An Efficient Access to Pyrimidine-based Polyfunctional Heterocycles with Anticipated Antibacterial Activity

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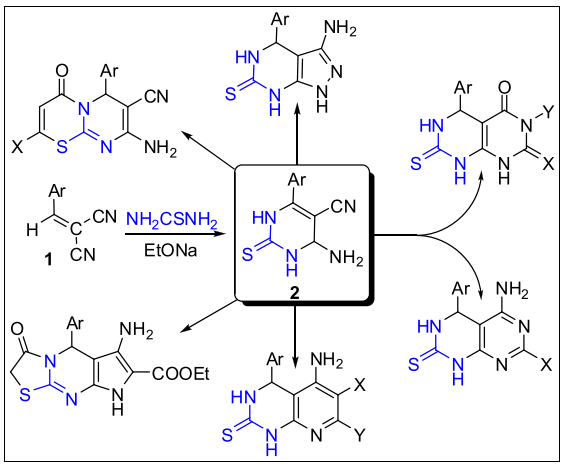


6-Amino-2-thioxotetrahydropyrimidine-5-carbonitrile derivative **2** was synthesized in a good yield *via* refluxing a mixture of arylidene **1** and thiourea in a highly basic sodium ethoxide solution. Subsequently, the synthesized pyrimidine-2-thione derivative **2** was allowed to interact with diversified nucleophiles and electrophiles under various reaction conditions in order to have a feasible access to further new and assorted fused heterocycles. Finally, the biological activity of the newly synthesized fused pyrimidines was screened *in vitro* against four different Gram-positive and Gram-negative bacterial strains. All the developed heterocycles were adequately characterized utilizing ^{1}H-NMR, ^{13}C-NMR, Fourier transform infrared, elemental analysis, and electrospray ionization–mass spectrum and tested for their antibacterial activity.

INTRODUCTION

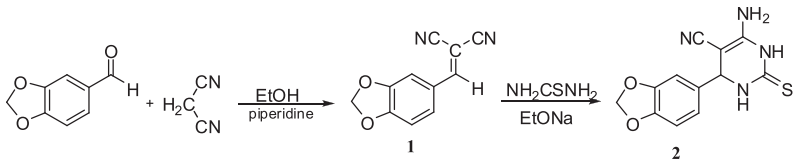
Fused pyrimidine heterocycles have attracted a sizeable attention over the last decades because of their versatile pharmacological and therapeutic merits [1,2]. Accordingly, pyrimidine and their sulfur analogues have been recognized to act as analgesics [3,4] and to have an immense array of biological activities [5,6] like antifungal [7], antiviral [8], antibacterial [9–12], anti-inflammatory [13,14], antioxidant [15], anticancer [16], and antihypertensive [17]. Interestingly, pyrimidines are not only revealing a profound antitumor activity [18] but also acting as unique HIV reverse transcriptase inhibitors [19,20]. Moreover, many pyrimidine derivatives are considered to be antibiotics, anticonvulsant, and calcium channel blockers [21–24]. Clearly, pyrimidines owe their therapeutic applications to the fact that pyrimidine base is existing in uracil, thymine, and cytosine, which are crucial building units of the two essential nucleic acids, deoxyribonucleic acid, and ribonucleic acid.

RESULTS AND DISCUSSION

In continuation of our ongoing endeavors to develop novel heterocyclic fused pyrimidine derivatives [25], arylidene **1** was obtained *via* Knoevenagel condensation reaction according to the reported procedure [26]. Subsequently, a cyclization reaction took place, and 6-amino-4-(benzo[*d*][1,3]dioxol-5-yl)-2-thioxo-1,2,3,4-tetra hydropyrimidine-5-carbonitrile (**2**) was produced, when a mixture of arylidene **1** and thiourea was refluxed in presence of strongly alkaline sodium ethoxide solution (Scheme 1).

The structure of tetrahydropyrimidine derivative **2** was asserted from the obtained spectral and analytical data, which were compatible with the expected structure **2** in which ^{1}H-NMR spectrum of **2** revealed single signals at δ 4.92 corresponding to pyrimidinethione-4H proton, 6.10 due to the resonance of NH_2 protons, and 9.48 and 9.70 ppm proving the existence of 2NH groups. In addition, the molecular ion peak of **2** was detected at m/z = 274.

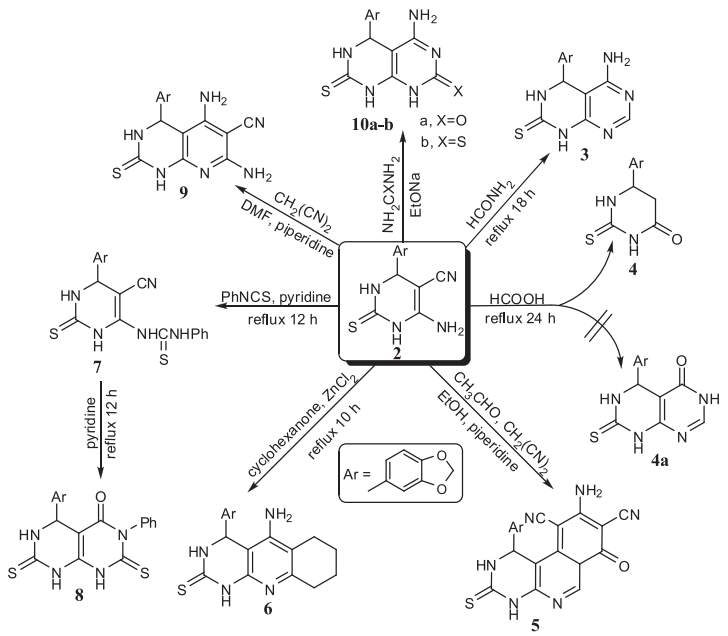
Scheme 1. Synthesis of pyrimidinethione derivative **2**.



Driven by the high functionality of compound **2**, the effect of nitrogen nucleophiles, acidic medium, and other electrophiles was studied. For instance, refluxing a mixture of tetrahydropyrimidine derivative **2** and formamide for 18 h furnished 5-amino-4-(benzo[*d*][1,3] dioxol-5-yl)-3,4-dihydropyrimido[4,5-*d*]pyrimidine-2(1*H*)-thione (**3**) (Scheme 2).

Interestingly, 7-thioxo-tetrahydropyrimido[4,5-*d*]pyrimi dinone derivative **4a** was expected to be the sole product of refluxing tetrahydropyrimidine derivative **2** with formic acid, but in a stark contrast to the proposed structure, 6-(benzo[*d*][1,3]dioxol-5-yl)-2-thioxotetrahydropyrimidin-4(1*H*)-one (**4**) was obtained instead of **4a**, which was in a total agreement with the product reported by Madkour *et al* (Scheme 2) [27]. Also, examination of the reaction product spectral data excluded compound **4a** as ^{1}H-NMR spectrum exhibited the disappearance of amino group signal and the appearance of doublet of doublet signals at δ 2.69 and 2.90 ppm attributed to methylene protons of 2-thioxotetrahydropyrimidin-4(1*H*)-one derivative **4**. Furthermore, condensation of tetrahydropyrimidine derivative **2** with acetaldehyde and malononitrile in absolute ethanol contains few drops of piperidine gave an access to isoquinoline derivative **5** (Scheme 2). Infrared (IR) spectrum of **5** displayed a new absorption band at 1680 cm^{-1} indicating the introduction of a new carbonyl group. Also, mass spectrum showed an ion peak at *m*/*z* = 416 equivalent to (M^+). Alternatively, quinoline derivative **6** was attainable through the condensation of pyrimidine-2-thione derivative **2** with cyclohexanone in the presence of Lewis acid (Scheme 2). However, refluxing compound **2** with phenylisothiocyanate in pyridine for 12 h gave rise to 1-(6-(benzo[*d*][1,3]dioxol-5-yl)-5-cyano-2-thioxo-1,2,3,6-tetrahydropyrimidin-4-yl)-3-phenylthiourea (**7**) (Scheme 2). IR spectrum of **7** revealed a strong absorption at 2207 cm^{-1} implying that **7** still has the nitrile moiety and no cyclization reaction took place. Subsequent cyclization was successfully achieved, and compound **8** was furnished when the isolated intermediate **7** was heated under reflux for extra 12 h in pyridine (Scheme 2). IR spectrum of pyrimidopyrimidinone derivative **8** showed a

Scheme 2. Reactions of tetrahydropyrimidine derivative **2**.



characteristic band of a new cyclic amide carbonyl group at 1664 cm^{-1} while no absorption was observed for the nitrile group. Furthermore, refluxing compound **2** with malononitrile in dimethylformamide and few drops of piperidine for 12 h furnished 2-thioxo-tetrahy dropyrido[2,3-*d*]pyrimidine derivative **9** (Scheme 2). Inspection of ^{1}H-NMR spectrum indicated the existence of two amino groups at δ 6.22 and 4.65 ppm while mass spectrum of pyridopyrimidine derivative **9** exhibited a molecular ion peak at *m*/*z* = 340 equivalent to (M^+).

In the same context, more fused pyrimidine heterocyclic systems were accessible through the reaction of **2** with an equimolar amount of urea or thiourea in sodium ethoxide solution, and 4-amino-5-(benzo[*d*][1,3] dioxol-5-yl)-7-thioxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]py rimidin-2(1*H*)-one (**10a**) or 5-amino-4-(benzo[*d*][1,3]dio xol-5-yl)-3,4-dihydropyrimido[4,5-*d*]pyrimidine-2,7(1*H*, 8*H*)-dithione (**10b**) was produced, respectively (Scheme 2). The structure of **10a** was substantiated on the basis of its spectroscopic data; for example, the IR spectrum was devoid of any absorption bands for the nitrile but exhibited an intense absorption at 1697 cm^{-1} corresponding to a new cyclic amide carbonyl group. Also, the molecular ion peak (M^+) of **10a** was observed at *m*/*z* = 317. Likewise, IR spectrum of **10b** showed the disappearance of the nitrile absorption, and the mass spectrum revealed the molecular ion peak (M^+) at *m*/*z* = 333.

