One-Step Synthesis of 1-(4,5-Diphenylpyrimidin-2-yl)thiourea

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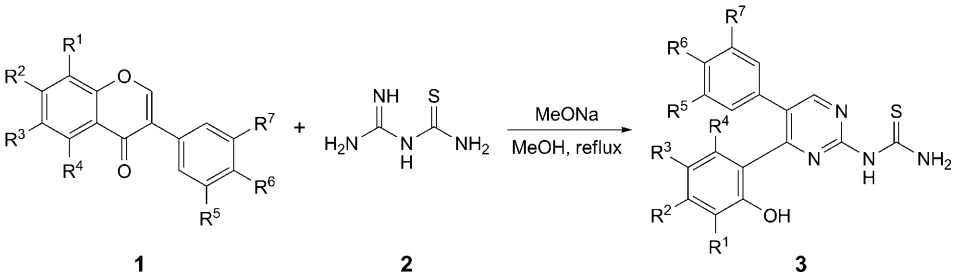
A simple and straightforward methodology toward the synthesis of novel 1-(4,5-diphenylpyrimidin-2-yl)thiourea has been developed by a one-step reaction of isoflavones with amidinothiourea. A series of 16 new compounds was synthesized. All compounds were characterized by FT-IR, NMR, and elemental analysis. The structure of a typical compound was established by X-ray diffraction. A variety of substrates can participate in the process with good yields and high purities, making this methodology suitable for library synthesis in drug discovery.

Introduction. – Pyrimidines are well-known and widely investigated six-membered N-containing heterocyclic compounds that exhibit important biological activities [1–4]. Thiourea and their related analogs have become the focus of interest in recent past on account of their pharmacological activities such as anti-HIV [5], antinociceptive [6], antibacterial [7], antiviral [8], and anticancer [8]. It is convenient to synthesize substituted pyrimidines by reaction of amidines or guanidines with α,β-unsaturated ketones [9][10], β-diketones [11][12], β-alkoxy- and β-aminovinyl ketones [13–16], and *N*-arylacetylenic imines [17][18]. Natural isoflavones display a wide range of biological activities [19]. For instance, soybean isoflavones (daidzein and genistein) have shown pharmacological effects such as antidysrhythmic [20], antioxidant [21], and anticardio-cerebral vascular disease activities [22]. Ipriflavone (= 7-(1-methylethoxy)-3-phenyl-4*H*-benzopyran-4-one) has been reported to be efficient in preventing and treating osteoporosis [23]. It was reported that the chromone fragment present in isoflavones can generate a 1,3-diketone equivalent which readily react with amidines [24], guanidine [2], carbamide [25], and sulfocarbamides [26] to form the corresponding 2-substituted pyrimidines. The use of combinatorial approaches for the high-throughput synthesis of this drug-like scaffold would be a powerful advance in helping to speed up drug discovery. Recently, we have reported the high-throughput synthesis of 3,4-diarylpyrazoles and 4,5-diphenylpyrimidin-2-ylguanidine by a one-pot reaction of hydrazine [27] or bisguanidine [28] with isoflavones. To the best of our knowledge, using isoflavone as starting material to synthesize the pyrimidinylthioureas has not been reported so far. Herein, we report a new way for the preparation of the unknown class of 1-(4,5-diphenylpyrimidin-2-yl)thiourea by the cyclocondensation of isoflavones (**1**) with amidinothiourea (**2**; *Table 1*).

Table 1. *Synthesis of 1-(4,5-Diphenylpyrimidin-2-yl)thiourea by Reaction of Various isoflavones with Amidinothiourea in MeOH* (for details, see *Exper. Part*)



1 **2** **3**

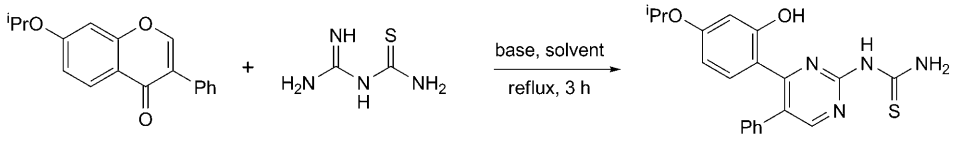
Entry	Substrate	R^1	R^2	R^3	R^4	R^5	R^6	R^7	Time [h]	Yield of **3** [%][a])
1	**1a**	H	^{i}PrO	H	H	H	H	H	3.0	69
2	**1b**	H	MeO	H	MeO	H	MeO	H	2.5	72
3	**1c**	H	MeO	H	H	H	MeO	H	2.5	80
4	**1d**	H	MeO	H	H	H	H	H	3.0	67
5	**1e**	H	MeO	MeO	MeO	H	MeO	H	2.0	72
6	**1f**	H	MeO	H	Me	H	H	H	3.5	65
7	**1g**	Br	^{i}PrO	H	H	H	H	H	2.5	73
8	**1h**	H	EtO	H	H	H	MeO	H	2.5	76
9	**1i**	H	BnO	H	H	H	BnO	H	3.0	68
10	**1j**	H	MeO	H	H	^{i}Pr	MeO	^{i}Pr	3.5	87[b])
11	**1k**	H	MeO	H	MeO	^{i}Pr	MeO	^{i}Pr	3.5	74
12	**1l**	H	MeO	H	H	H	OH	H	4.0	53
13	**1m**	H	MeO	H	H	^{i}Pr	OH	^{i}Pr	4.5	60
14	**1n**	H	MeO	H	H	H	OH	NO_2	4.0	57
15	**1o**	H	MeO	Br	H	Br	OH	Br	5.0	54
16	**1p**	H	OH	H	H	H	MeO	H	24	–[c])

