 53%; mp: >280 °C; (ethanol) IR (KBr) υ (cm^{-1}): 3375, 3342 (-NH_2), 3069, 3204 (2-NH), 2931, 2886 (C-H str.), 1650 (-C=N), 1353, 1236 (2>C=S), 1129, 1050 (C-O-C), 753 (C-Br); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.89 (s, 2H, 2-NH), 7.83–7.14 (m, 9H, Ar-H), 5.42 (s, 2H, -NH_2), 4.93 (s, 1H, -CH), 2.37 (s, 3H, -CH_3); Anal. Calcd for $C_{22}H_{17}N_6OBrS_2$: C, 50.29; H, 3.26; N, 15.99; Found: C, 50.25; H, 3.29; N, 15.95.

***N*-[4-(4-Methylphenyl)-3-methyl-1-phenyl-7-thioxo-1,4,7,8-tetrahydro-pyrazolo[4′,3′:5,6]pyrano[2,3-*d*]pyrimidine-5-yl]thiourea (4j).** Gray; 61%; mp: 266 °C–270 °C; (ethanol) IR (KBr) υ (cm^{-1}): 3366, 3327 (-NH_2), 3077, 3191 (2-NH), 2927, 2879 (C-H str.), 1643 (-C=N), 1347, 1229 (2>C=S), 1145, 1079 (C-O-C); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.91 (s, 2H, 2-NH), 7.76–7.15 (m, 9H, Ar-H), 5.40 (s, 2H, -NH_2), 4.92 (s, 1H, -CH), 2.36 (s, 3H, -CH_3), 1.97 (s, 3H, -CH_3); Anal. Calcd for $C_{23}H_{20}N_6OS_2$: C, 59.98; H, 4.38; N, 18.25; Found: C, 59.95; H, 4.35; N, 18.28.

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