Acid catalyzed hydrolysis of the nitrile group in pyrimidine-2-thione **2** into amide group afforded compound **11**, which was subjected to subsequent cyclization to produce 2,7-dithioxo-hexahydropyrimido [4,5-*d*]pyrimidin-4(1*H*)-one derivative **12** (Scheme 3). IR spectrum of **11** showed no absorption for the nitrile, but a characteristic absorption band at 1674 cm^{-1} was observed indicating the formation of a new amide carbonyl. Also, the structure of compound **11** was proven chemically *via* its cyclization in basic medium to pyrimidopyrimidine derivative **12** (Scheme 3).

In addition, *N*-acetylation of NH and NH_2 groups took place when pyrimidine-2-thione derivative **2** was treated with acetyl chloride in dry dioxane and *N*-(1,3-diacetyl-6-(benzo[*d*][1,3]dioxol-5-yl)-5-cyano-2-thioxo-1,2,3,6-tetra hydropyrimidin-4-yl)acetamide (**13**) was formed (Scheme 3). IR spectrum of compound **13** exhibited a characteristic peak at 1692 cm^{-1} corresponding to amide carbonyl group. Another piece of evidence for the proposed structure **13** was gained from ^{1}H-NMR data, which exhibited three singlet signals at δ 2.33, 2.46, and 2.50 ppm, all were integrated for three protons implying the existence of three methyl groups. Similarly, treatment of compound **2** with chloroacetyl chloride in dry dioxane afforded *N*-(6-(benzo[*d*][1,3]dioxol-5-yl)-1,3-bis(2-chloro acetyl)-5-cyano-2-thioxo-1,2,3,6-tetrahydropyrimidin-4-yl)-2-chloroacetamide (**14**) (Scheme 3).

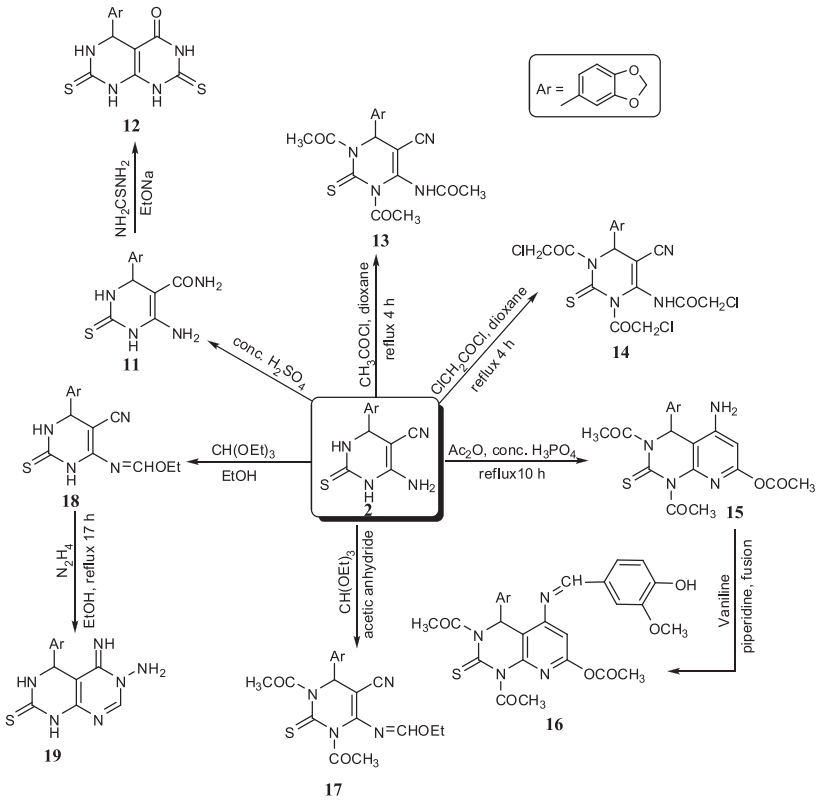
Noteworthy, a cyclization reaction took place, and 1,3-diacetyl-2-thioxo-tetrahydropyrido[2,3-*d*]pyrimidin-7-yl a cetate derivative **15** was furnished when tetrahydro pyrimidine derivative **2** was refluxed with a mixture of acetic anhydride and concentrated phosphoric acid (Scheme 3). Later, compound **15** was fused with an aromatic aldehyde, namely, vanillin, in presence of drops of piperidine to afford the corresponding Schiff's base **16** (Scheme 3). Spectroscopic data confirmed the formation of **15** and **16** as IR spectrum of **15** displayed the absence of the nitrile absorption frequency and the appearance of two new absorptions at 1713 and 1659 cm^{-1} indicating the introduction of new ester and amide carbonyl groups, respectively, whereas IR spectrum of **16** showed no absorption frequency in amino group region but a broad absorption band at 3435 cm^{-1} corresponding to new hydroxyl group was detected.

Also, *N*-acetylation reaction was observed, and the imidate derivative **17** was formed when pyrimidinethione derivative **2** was allowed to react with triethyl orthoformate in acetic anhydride (Scheme 3). Interestingly, conducting the aforementioned reaction of **2** with triethyl orthoformate in refluxing ethanol instead of acetic anhydride submitted 2-thioxotetrahydropyrimidin-4-ylformimidate derivative **18** (Scheme 3). ^{1}H-NMR data of **18** showed the characteristic triplet–quartet splitting pattern of the ethoxy group at δ 1.19 and 3.33 ppm; it also showed a characteristic band at δ 7.08 ppm for imidate (–N=CHOR) group. Furthermore, the structure of the later compound **18** was established chemically when a subsequent cyclization reaction took place *via* refluxing it with hydrazine hydrate in ethanol to furnish tetrahydropyrimido[4,5-*d*]pyrimidine-2-thione derivative **19** (Scheme 3).

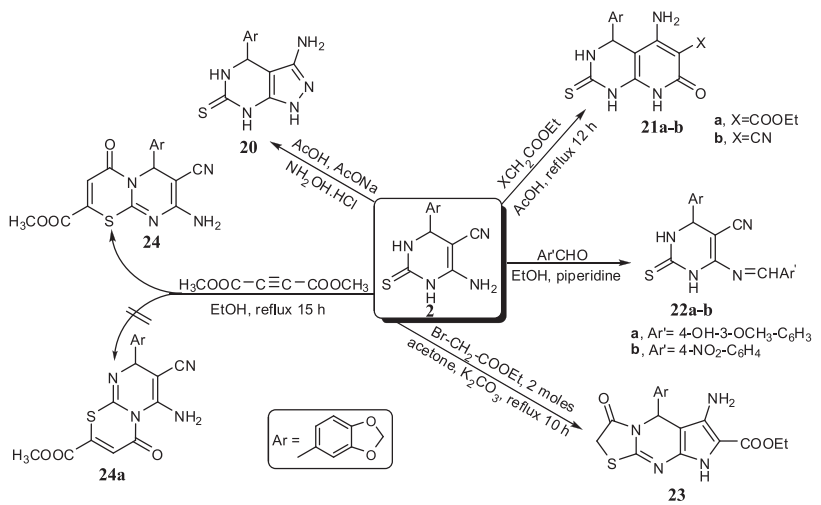
A different approach for substituted pyrazolopyrimidine derivative **20** formation was adopted through refluxing of pyrimidinethione derivative **2** with hydroxylamine hydrochloride in acetic acid containing catalytic amount of anhydrous sodium acetate (Scheme 4).

An additional pathway for building up polyfunctionally fused pyrimidine was achieved *via* the treatment of **2** with an equimolar amount of diethyl malonate or ethyl cyanoacetate in refluxing glacial acetic acid to afford ethyl 5-amino-4-(benzo[*d*][1,3]dioxol-5-yl)-7-oxo-2-thioxo-1,2,3,4,7,8-hexahydropyrido[2,3-*d*]pyrimidi ne-6-carboxylate (**21a**) or 5-amino-4-(benzo[*d*][1,3]dioxol-5-yl)-7-oxo-2-thioxo-1,2,3,4,7,8-hexahydropyrido[2,3-*d*] pyrimidine-6-carbonitrile (**21b**), respectively (Scheme 4). IR spectrum of **21a** revealed the disappearance of the nitrile group absorption frequency and the appearance of two new absorptions at 1733 and 1669 cm^{-1} indicating the presence of ester and cyclic amide carbonyl groups, respectively. An additional evidence for the suggested structure of **21a** was acquired from ^{1}H-NMR data, which

Scheme 3. Reactions of tetrahydropyrimidine derivative **2**.



Scheme 4. Reactions of tetrahydropyrimidine derivative **2**.



showed the distinctive triplet–quartet splitting pattern of the ethyl group at δ 1.87 and 4.35 ppm, it also showed characteristic peaks at δ 6.10, 9.96, 10.11, and 10.43 ppm confirming the existence of NH_2 and three NH groups, respectively. Similarly, spectral data and elemental analysis were agreeable with the proposed structure of compound **21b**. Schiff's bases **22a** and **22b** were attainable through the fusion of compound **2** with an aromatic aldehyde, namely, vanillin or *p*-nitrobenzaldehyde, and few drops of piperidine (Scheme 4). Mass spectrum of **22a** revealed the molecular ion peak at *m*/*z* = 408; however, the molecular

ion peak of **22b** was detected at *m*/*z* = 407, and it was equivalent to molecular formula $C_{19}H_{13}N_5O_4S$.