[a]) Yield of product after recrystallization from EtOH. [b]) Yield of product after chromatography on silica gel. [c]) Target compound **3p** was not obtained.

Results and Discussion. – We turned our attention to optimize the condition of the cyclocondensations of isoflavones **1** with amidinothiourea (**2**) and designed a process based on the cyclocondensation of ipriflavone (**1a**) with amidinothiourea (**2**) as a model substrate (*Table 2*). As shown in *Table 2*, we used NaOH as base, and **3a** was obtained in 36% yield (*Entry 1*). It was also found that K_2CO_3 was ineffective in providing the desired condensation product (*Entry 2*). A comparative reactivity study of bases in the reaction showed that MeONa proved to be more effective for this cyclocondensation (*Entry 3*). From the solvents tried, MeOH, EtOH, THF, MeCN, BuOH, and DMF, MeOH gave the expected result (*Entry 3*). Further study with varying MeONa equivalents revealed that 3.0 equiv. of base is necessary to obtain a high yield of the condensation product (*Entry 10*). Finally, the ratio **1a**/**2** was also evaluated. In the case of a ratio **1a**/**2** of 1:3, the yield of **3a** was high for the cyclocondensation reaction (*Entry 13*).

With the optimized reaction conditions and results in hand, the condensation of a variety of structurally divergent isoflavones (**1**) and amidinothiourea (**2**) were studied

Table 2. *Optimization of Cyclocondensation of Ipriflavone* (**1a**) *with Amidinothiourea* (**2**)[a])



1a **2** **3a**

Entry	Solvent	Base	Molar ratio **1a**/**2**/base	Yield of **3a** [%][b])
1	MeOH	NaOH	1:1:1	36
2	MeOH	K_2CO_3	1:1:1	29
3	MeOH	MeONa	1:1:1	61
4	EtOH	MeONa	1:1:1	52
5	THF	MeONa	1:1:1	trace
6	MeCN	MeONa	1:1:1	38
7	BuOH	MeONa	1:1:1	30
8	DMF	MeONa	1:1:1	28
9	MeOH	MeONa	1:1:2	72
10	MeOH	MeONa	1:1:3	79
11	MeOH	MeONa	1:1:4	66
12	MeOH	MeONa	1:2:3	85
13	MeOH	MeONa	1:3:3	93
14	MeOH	MeONa	1:4:3	91

[a]) All reactions were carried out in the appropriate solvent (15 ml) using ipriflavone (**1a**), amidinothiourea (**2**), and base until complete disappearance of **1a** (reflux for 3 h, TLC check). [b]) Yield of product after chromatography on silica gel.

to illustrate this concise and general method for the synthesis of 1-(4,5-diphenylpyrimidin-2-yl)thiourea. All substrates smoothly reacted for 2–5 h to give the corresponding 1-(4,5-diphenylpyrimidin-2-yl)thiourea in good-to-excellent yields, and the results are summarized in *Table 1*. All products were characterized by IR, ^{1}H- and ^{13}C-NMR spectroscopy, and elemental analysis. Single-crystal X-ray diffraction analysis of **3a** (*Fig.*) was used to corroborate the postulated structures unequivocally, which added clear evidence for the structure.

In general, isoflavone **1** substituted with RO and BnO groups gave high yields. In contrast, the presence of OH groups led to lower yields. As shown in *Table 1*, isoflavones **1a**–**1k** (*Entries 1–11*), which do not contain OH groups, gave **3** in *ca.* 70% yields. Isoflavones with one OH group at C(4′), **1l**–**1o** (R^6 = OH, *Entries 12–15*) gave **3** in only *ca.* 55% yields. However, when one free OH group in engaged on the benzopyranone ring, at C(7), it would be the O^- part under basic condition which possessed stronger electron-donor quality than RO and BnO groups of the isoflavone, and it was not favorable for the condensation of **1** with **2**. Using **1p** as starting material, 2-amino-4-(2,4-dihydroxyphenyl)-5-(4-methoxyphenyl)pyrimidine was obtained instead of the expected product **3p** (*Entry 16*). In a longer reaction time, **3p** was hydrolyzed, lost thioureido fragment, and was converted to 2-amino-4-(2,4-dihydroxyphenyl)-5-(4-methoxyphenyl)pyrimidine.