In our attempts to synthesize more fused heterocyclic systems, a new approach to construct a pyrrole ring fused to pyrimidine moiety of pyrimidine-2-thione derivative **2** was embrace on the basis of the alkylation of **2** with *α*-halo acetic acid derivative, namely, ethyl bromoacetate, followed by the cyclization of the alkylated product in basic medium. As pyrimidine-2-thione derivative **2** contains NH_2 and SH groups, they were both liable to alkylation using the utilized conditions. The isolated product revealed that both *S*- and *N*-alkylation took place and ethyl-3-oxo-tetrahydropyrrolo[2,3-*d*]thiazolo[3,2-*a*] pyrimidine-7-carboxylate derivative **23** was furnished (Scheme 4). IR spectrum of **23** revealed no absorption frequency for the nitrile group, but two new absorption frequencies at 1733 and 1678 cm^{-1} corresponding to ester and cyclic amide carbonyl groups were observed. An additional proof for the proposed structure of **23** was obtained from ^{1}H-NMR data, which showed a triplet–quartet splitting pattern for the ethoxy group at δ 1.46 and 4.88 ppm. Also, it showed a new peak at δ 3.78 ppm confirming the existence of methylene group while mass spectrum of **23** exhibited the molecular ion peak (M^+) at *m*/*z* = 400. Interestingly, reaction of pyrimidine-2-thione derivative **2** with dimethyl acetylenedicarboxylate in refluxing ethanol furnished 4,6-dihydropyrimido[2,1-*b*][1,3]thiazine-2-carboxylate derivative **24** rather than 4,8-dihydropyrimido[2,1-*b*][1,3]thiazine-2-carboxylate derivative **24a** (Scheme 4). In addition to IR spectrum of **24** that showed new ester and cyclic amide carbonyl absorption bands, another piece of evidence for the proposed structure of **24** was acquired from ^{1}H-NMR data, which exhibited a singlet signal at δ 3.74 ppm equivalent to the three protons of methyl group and revealed another peak at δ 6.82 ppm characteristic of thiazine moiety proton. Finally, mass spectrum of **24** showed the molecular ion peak (M^+) at *m*/*z* = 384.

ANTIMICROBIAL ACTIVITIES

Antibiotics bearing pyrimidine moiety are of utmost importance because of their potent inhibition effect of dihydrofolate reductase enzyme, a crucial enzyme for bacterial deoxyribonucleic acid assembly [28]. The *in vitro* antimicrobial properties of the investigated compounds were assessed against *Bacillus subtilis*

Table 1

In vitro antimicrobial activity of the synthesized compounds.

		Gram-positive bacteria				Gram-negative bacteria			
		Bacillus subtilis		*Staphylococcus enteritis*		*Pseudomonas aeruginosa*		*Escherichia coli*	
Entry	Compound	IZ	%Activity index	IZ	%Activity index	IZ	%Activity index	IZ	%Activity index
1	**2**	7	116.6	8	106.6	9	112.5	6	100
2	**3**	6	100	NA	—	9	112.5	6	100
3	**4**	5	83.3	5	66.6	9	112.5	6	100
4	**5**	NA	—	7	93.3	3	37.5	6	100
5	**6**	12	200	3	40.0	4	50	6	100
6	**8**	NA	—	NA	—	8	100	7	116.6
7	**9**	5	83.3	5	66.6	NA	—	NA	—
8	**10a**	5	83.3	4	53.3	NA	—	3	50
9	**10b**	6	100	12	160	4	50	NA	—
10	**11**	NA	—	NA	—	NA	—	NA	—
11	**12**	5	83.3	NA	—	NA	—	NA	—
12	**13**	7	116.6	4	53.3	9	112.5	3	50
13	**14**	11	183.3	8	106.6	4	50	3	50
14	**15**	NA	—	NA	—	NA	—	7	116.6
15	**16**	NA	—	8	106.6	8	100	12	200
16	**17**	6	100	8	106.6	NA	—	12	200
17	**18**	6	100	10	133.3	NA	—	7	116.6
18	**19**	6	100	4	53.3	8	100	NA	—
19	**20**	5	83.3	NA	—	NA	—	NA	—
20	**21a**	7	116.6	NA	—	3	37.5	NA	—
21	**21b**	7	116.6	4	53.3	NA	—	5	83.3
22	**22a**	11	183.3	NA	—	9	112.5	NA	—
23	**22b**	NA	—	NA	—	NA	—	NA	—
24	**23**	6	100	12	160	4	50	6	100
25	**24**	6	100	11	146.6	NA	—	5	83.3
26	Norfloxacin	6	100	7.5	100	8	100	6	100

IZ, inhibition diameter zones expressed in millimeters (mm); NA, no observed antimicrobial activity.

and *Staphylococcus enteritis* as representative examples of Gram-positive bacteria and *Pseudomonas aeruginosa* and *Escherichia coli* as representative examples of Gram-negative bacteria. Antibiotic norfloxacin was utilized as control criterion. Antimicrobial activity was recorded as inhibition diameter zones in millimeters (mm) of investigated compounds against the patholo gical strains (Table 1).

The compounds under investigation exhibited variation in their antibacterial activities (Table 1). Among the synthesized heterocycles, only pyrimidine-2-thione derivative **2** showed robust activity against all tested Gram-positive and Gram-negative bacteria (Table 1; entry 1). Contrarily, **11** and **22b** were biologically inactive against the four tested bacterial strains (Table 1; entries 10 and 23, respectively). Compounds **10a**, **17**, **18**, **21b**, and **24** exhibited moderate to excellent activities against both Gram-positive and Gram-negative bacteria except for *P. aeruginosa* (Table 1; entries 8, 16, 17, 21, and 25, respectively). Furthermore, compound **9** displayed no antibacterial activity against Gram-negative bacteria while compound **15** exhibited no effect against Gram-positive bacteria (Table 1; entries 7 and 14, respectively). However, compound **8** expressed excellent effect against Gram-negative bacteria only (Table 1; entry 6). Finally, compounds **12** and **20** were found to be active only against *B. subtilis* with the exact activity index percentage (Table 1; entries 11 and 19, respectively).

CONCLUSION

In conclusion, arylidene **1** was exploited as a precursor to synthesize pyrimidine-2-thione derivative **2**. Subsequently, compound **2** was utilized as a valuable building scaffold to construct novel and diverse heterocycles bearing pyrimidinethione moiety. Fused pyrimidine, pyridine, isoquinoline, quinoline, pyrazole, and thiazine rings were accessible through simple and straightforward reactions. Finally, the preliminary *in vitro* antimicrobial activity of synthesized compounds was screened.

EXPERIMENTAL

Melting points were determined by an electrothermal melting point apparatus (GALLENKAMP) and are uncorrected. All the reactions were followed up by the thin-layer chromatography technique with fluorescent silica gel plates HF_{245} (Merck), and plates were viewed with iodine. Silica gel (230–400 mesh) was used for flash chromatography separations. Elemental analysis was carried out by microanalytical unit (Faculty of Science, Cairo University). IR (KBr) spectra were recorded on a Pye-Unicam IR spectrophotometer sp 2000 (Faculty of Science, Fayoum University), the mass spectra were run by a Shimadzu-GC-MS-GP 1000 EX using the direct inlet system, and nuclear magnetic resonance spectra were recorded on Varian Mercury 300 MHz spectrometer using tetramethylsilane as internal standard; chemical shifts are recorded in δ units (National Center Researcher).

Synthesis of 2-(benzo[*d*][1,3]dioxol-5-ylmethylene)malono nitrile (1).

A mixture of piperonal (0.01 mol) and malononitrile (0.01 mol) in absolute ethanol with few drops of piperidine was refluxed for 2 h then allowed to cool down at room temperature; the product was filtered off, dried, and recrystallized from ethanol as yellow crystals [26]. Yield (1.86 g, 94%), mp 188°C; IR (KBr, cm^{-1}): 3097 (CH aromatic), 2926 (CH aliphatic), 2224 (C≡N). *Ana*l. Calcd for $C_{11}H_6N_2O_2$: C: 66.66, H: 3.03, N: 14.14. Found C: 66.83, H: 3.12, N: 14.01.

Synthesis of 6-amino-4-(benzo[*d*][1,3]dioxol-5-yl)-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carbonitrile (2).

A mixture of equimolar amounts of compound **1** (1.98 g, 0.01 mol) and thiourea (0.76 g, 0.01 mol) in sodium ethoxide solution, 0.23 g of sodium metal in 25 mL absolute ethanol, was refluxed for 4 h; the reaction mixture was cooled down then poured into crushed ice and neutralized with hydrochloric acid (2*N*, 3 mL); the product was filtered off, dried, and recrystallized from ethanol as yellow crystals. Yield (2.44 g, 89%), mp 209–210°C; IR (KBr, cm^{-1}): 3444, 3303, 3104 (NH_2, 2NH), 3032 (CH aromatic), 2920 (CH aliphatic), 2211 (C≡N), 1627 (C═N), 1257 (C═S); ^{1}H-NMR (DMSO-d_6, 300 MHz, ppm) δ: 4.92 (s, 1H, pyrimidinethione-4H), 5.98 (s, 2H, 1,3-dioxole-CH_2), 6.10 (s, 2H, NH_2), 6.66–6.89 (m, 3H, Ar–H), 9.48 (s, 1H, NH), 9.70 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 100 MHz, ppm) δ: 50.4, 58.7, 103.1, 106.6, 108.2, 113.5, 119.4, 132.3, 136.5, 143.2, 146.1, 175.3; MS (70 eV) *m*/*z* (%): 274 (M^+, 6.65), 272 (M^+-2, 100). *Ana*l. Calcd for $C_{12}H_{10}N_4O_2S$: C: 52.55, H: 3.64, N: 20.43, S: 11.67. Found: C: 52.03, H: 3.22, N: 20.60, S: 12.04.

Synthesis of 5-amino-4-(benzo[*d*][1,3]dioxol-5-yl)-3,4-dihy dropyrimido[4,5-*d*] pyrimidine-2(1*H*)-thione (3).

A mixture of compound **2** (2.74 g, 0.01 mol) and formamide (30 mL) was heated under reflux for 18 h, cooled down, and poured into crushed ice, and then the product was filtered off, dried, and recrystallized from benzene as yellow crystals. Yield (1.76 g, 58%), mp 197–198°C; IR (KBr, cm^{-1}): 3293, 3213, 3132 (NH_2, 2NH), 3068 (CH aromatic), 2961 (CH aliphatic), 1601 (C═N), 1206 (C═S); ^{1}H NMR (DMSO-d_6,

300 MHz, ppm) δ: 5.25 (s, 1H, pyrimidinethione-4H), 5.93 (s, 2H, 1,3-dioxole-CH_2), 6.32 (s, 2H, NH_2), 6.72–7.11 (m, 3H, Ar–H), 7.86 (s, 1H, CH═N), 9.34 (s, 1H, NH), 9.56 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 100 MHz, ppm) δ: 49.6, 90.1, 102.9, 107.7, 109.3, 120.4, 131.8, 143.2, 146.1, 149.6, 151.3, 158.3, 175.1; MS (70 eV) *m/z* (%): 302 (M^++1, 0.35), 301 (M^+, 0.08), 284 (100). *Anal*. Calcd for $C_{13}H_{11}N_5O_2S$: C: 51.82, H: 3.65, N: 23.25, S: 10.63. Found C: 51.31, H: 3.47, N: 23.51, S: 10.71.

Synthesis of 6-(benzo[*d*][1,3]dioxol-5-yl)-2-thioxotetrahydropyrimidin-4(1*H*)-one (4).

A mixture of compound **2** (2.74 g, 0.01 mol) and formic acid (40 mL) was refluxed for 24 h, left to cool, and then the crude precipitated product was collected by filtration, dried, and recrystallized from ethanol as white crystals. Yield (1.73 g, 69%), mp 270°C; IR (KBr, cm^{-1}): 3161, 3113 (2NH), 3050 (CH aromatic), 2958 (CH aliphatic), 1696 (C═O), 1241 (C═S); ^{1}H-NMR (DMSO-d_6, 300 MHz, ppm) δ: 2.69 (dd, 1H, *J* = 7.0 and 7.9 Hz, pyrimidinethione-5H), 2.90 (dd, 1H, *J* = 7.9 and 8.1 Hz, pyrimidinethione-5H), 4.68 (m, 1H, pyrimidinethione-4H), 5.98 (s, 2H, 1,3-dioxole-CH_2), 6.82–6.88 (m, 3H, Ar–H), 9.96 (s, 1H, NH), 11.09 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 100 MHz, ppm) δ: 40.1, 56.5, 102.2, 107.5, 109.4, 119.8, 136.5, 144.9, 146.8, 165.7, 174.5; MS (70 eV) *m/z* (%): 250 (M^+, 100). *Anal*. Calcd for $C_{11}H_{10}N_2O_3S$: C: 52.81, H: 4.07, N: 11.25, S: 12.80. Found C: 52.41, H: 4.32, N: 11.08, S: 12.53.

Synthesis of 9-amino-1-(benzo[*d*][1,3]dioxol-5-yl)-7-oxo-3-thioxo-1,2,3,4,6a,7-hexahydropyrimido[4,5-*c*]isoquinoline-8,10-dicarbonitrile (5).

A solution of acetaldehyde (0.01 mol) and malononitrile (0.02 mol) in absolute ethanol (20 mL) was added to a suspension of compound **2** (2.74 g, 0.01 mol) in absolute ethanol and drops of piperidine; the reaction mixture was heated under reflux for 4 h, left to cool, and then the solid product that precipitated was filtered off, dried, and recrystallized from dioxane as pale brown crystals. Yield (2.30 g, 55%), mp 292°C; IR (KBr, cm^{-1}): 3447, 3340, 3236 (NH_2, 2NH), 3030 (CH aromatic), 2943 (CH aliphatic), 2213 (C≡N), 1680 (C═O, cyclic amide), 1644 (C═N), 1250 (C═S); ^{1}H NMR (DMSO-d_6, 300 MHz, ppm) δ: 4.89 (d, 1H, *J* = 7.0 Hz, isoquinoline-CH), 5.32 (s, 1H, pyrimidinethione-1H), 5.90 (s, 2H, 1,3-dioxole-CH_2), 6.22 (s, 2H, NH_2), 6.72–6.89 (m, 3H, ArH), 7.85 (d, *J* = 7.0 Hz, 1H, isoquinoline-CH), 9.48 (s, 1H, NH), 9.65 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 100 MHz, ppm) δ: 58.2, 71.7, 82.6, 102.3, 108.0, 109.2, 111.8, 112.7, 119.6, 120.3, 135.4, 139.8, 140.3, 145.0, 146.6, 150.6, 170.3, 175.2, 181.1; MS (70 eV) *m/z* (%): 416 (M^+, 5.92), 271 (100). *Anal*. Calcd for $C_{20}H_{12}N_6O_3S$: C: 57.69, H: 2.88, N: 20.19, S: 7.69. Found C: 57.81, H: 2.93, N: 20.02, S: 7.52.

Synthesis of 5-amino-4-(benzo[*d*][1,3]dioxol-5-yl)-3,4,6,7,8,9-hexahydropyrimido[4,5-*b*]quinoline-2(1*H*)-thione (6).

A mixture of compound **2** (2.74 g, 0.01 mol), cyclohexanone (5 mL, excess), and anhydrous zinc chloride (1.0 g, 0.005 mol) was fused together under dry conditions for 10 h. The reaction was left to cool down, triturated with ethanol, and diluted with water; the precipitated product was collected by filtration, dried, and recrystallized from benzene as brown crystals. Yield (2.05 g, 58%), mp 231–232°C; IR (KBr, cm^{-1}): 3436, 3369, 3260 (NH_2, 2NH), 3045 (CH aromatic), 2920 (CH aliphatic), 1616 (C═N), 1221 (C═S); ^{1}H NMR (DMSO-d_6, 300 MHz, ppm) δ: 1.78 (m, 4H, $CH_2CH_2CH_2CH_2$), 2.67 (m, 2H, hydroquinoline-CH_2), 3.04 (m, 2H, hydroquinoline-CH_2), 5.34 (s, 1H, pyrimidinethione-4H), 5.92 (s, 2H, 1,3-dioxole-CH_2), 6.25 (s, 2H, NH_2), 6.75–6.88 (m, 3H, ArH), 9.31 (s, 1H, NH), 9.59 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 100 MHz, ppm) δ: 23.3, 24.5, 28.9, 32.1, 49.2, 90.1, 102.0, 107.8, 108.4, 109.3, 120.3, 135.4, 145.1, 146.8, 147.1, 150.2, 155.1, 174.6; MS (70 eV) *m/z* (%): 355 (M^++1, 6.59), 207 (100). *Anal*. Calcd for $C_{18}H_{18}N_4O_2S$: C: 61.01, H: 5.08, N: 15.81, S: 9.03. Found C: 61.43, H: 5.28, N: 15.62, S: 9.12.

Synthesis of 1-(6-(benzo[*d*][1,3]dioxol-5-yl)-5-cyano-2-thioxo-1,2,3,6-tetrahydropyrimidin-4-yl)-3-phenylthiourea (7).

A mixture of compound **2** (2.74 g, 0.01 mol) and phenylisothiocyanate (1.2 mL, 0.01 mol) in pyridine (10 mL) was fused together for 12 h. The reaction mixture was cooled down and triturated with ethanol; the product was filtered off, dried, and recrystallized from ethanol as brown crystals. Yield (1.88 g, 46%), mp >360°C; IR (KBr, cm^{-1}): 3319, 3214 (4NH), 3065 (CH aromatic), 2918 (CH aliphatic), 2207 (C≡N), 1622 (C═N), 1243 (C═S); ^{1}H NMR (DMSO-d_6, 300 MHz, ppm) δ: 5.39 (s, 1H, pyrimidinethione-6H), 5.90 (s, 2H, 1,3-dioxole-CH_2), 6.98–7.39 (m, 3H, ArH), 7.14 (m, 1H, ArH), 7.26 (m, 2H, ArH), 7.34 (m, 2H, ArH), 7.87 (s, 1H, NH), 8.03 (s, 1H, NH), 8.76 (s, 1H, NH), 9.80 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 100 MHz, ppm) δ: 58.6, 72.1, 102.3, 108.7, 109.3, 118.4, 120.3, 121.4, 124.6, 128.1, 128.4, 135.2, 139.1, 144.8, 146.2, 147.5, 174.1, 175.0. *Anal*. Calcd for $C_{19}H_{15}N_5O_2S_2$: C: 55.74, H: 3.66, N: 17.11, S: 15.64. Found C: 55.38, H: 3.57, N: 17.28, S: 15.86.

Synthesis of 5-(benzo[*d*][1,3]dioxol-5-yl)-3-phenyl-2,7-dithioxo-2,3,5,6,7,8-hexahydropyrimido[4,5-*d*]pyrimidin-4(1*H*)-one (8).