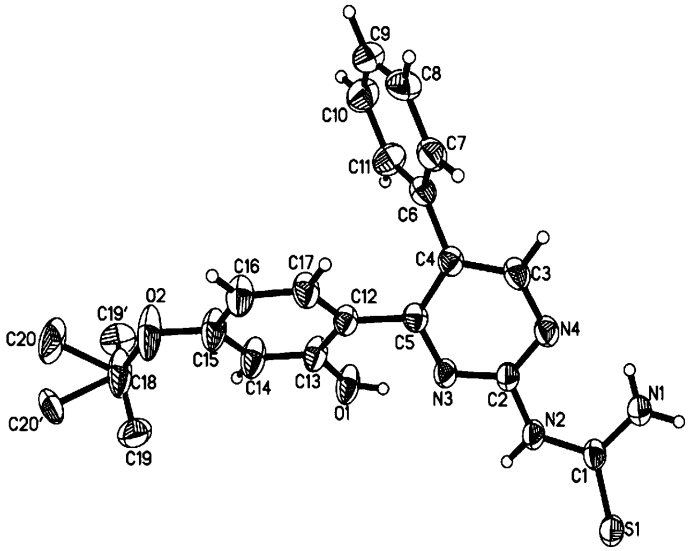


Figure. *Single-crystal X-ray structure of* **3a**. Displacement ellipsoids are shown at the 30%-probability level. In the case of **3a**, one ^{i}PrO group is disordered.

To rationalize the mechanism of the formation of 1-(4,5-diphenylpyrimidin-2-yl)thiourea **3** by the cyclocondensation of isoflavones **1** with amidinothiourea (**2**) in the presence of MeONa, a postulated reaction course is illustrated in the *Scheme*. As it has been already reported, isoflavone may undergo ring-opening reaction, when refluxing in the presence of alkali, to form a α,β-unsaturated ketone intermediate **4** [29]. Subsequent attack of the primary amine group of the amidinothiourea (**2**) at the β-C-atom of **4**, followed by ring-closure reaction between secondary amine and the C=O C-atom, led to **3**. Meanwhile, intermediate **4** at a high concentration of base may eliminate $HC(OMe)_3$ to generate a by-product **5** [29].

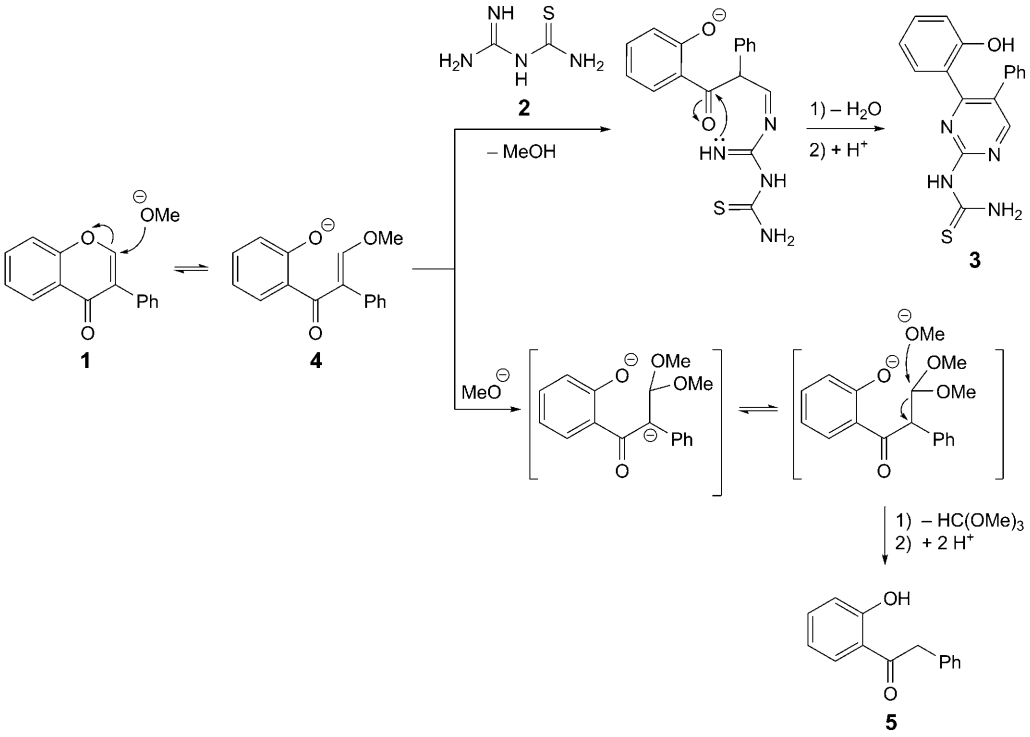
Conclusions. – In summary, a convenient method for the synthesis of substituted pyrimidines bearing thiourea moiety at C(2) was described. The protocol was applicable to a variety of isoflavones and amidinothiourea as starting materials and gave 1-(4,5-biphenylpyrimidin-2-yl)thiourea in good-to-excellent yields. Efforts to extend the scope of the method in combination with its application to the synthesis of pharmaceutically relevant molecules are ongoing in our laboratory.