A solution of **7** (4.09 g, 0.01 mol) in absolute pyridine was refluxed for 12 h, and then the reaction mixture was cooled down and poured on ice-cold water acidified with hydrochloric acid. The solid precipitate was filtered off, dried, and recrystallized from dioxane as brown crystals. Yield (2.45 g, 60%), mp 285°C; IR (KBr, cm^{-1}): 3245,

3129 (3NH), 3030 (CH aromatic), 2961 (CH aliphatic), 1664 (C=O, cyclic amide), 1266 (C=S); ^{1}H NMR (DMSO-d_6, 300 MHz, ppm) δ: 5.34 (s, 1H, pyrimidinethione-5H), 5.96 (s, 2H, 1,3-dioxole-CH_2), 6.78–6.97 (m, 3H, ArH), 7.12 (m, 1H, ArH), 7.24 (m, 2H, ArH), 7.38 (m, 2H, ArH), 8.22 (s, 1H, NH), 8.56 (s, 1H, NH), 9.08 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 100 MHz, ppm) δ: 57.6, 92.2, 102.7, 108.1, 109.5, 120.4, 127.5, 128.1, 128.4, 129.1, 135.0, 138.5, 145.3, 146.1, 150.7, 155.1, 170.9, 174.6; MS (70 eV) *m/z* (%): 410 (M^+, 6.70), 85 (100). *Anal*. Calcd for $C_{19}H_{14}N_4O_3S_2$: C: 55.60, H: 3.41, N: 13.65, S: 15.60. Found C: 55.31, H: 3.63, N: 13.82, S: 15.42.

Synthesis of 5,7-diamino-4-(benzo[*d*][1,3]dioxol-5-yl)-2-thioxo-1,2,3,4-tetrahydropyrido[2,3-*d*]pyrimidine-6-carbonitrile (9).

A mixture of compound **2** (2.74 g, 0.01 mol), malononitrile (0.66 g, 0.01 mol) in DMF (40 mL), and few drops of piperidine was refluxed for 12 h, and the reaction mixture was allowed to cool to room temperature and then poured over crushed ice. The precipitate was collected by filtration, dried, and recrystallized from toluene as dark red crystals. Yield (2.30 g, 68%), mp 252°C; IR (KBr, cm^{-1}): 3444, 3353, 3214 ($2NH_2$, 2NH), 3007 (CH aromatic), 2918 (CH aliphatic), 2200 (C≡N), 1630 (C=N), 1246 (C=S); ^{1}H NMR (DMSO-d_6, 300 MHz, ppm) δ: 5.42 (s, 1H, pyrimidinethione-4H), 5.98 (s, 2H, 1,3-dioxole-CH_2), 6.22 (s, 2H, NH_2), 4.65 (s, 2H, NH_2), 6.78–6.87 (m, 3H, ArH), 9.11 (s, 1H, NH), 9.40 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 100 MHz, ppm) δ: 49.6, 58.7, 73.2, 102.5, 108.1, 109.2, 113.1, 120.5, 135.3, 145.4, 146.6, 150.7, 158.1, 162.4, 174.7; MS (70 eV) *m/z* (%): 340 (M^+, 0.23), 307 (100). *Anal*. Calcd for $C_{15}H_{12}N_6O_2S$: C: 52.94, H: 3.52, N: 24.70, S: 9.41. Found C: 52.76, H: 3.71, N: 24.56, S: 9.50.

Synthesis of 4-amino-5-(benzo[*d*][1,3]dioxol-5-yl)-7-thioxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-2(1*H*)-one (10a).

A mixture of equimolar amounts of compound **2** (2.74 g, 0.01 mol) and urea (0.6 g, 0.01 mol) in sodium ethoxide solution, 0.23 g of sodium metal in 20 mL absolute ethanol, was refluxed for 12 h. The reaction mixture was poured into crushed ice and neutralized with hydrochloric acid (10 mL, 6*N*). The formed precipitate was collected by filtration, dried, and recrystallized from toluene as yellow crystals. Yield (1.90 g, 60%), mp 237–238°C; IR (KBr, cm^{-1}): 3423, 3314, 3167 (NH_2, 3NH), 3090 (CH aromatic), 2953 (CH aliphatic), 1697 (C=O, cyclic amide), 1634 (C=N), 1245 (C=S); ^{1}H NMR (DMSO-d_6, 300 MHz, ppm) δ: 5.38 (s, 1H, pyrimidinethione-5H), 5.87 (s, 2H, 1,3-dioxole-CH_2), 6.31 (s, 2H, NH_2), 6.71–6.86 (m, 3H, ArH), 8.74 (s, 1H, NH), 9.24 (s, 1H, NH), 9.59 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 100 MHz, ppm) δ: 58.3, 102.3, 103.5, 108.7, 109.2, 120.4, 134.9, 145.2, 146.8, 151.3, 157.4, 162.1, 176.3; MS (70 eV) *m/z* (%): 317 (M^+, 1.15), 315 (M^+-2, 2.63), 207 (100). *Anal*. Calcd for $C_{13}H_{11}N_5O_3S$: C: 49.21, H: 3.47, N: 22.08, S: 10.09. Found C: 49.62, H: 3.38, N: 22.16, S: 10.13.

Synthesis of 5-amino-4-(benzo[*d*][1,3]dioxol-5-yl)-3,4-dihydropyrimido[4,5-*d*] pyrimidine-2,7(1*H*,8*H*)dithione (10b).

A mixture of equimolar amounts of compound **2** (2.74 g, 0.01 mol) and thiourea (0.76 g, 0.01 mol) in sodium ethoxide solution, 0.23 g of sodium metal in 20 mL absolute ethanol, was refluxed for 12 h. The reaction mixture was poured into crushed ice and neutralized with hydrochloric acid (10 mL, 6*N*). The formed precipitate was collected by filtration, dried, and recrystallized from ethanol as yellow crystals. Yield (1.74 g, 52%), mp 263°C; IR (KBr, cm^{-1}): 3300, 3198 (NH_2, 3NH), 3043 (CH aromatic), 2949 (CH aliphatic), 1645 (C=N), 1251 (C=S); ^{1}H NMR (DMSO-d_6, 300 MHz, ppm) δ: 5.53 (s, 1H, pyrimidinethione-5H), 5.88 (s, 2H, 1,3-dioxole-CH_2), 6.20 (s, 2H, NH_2), 6.88–7.03 (m, 3H, ArH), 8.55 (s, 1H, NH), 9.13(s, 1H, NH), 9.49 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 100 MHz, ppm) δ: 58.5, 102.5, 108.7, 109.6, 108.3, 120.6, 134.8, 145.2, 146.4, 156.9, 161.7, 174.2, 176.4; MS (70 eV) *m/z* (%): 333 (M^+, 0.34), 216 (100). *Anal*. Calcd for $C_{13}H_{11}N_5O_2S_2$: C: 46.84, H: 3.30, N: 21.02, S: 19.21. Found C: 46.71, H: 3.62, N: 21.37, S: 19.11.

Synthesis of 6-amino-4-(benzo[*d*][1,3]dioxol-5-yl)-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide (11).

Concentrated sulfuric acid (30 mL) was cooled down to 20°C, and then compound **2** (2.74 g, 0.01 mol) was added with contentious stirring to keep the reaction temperature below 30°C. The addition of **2** was completed after 0.5 h, and the reaction was stirred at room temperature for 4 h and then poured with stirring into 200 mL of ice-cold water and neutralized with solid sodium carbonate till PH = 7. The resulted solution was left overnight in the refrigerator, and the product was precipitated, collected by filtration, and washed many times with water, dried, and recrystallized from dioxane as brown crystals. Yield (1.78 g, 61%), mp >360°C; IR (KBr, cm^{-1}): 3328, 3195 ($2NH_2$, 2NH), 2923 (CH aliphatic), 1674 (C=O), 1210 (C=S); ^{1}H NMR (DMSO-d_6, 300 MHz, ppm) δ: 5.13 (s, CH, pyrimidinethione-4H), 5.89 (s, 2H, 1,3-dioxole-CH_2), 6.45 (s, 2H, NH_2), 6.70–6.86 (m, 3H, ArH), 7.22 (s, 2H, NH_2), 8.87 (s, 1H, NH), 9.42 (s, H, NH); ^{13}C NMR (DMSO-d_6, 100 MHz, ppm) δ: 54.7, 79.8, 102.4, 108.7, 109.2, 120.2, 135.7, 138.8, 145.2, 146.7, 162.7, 175.5. *Anal*. Calcd for $C_{12}H_{12}N_4O_3S$: C: 49.31, H: 4.10, N: 19.17, S: 10.95. Found C: 49.03, H: 3.78, N: 19.42, S: 11.12.

Synthesis of 5-(benzo[*d*][1,3]dioxol-5-yl)-2,7-dithioxo-2,3,5,6,7,8-hexahydropyrimido-[4,5-*d*]pyrimidin-4(1*H*)-one (12).

A mixture of equimolar amounts of compound **11** (2.93 g, 0.01 mol) and thiourea (0.76 g, 0.01 mol) in

sodium ethoxide solution, 0.23 g of sodium metal in 20 mL absolute ethanol, was refluxed for 8 h; the reaction mixture was poured into crushed ice and neutralized with hydrochloric acid; the precipitate formed was collected by filtration, dried, and recrystallized from dioxane as brown crystals. Yield (2.20 g, 66%), mp 146–148°C; IR (KBr, cm^{-1}): 3246, 3171 (4NH), 3076 (CH aromatic), 2981(CH aliphatic), 1723 (C═O, cyclic amide), 1240 (C═S); ^{1}H NMR (DMSO-d_6, 300 MHz, ppm) δ: 5.24 (s, 1H, pyrimidinethione-5H), 5.78 (s, 2H, 1,3-dioxole-CH_2), 6.57–7.02 (m, 3H, ArH), 8.22 (s, 1H, NH), 8.42 (s, 1H, NH), 9.51 (s, 1H, NH), 10.18 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 100 MHz, ppm) δ: 56.4, 98.7, 102.3, 108.7, 109.6, 120.4, 135.1, 145.2, 146.6, 150.2, 158.5, 174.3, 178.4; MS (70 eV) *m*/*z* (%): 332 (M^+-2, 0.05), 216 (100). *Anal*. Calcd for $C_{13}H_{10}N_4O_3S_2$: C: 46.70, H: 2.99, N: 16.76, S: 19.16. Found C: 46.95, H: 3.24, N: 16.82, S: 19.01.

Synthesis of *N*-(1,3-diacetyl-6-(benzo[*d*][1,3]dioxol-5-yl)-5-cyano-2-thioxo-1,2,3,6-tetrahydropyrimidin-4-yl)acetamide (13).

A mixture of compound **2** (2.74 g, 0.01 mol) and acetyl chloride (0.03 mol) in dioxane (30 mL) was refluxed for 4 h. The reaction mixture was cooled down and poured over crushed ice. The product was collected by filtration, washed with water, dried, and recrystallized from ethanol as brown crystals. Yield (2.70 g, 68%), mp 260°C (decomposition); IR (KBr, cm^{-1}): 3111 (NH), 3032 (CH aromatic), 2960 (CH aliphatic), 2213 (C≡N), 1692 (C═O), 1249 (C═S); ^{1}H-NMR (DMSO-d_6, 300 MHz, ppm) δ: 2.33 (s, 3H, CH_3), 2.46 (s, 3H, CH_3), 2.50 (s, 3H, CH_3), 5.63 (s, 1H, pyrimidine-4H), 5.84 (s, 1H, NH), 5.98 (s, 2H, 1,3-dioxole-CH_2), 7.20–7.41 (m, 3H, Ar–H); ^{13}C NMR (DMSO-d_6, 100 MHz, ppm) δ: 23.2, 23.5, 24.3, 55.3, 60.3, 102.2, 108.1, 109.0, 119.5, 120.8, 131.0, 131.3, 146.1, 150.8, 168.3, 170.7, 172.3, 173.9; MS (70 eV) *m*/*z* (%): 400 (M^+, 2.45), 275 (100). *Anal*. Calcd for $C_{18}H_{16}N_4O_5S$: C: 54.00, H: 4.00, N: 14.00, S: 8.00. Found C: 54.36, H: 3.91, N: 14.17, S: 8.09.

Synthesis of *N*-(6-(benzo[*d*][1,3]dioxol-5-yl)-1,3-bis(2-chloroacetyl)-5-cyano-2-thioxo-1,2,3,6-tetrahydropyrimidin-4-yl)-2-chloroacetamide (14).

A mixture of compound **2** (2.74 g, 0.01 mol) and chloroacetyl chloride (0.03 mol) in dioxane (30 mL) was heated under reflux for 4 h. The reaction mixture was cooled and poured over crushed ice; the product was collected by filtration, washed with water, dried, and recrystallized from ethanol as dark brown crystals. Yield (4.10 g, 82%), mp 274°C (decomposition); IR (KBr, cm^{-1}): 3138 (NH), 3038 (CH aromatic), 2918 (CH aliphatic), 2214 (C≡N), 1680 (C═O), 1242 (C═S); ^{1}H NMR (DMSO-d_6, 300 MHz, ppm) δ: 4.30 (s, 2H, $COCH_2$), 4.52 (s, 2H, $COCH_2$), 4.68 (s, 2H, $COCH_2$), 5.65 (s, 1H, pyrimidinethione-6H), 5.94 (s, 2H, 1,3-dioxole-CH_2), 6.82–7.25 (m, 3H, ArH), 8.45 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 100 MHz, ppm) δ: 41.3, 44.0, 45.1, 58.2, 60.7, 102.8, 108.4, 110.3, 119.5, 121.0, 129.9, 130.3, 148.0, 150.2, 158.1, 160.8, 172.2, 174.6; MS (70 eV) *m*/*z* (%): 503 (M^+, 3.43), 365 (100). *Anal*. Calcd for $C_{18}H_{13}N_4O_5SCl_3$: C: 42.89, H: 2.58, N: 11.12, S: 6.35, Cl: 21.15. Found C: 42.63, H: 2.41, N: 11.09, S: 6.22, Cl: 21.30.

Synthesis of 1,3-diacetyl-5-amino-4-(benzo[*d*][1,3]dioxol-5-yl)-2-thioxo-1,2,3,4-tetrahydropyrido[2,3-*d*]pyrimidin-7-yl acetate (15).

To a solution of compound **2** (2.74 g, 0.01 mol) in acetic anhydride (15 mL), 15 mL of concentrated phosphoric acid was added. After addition completion, the reaction mixture became very hot, and on reflux, it turned to dark brown; the reflux was continued for extra 10 h and then poured into ice-cold water and neutralized with solid sodium carbonate till PH = 7. The solid precipitate that separated out was filtered off and recrystallized from acetic acid as brown crystals. Yield (3.40 g, 77%), mp >360°C; IR (KBr, cm^{-1}): 3379, 3211 (NH_2), 3089 (CH aromatic), 2918 (CH aliphatic), 1713 (C═O, ester carbonyl gp), 1659 (C═O, amide carbonyl gp), 1294 (C═S); ^{1}H NMR (DMSO-d_6, 300 MHz, ppm) δ: 2.21 (s, 3H, CH_3), 2.43 (s, 3H, CH_3), 2.54 (s, 3H, CH_3), 5.12 (s, 1H, pyridine-H), 5.40 (s, 1H, pyrimidinethione-4H), 5.92 (s, 2H, 1,3-dioxole-CH_2), 6.32 (s, NH_2), 6.89–7.40 (m, 3H, ArH); ^{13}C NMR (DMSO-d_6, 100 MHz, ppm) δ: 21.1, 23.6, 25.7, 58.6, 96.1, 102.3, 107.1, 108.9, 110.8, 120.8, 131.9, 145.0, 146.2, 149.6, 152.1, 154.7, 165.9, 170.3, 171.4, 175.0; MS (70 eV) *m*/*z* (%): 444 (M^++2, 22.61), 417 (100). *Anal*. Calcd for $C_{20}H_{18}N_4O_6S$: C: 54.29, H: 4.07, N: 12.66, S: 7.23. Found C: 54.32, H: 3.89, N: 12.47, S: 7.61.

Synthesis of 1,3-diacetyl-4-(benzo[*d*][1,3]dioxol-5-yl)-5-(4-hydroxy-3-methoxybenzylideneamino)-2-thioxo-1,2,3,4-tetra hydropyrido[2,3-*d*]pyrimidin-7-yl acetate (16).

A mixture of compound **15** (4.42 g, 0.01 mol) and vanillin (1.52 g, 0.01 mol) was fused in oil bath in presence of few drops of piperidine for 0.5 h, and then the reaction was left to cool down, and the resulting precipitate was dissolved in ethanol. The resulting solution was diluted with ice-cold water, and the formed precipitate was filtered off, dried, and recrystallized from ethanol as brown crystals. Yield (3.62 g, 63%), mp 261–262°C; IR (KBr, cm^{-1}): 3435 (OH), 3045 (CH aromatic), 2922 (CH aliphatic), 1733 (C═O, ester carbonyl gp), 1669 (C═O, amide carbonyl gp), 1617 (C═N), 1255 (C═S); ^{1}H NMR (DMSO-d_6, 300 MHz, ppm) δ: 2.26 (s, 3H, CH_3), 2.39 (s, 3H, CH_3), 2.51 (s, 3H, CH_3), 3.70 (s, 3H, OCH_3), 5.43 (s, CH, pyrimidinethione), 5.60 (s, 1H, OH), 5.89 (s, 2H, 1,3-

dioxole-CH_2), 6.86–7.78 (m, 6H, ArH), 7.83 (s, 1H, Pyridine 6-H), 8.56 (s, 1H, CH═N); ^{13}C NMR (DMSO-d_6, 100 MHz, ppm) δ: 20.9, 23.4, 25.6, 55.8, 58.3, 102.6, 104.3, 108.1, 109.5, 111.8, 113.2, 115.0, 121.9, 125.5, 126.1, 131.3, 145.6, 146.7, 148.0, 150.2, 151.9, 154.6, 158.1, 165.2, 168.6, 170.6, 175.0, 182.4; MS (70 eV) *m/z* (%): 576 (M^+, 74.88), 213 (100). *Anal*. Calcd for $C_{28}H_{24}N_4O_8S$: C: 58.33, H: 4.16, N: 9.72, S: 5.55. Found C: 58.62, H: 4.03, N: 9.81, S: 5.50.

Synthesis of ethyl *N*-1,3-diacetyl-6-(benzo[*d*][1,3]dioxol-5-yl)-5-cyano-2-thioxo-1,2,3,6-tetrahydropyrimidin-4-ylformi midate (17).

To a solution of compound **2** (2.74 g, 0.01 mol) in acetic anhydride (30 mL), triethyl orthoformate (1.4 mL, 0.01 mol) was added, and then the reaction mixture was heated under reflux for 5 h; the solvent was left to evaporate, and the solid product was filtered off, dried, and recrystallized from toluene as reddish brown crystals. Yield (2.45 g, 59%), mp 228°C; IR (KBr, cm^{-1}): 3115 (CH aromatic), 2976 (CH aliphatic), 2208 (C≡N), 1680 (C═O), 1628 (C═N), 1250 (C═S); ^{1}H NMR (DMSO-d_6, 300 MHz, ppm) δ: 1.21 (t, 3H, J = 6.0 Hz, CH_3), 2.17 (s, 3H, CH_3), 2.28 (s, 3H, CH_3), 3.42 (q, 2H, J = 6.0 Hz, CH_2), 5.25 (s, 1H, pyrimidinethione-6H), 5.88 (s, 2H, 1,3-dioxole-CH_2), 6.82 (s, 1H, N═CH), 7.15–7.52 (m, 3H, ArH); ^{13}C NMR (DMSO-d_6, 100 MHz, ppm) δ: 15.6, 22.7, 24.9, 59.3, 63.2, 64.7, 102.2, 108.3, 109.1, 118.6, 121.0, 131.6, 145.3, 146.4, 150.4, 168.1, 170.1, 174.4, 178.5; MS (70 eV) *m/z* (%): 414 (M^+, 99.69), 268 (100). *Anal*. Calcd for $C_{19}H_{18}N_4O_5S$: C: 55.07, H: 4.34, N: 13.52, S: 7.72. Found C: 55.28, H: 4.51, N: 13.32, S: 7.81.

Synthesis of ethyl *N*-6-(benzo[*d*][1,3]dioxol-5-yl)-5-cyano-2-thioxo-1,2,3,6-tetrahydropyrimidin-4-ylformimidate (18).

A mixture of compound **2** (2.74 g, 0.01 mol) and triethyl orthoformate (10 mL) in ethanol (30 mL) was stirred under reflux for 8 h. After cooling to room temperature, the separated precipitate was filtered off, dried, and recrystallized from methanol as brown crystals. Yield (2.15 g, 65%), mp >360°C; IR (KBr, cm^{-1}): 3218, 3129 (2NH), 3045 (CH aromatic), 2919 (CH aliphatic), 2220 (C≡N), 1612 (C═N), 1256 (C═S); ^{1}H-NMR (DMSO-d_6, 300 MHz, ppm) δ: 1.19 (t, 3H, J = 4.2 Hz, CH_3), 3.33 (q, 2H, J = 5.9 Hz, CH_2), 5.02 (s, 1H, pyrimidinethione-6H), 6.12 (s, 2H, 1,3-dioxole-CH_2), 7.08 (s, 1H, N═CH), 7.14–7.48 (m, 3H, Ar–H), 7.65 (s, 1H, NH), 8.64 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 100 MHz, ppm) δ: 15.5, 68.8, 62.2, 64.5, 102.3, 108.2, 109.5, 117.6, 120.8, 132.2, 145.3, 146.6, 150.6, 168.6, 175.0; MS (70 eV) *m/z* (%): 332 (M^++2, 2.23), 300 (100). *Anal*. Calcd for $C_{15}H_{14}N_4O_3S$: C: 54.54, H: 4.24, N: 16.96, S: 9.69. Found C: 54.21, H: 4.38, N: 17.23, S: 9.51.

Synthesis of 6-amino-4-(benzo[*d*][1,3]dioxol-5-yl)-5-imino-3,4,5,6-tetrahydropyrimido [4,5-*d*]pyrimidine-2(1*H*)-thione (19).

To a solution of compound **18** (3.3 g, 0.01 mol) in ethanol (30 mL), hydrazine hydrate (0.5 mL, 0.01 mol) was added, and the reaction mixture was refluxed for 17 h and then poured into ice-cold water. The product was filtered off, dried, and recrystallized from ethanol as brown crystals. Yield (1.67 g, 53%), mp 219°C; IR (KBr, cm^{-1}): 3469, 3399, 3247 (NH_2, 3NH), 3055 (CH aromatic), 1619 (C═N), 1227 (C═S); ^{1}H NMR (DMSO-d_6, 300 MHz, ppm) δ: 4.97 (s, 1H, pyrimidinethione-4H), 5.89 (s, 2H, 1,3-dioxole-CH_2), 6.20 (s, 1H, imine-H), 6.97–7.41 (m, 3H, ArH), 7.96 (s, 2H, NH_2), 7.96 (s, 1H, NH), 8.55 (s, 1H, NH), 8.87 (s, 1H, pyrimidine-H); ^{13}C NMR (DMSO-d_6, 100 MHz, ppm) δ: 57.5, 96.8, 102.2, 108.8, 109.3, 121.0, 133.6, 138.3, 140.7, 145.4, 146.8, 157.3, 175.5; MS (70 eV) *m/z* (%): 316 (M^+, 38.13), 180 (100). *Anal*. Calcd for $C_{13}H_{12}N_6O_2S$: C: 49.36, H: 3.79, N: 26.58, S: 10.12. Found C: 49.77, H: 3.42, N: 26.41, S: 10.53.

Synthesis of 3-amino-4-(benzo[*d*][1,3]dioxol-5-yl)-4,5-dihydro-1*H*-pyrazolo[3,4-*d*]-pyrimidine-6(7*H*)-thione (20).

A mixture of compound **2** (2.74 g, 0.01 mol) and hydroxylamine hydrochloride (0.695 g, 0.01 mol) in glacial acetic acid (30 mL) containing anhydrous sodium acetate (0.2 g) was refluxed for 7 h. The reaction mixture was left to stand overnight at room temperature and then poured into crushed ice. The separated product was collected by filtration, washed with water, dried, and recrystallized from ethanol as white crystals. Yield (1.67 g, 58%), mp >360°C; IR (KBr, cm^{-1}): 3435, 3383, 3190 (NH_2, 3NH), 3030 (CH aromatic), 2921 (CH aliphatic), 1613 (C═N), 1258 (C═S); ^{1}H NMR (DMSO-d_6, 300 MHz, ppm) δ: 5.01 (s, 1H, pyrimidinethione-4H), 5.90 (s, 2H, 1,3-dioxole-CH_2), 6.72 (s, 2H, NH_2), 6.91–7.36 (m, 3H, ArH), 8.56 (s, 1H, NH), 9.42 (s, 1H, NH), 9.82 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 100 MHz, ppm) δ: 55.1, 102.6, 103.5, 108.7, 109.6, 120.5, 133.7, 144.8, 146.1, 147.6, 158.4, 174.6; MS (70 eV) *m/z* (%): 293 (M^++4, 15.42), 291 (M^++2, 3.03), 274 (100). *Anal*. Calcd for $C_{12}H_{11}N_5O_2S$: C: 49.82, H: 3.80, N: 24.22, S: 11.07. Found C: 50.12, H: 3.54, N: 24.67, S: 11.31.

Synthesis of ethyl 5-amino-4-(benzo[*d*][1,3]dioxol-5-yl)-7-oxo-2-thioxo-1,2,3,4,7,8-hexahydropyrido[2,3-*d*]pyrimidine-6-carboxylate (21a).

A mixture of compound **2** (2.74 g, 0.01 mol), diethyl malonate (1.52 mL, 0.01 mol), and glacial acetic acid (20 mL) was refluxed for 12 h. The reaction mixture was left to cool down to room temperature, and the formed product was collected by filtration, dried, and recrystallized from ethanol as yellow crystals. Yield (2.32 g, 60%), mp 242°C; IR (KBr, cm^{-1}): 3245, 3214,

3118 (NH_2, 3NH), 3095 (CH aromatic), 2923 (CH aliphatic), 1733 (C═O, ester carbonyl gp), 1669 (C═O, cyclic amide), 1256 (C═S); ^{1}H-NMR (DMSO-d_6, 300 MHz, ppm) δ: 1.87 (t, 3H, J = 5.3 Hz, CH_3), 4.35 (q, 2H, J = 6.0 Hz, CH_2), 5.10 (s, 1H, pyrimidinethione-4H), 6.02 (s, 2H, 1,3-dioxole), 6.10 (s, 2H, NH_2), 6.86–6.93 (m, 3H, Ar–H), 9.96 (s, 1H, NH), 10.11 (s, 1H, NH), 10.43 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 100 MHz, ppm) δ: 15.8, 60.5, 61.3, 94.3, 96.5, 102.6, 108.0, 109.7, 120.3, 134.1, 145.4, 146.5, 150.6, 158.1, 158.9, 162.6, 174.3; MS (70 eV) *m*/*z* (%): 387 (M^+-1, 0.75), 275 (100). *Anal*. Calcd for $C_{17}H_{16}N_4O_5S$: C: 52.57, H: 4.12, N: 14.43, S: 8.24. Found C: 52.14, H: 4.37, N: 14.81, S: 8.01.

Synthesis of 5-amino-4-(benzo[*d*][1,3]dioxol-5-yl)-7-oxo-2-thioxo-1,2,3,4,7,8-hexahydropyrido[2,3-*d*]pyrimidine-6-carbo nitrile (21b).

A mixture of compound **2** (2.74 g, 0.01 mol), ethyl cyanoacetate (1.06 mL, 0.01 mol), and glacial acetic acid (20 mL) was refluxed for 12 h. The reaction mixture was left to cool down to room temperature, and then the separated solid was collected by filtration, dried, and recrystallized from ethanol as yellow crystals. Yield (2.50 g, 73%), mp 258°C; IR (KBr, cm^{-1}): 3323, 3187 (NH_2, 3NH), 3026 (CH aromatic), 2899 (CH aliphatic), 2185 (C≡N), 1725 (C═O, cyclic amide), 1246 (C═S); ^{1}H NMR (DMSO-d_6, 300 MHz, ppm) δ: 5.18 (s, 1H, pyrimidinethione-4H), 5.98 (s, 1H, 1,3-dioxole-CH_2), 6.40 (s, 2H, NH_2), 6.68–6.89 (m, 3H, ArH), 7.98 (s, 1H, NH), 8.88 (s, 1H, NH), 9.21 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 100 MHz, ppm) δ: 61.0, 93.7, 101.8, 108.7, 109.4, 115.6, 117.3, 120.6, 134.7, 145.2, 146.3, 148.8, 160.3, 163.5, 176.0; MS (70 eV) *m*/*z* (%): 341 (M^+, 28.76), 157 (100). *Anal*. Calcd for $C_{15}H_{11}N_5O_3S$: C: 52.78, H: 3.22, N: 20.52, S: 9.38. Found C: 52.59, H: 3.67, N: 20.86, S: 9.07.

Synthesis of 4-(benzo[*d*][1,3]dioxol-5-yl)-6-(4-hydroxy-3-methoxybenzylideneamino)-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carbonitrile (22a).

A mixture of compound **2** (2.74 g, 0.01 mol) and vanillin (1.52 g, 0.01 mol) in presence of few drops of piperidine was subjected to fusion in oil bath for 0.5 h, and then the reaction mixture was left to cool down, and the resulting product was dissolved in ethanol and diluted with ice-cold water. The separated solid was filtered off, dried, and recrystallized from benzene as orange crystals. Yield (2.70 g, 66%), mp 221°C; IR (KBr, cm^{-1}): 3327, 3180 (2NH, OH), 3011 (CH aromatic), 2918 (CH aliphatic), 2186 (C≡N), 1623 (C═N), 1242 (C═S); ^{1}H NMR (DMSO-d_6, 300 MHz, ppm) δ: 3.78 (s, 3H, OCH_3), 5.52 (s, 1H, pyrimidinethione-4H), 5.58 (s, 1H, OH), 6.04 (s, 2H, 1,3-dioxole-CH_2), 6.70–7.20 (m, 6H, ArH), 8.25 (s, 1H, NH), 8.60 (s, 1H, CH═N), 9.32 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 100 MHz, ppm) δ: 56.1, 60.2, 72.8, 102.3, 108.4, 109.3, 113.2, 115.0, 118.6, 120.9, 125.7, 126.9, 134.6, 142.2, 146.6, 148.4, 150.1, 151.8, 161.2, 174.6; MS (70 eV) *m*/*z* (%): 408 (M^+, 2.02), 406 (M^+-2, 19.24), 323 (100). *Anal*. Calcd for $C_{20}H_{16}N_4O_4S$: C: 58.82, H: 3.92, N: 13.72, S: 7.84. Found C: 59.12, H: 3.88, N: 13.81, S: 7.51.

Synthesis of 4-(benzo[*d*][1,3]dioxol-5-yl)-6-(4-nitrobenzylideneamino)-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carbonitrile (22b).

A mixture of compound **2** (2.74 g, 0.01 mol) and *p*-nitrobenzaldehyde (1.51 g, 0.01 mol) in presence of few drops of piperidine was subjected to fusion in oil bath for 0.5 h, and then the reaction mixture was left to cool down, and the resulting product was dissolved in ethanol and diluted with ice-cold water. The separated solid was filtered off, dried, and recrystallized from toluene as brown crystals. Yield (3.10 g, 76%), mp 167°C; IR (KBr, cm^{-1}): 3358, 3219 (2NH), 3005 (CH aromatic), 2929 (CH aliphatic), 2195 (C≡N), 1604 (C═N), 1243 (C═S); ^{1}H NMR (DMSO-d_6, 300 MHz, ppm) δ: 5.35 (s, CH, pyrimidinethione-4H), 5.90 (s, 2H, 1,3-dioxole-CH_2), 6.81–7.20 (m, 3H, ArH), 7.58 (d, 2H, J = 7.5 Hz, ArH), 8.23 (s, 1H, NH), 8.32 (d, 2H, J = 7.5 Hz, ArH), 8.75 (s, 1H, CH═N), 9.83 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 100 MHz, ppm) δ: 58.2, 72.8, 102.5, 108.9, 109.6, 117.0, 120.3, 124.6, 131.5, 134.6, 140.2, 145.1, 146.5, 150.7, 151.8, 162.1, 175.6; MS (70 eV) *m*/*z* (%): 407 (M^+, 1.16), 323 (100). *Anal*. Calcd for $C_{19}H_{13}N_5O_4S$: C: 56.01, H: 3.19, N: 17.19, S: 7.86. Found C: 56.43, H: 3.38, N: 17.01, S: 7.53.

Synthesis of ethyl 6-amino-5-(benzo[*d*][1,3]dioxol-5-yl)-3-oxo-2,3,5,8-tetrahydropyrrolo-[2,3-*d*]thiazolo[3,2-*a*]pyrimi dine-7-carboxylate (23).

A mixture of compound **2** (2.74 g, 0.01 mol), ethyl bromoacetate (2.22 mL, 0.02 mol), and anhydrous potassium carbonate (1.37 g, 0.01 mol) in dry acetone (40 mL) was heated under reflux with contentious stirring for 10 h; the reaction was left to stand overnight at room temperature and then poured over crushed ice. The separated solid was filtered off, washed with water, dried, and recrystallized from dioxane as orange crystals. Yield (3.15 g, 79%), mp 156°C; IR (KBr, cm^{-1}): 3357, 3190 (NH_2, NH), 3099 (CH aromatic), 2983 (CH aliphatic), 1733 (C═O, ester carbonyl gp), 1678 (C═O, cyclic amide); ^{1}H-NMR (DMSO-d_6, 300 MHz, ppm) δ: 1.46 (t, 3H, J = 5.1 Hz, CH_3), 3.78 (s, 2H, thiazole-CH_2), 4.88 (q, 2H, J = 5.3 Hz, CH_2), 5.98 (s, 2H, 1,3-dioxole-CH_2), 6.13 (s, 1H, pyrimidine-H), 6.66 (s, 2H, NH_2), 6.70–7.01 (m, 3H, Ar–H), 9.70 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 100 MHz, ppm) δ: 15.3, 31.7, 58.3, 61.2, 102.0, 107.6, 108.5, 109.2, 110.6, 120.9, 124.0, 131.3, 141.1, 145.5, 146.6, 150.1, 164.1, 168.8; MS (70 eV) *m*/*z* (%): 400 (M^+, 19.57), 271 (100). *Anal*. Calcd for $C_{18}H_{16}N_4O_5S$:

C: 54.00, H: 4.00, N: 14.00, S: 8.00. Found C: 54.37, H: 4.13, N: 14.31, S: 7.84.

Synthesis of methyl 8-amino-6-(benzo[*d*][1,3]dioxol-5-yl)-7-cyano-4-oxo-4,6-dihydropyrimido[2,1-*b*][1,3]thiazine-2-carboxylate (24).

A mixture of compound **2** (2.74 g, 0.01 mol) and dimethyl acetylene dicarboxylate (1.22 mL, 0.01 mol) in ethanol (30 mL) was refluxed for 15 h. The crude solid product that precipitated out was collected by filtration, dried, and recrystallized from ethanol as red crystals. Yield (2.70 g, 70%), mp 268°C; IR (KBr, cm^{-1}): 3442, 3337 (NH_2), 3057 (CH aromatic), 2950 (CH aliphatic), 2207 (C≡N), 1725 (C═O, ester carbonyl), 1698 (C═O, cyclic amide), 1640 (C═N); ^{1}H-NMR (DMSO-d_6, 300 MHz, ppm) δ: 3.74 (s, 3H, OCH_3), 5.60 (s, 1H, pyrimidine-H), 5.98 (s, 2H, 1,3-dioxole), 6.04 (s, 2H, NH_2), 6.82 (s, 1H, thiazine-CH), 6.79–6.91 (m, 3H, Ar–H); ^{13}C NMR (DMSO-d_6, 100 MHz, ppm) δ: 50.3, 55.1, 68.5, 102.6, 108.5, 110.5, 117.7, 120.8, 121.1, 131.3, 141.3, 145.1, 146.5, 148.2, 157.8, 163.2, 166.8; MS (70 eV) *m/z* (%): 384 (M^+, 11.92), 207 (100). *Anal*. Calcd for $C_{17}H_{12}N_4O_5S$: C: 53.12, H: 3.12, N: 14.58, S: 8.33. Found C: 53.41, H: 3.35, N: 14.18, S: 8.07.

ANTIMICROBIAL ACTIVITY ASSAY

Disc diffusion protocol utilizing sterile Whatman No. 5 filter paper discs (11 mm diameter) was used to screen the *in vitro* antimicrobial properties of compounds under investigation towards selected microbial strains [29]. Accordingly and after purification by recrystallization, the tested compounds were dissolved in ethanol, 11 mm filter paper discs were loaded with 10 mg/mL of compounds under investigation (50 μL), and total dryness was accessible through placing the discs with caution under a stream of hot air.

Posteriorly, 10 mL freshly prepared Muller–Hinton agar medium seeded with the test bacterial strain was poured in each test plate. The discs were placed on the top of agar plates' surfaces, which were incubated at 5°C for 1 h to permit a good diffusion. The incubation was performed for 24 h at 37°C. After incubation, the microorganism's outgrowth was observed. The average inhibition zone diameters were recorded in millimeters and used as norm for the antimicrobial activity. Noteworthy, the plates were done in triplicate to obtain the average growth. The inhibitory effect of the investigated compounds is proportional to the observed clear zone size. In each experiment, solvent disc control was incorporated as negative criterion. For comparison, norfloxacin (standard drug) was also screened for antibacterial activity using the same conditions.

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