Experimental Part

General. TLC: silica-gel *60 GF$_{254}$* plates (SiO_2); visualization under UV light (254 nm). M.p.: *X-5 Macro* melting point tester; uncorrected. IR Spectra: *Nicolet 170SX* FT-IR spectrophotometer in KBr pellets; $\tilde{\nu}$ in cm^{-1}. ^{1}H- and ^{13}C-NMR spectra: *Bruker Avance 300* at 300 and 75 MHz, resp., in (D_6)DMSO unless otherwise indicated; δ in ppm rel. to Me_4Si as internal standard, *J* in Hz. X-Ray crystallography: *Bruker Smart-1000 CCD* diffractometer.

General Procedure for the Synthesis of **3a**–**3o** (*Table 1*, *Entries 1–15*). The mixture of corresponding isoflavones **1** (1 mmol), amidinothiourea **2** (3 mmol), and MeONa (3 mmol) was refluxed in MeOH

Scheme. *Proposed Mechanism for the Formation of* **3**



(15 ml) for 2–5 h. All reactions were monitored by TLC, which showed the disappearance of **1** that was indicative of the completion of the reaction. The mixture was poured into a soln. of 10% aq. HCl (40 ml), and a yellow precipitate formed. The precipitate was filtered and washed with dist. H_2O until neutrality. The crude product was recrystallized from EtOH or purified by column chromatography (CC) on SiO_2 with $CHCl_3$/MeOH 20:1 to give the corresponding pure product. With **1p** as starting material, 2-amino-4-(2,4-dihydroxyphenyl)-5-(4-methoxyphenyl)pyrimidine was obtained instead of **3p** (*Table 1*, *Entry 16*).

1-[4-[2-Hydroxy-4-(1-methylethoxy)phenyl]-5-phenylpyrimidin-2-yl]thiourea (**3a**). Yellow solid. M.p. 247.2–248.5°. IR: 3370, 3188, 2978, 1623, 1571, 1526, 1422, 1357, 1324, 1262, 1194, 1110, 992, 850, 700. ^{1}H-NMR: 1.23 (*d*, *J* = 5.4, 6 H); 4.53 (*m*, 1 H); 6.26 (*d*, *J* = 8.4, 1 H); 6.33 (*s*, 1 H); 6.92 (*d*, *J* = 8.4, 1 H); 7.23–7.31 (*m*, 5 H); 8.60 (*s*, 1 H); 9.18 (*s*, 1 H); 10.09 (*s*, 1 H); 10.32 (*s*, 1 H); 10.89 (*s*, 1 H). ^{1}H-NMR ((D$_6$)DMSO/D$_2$O): 1.18 (*d*, *J* = 5.2, 6 H); 4.47 (*m*, 1 H); 6.25 (*s*, 1 H); 6.28 (*s*, 1 H); 6.88 (*s*, 1 H); 7.17–7.27 (*m*, 5 H); 8.55 (*s*, 1 H). ^{13}C-NMR ((D$_6$)DMSO/D$_2$O): 21.6; 69.5; 102.9; 106.5; 115.7; 127.6; 127.9; 128.4; 129.3; 131.8; 135.9; 155.4; 156.6; 158.5; 159.8; 162.8; 180.2. Anal. calc. for $C_{20}H_{20}N_4O_2S$ (380.46): C 63.14, H 5.30, N 14.73; found: C 63.40, H 5.03, N 14.34.

Suitable crystals for an X-ray crystal-structure determination were obtained from EtOH.

1-[4-(2-Hydroxy-4,6-dimethoxyphenyl)-5-(4-methoxyphenyl)pyrimidin-2-yl]thiourea (**3b**). Yellow solid. M.p. 238.6–239.3°. IR: 3385, 3186, 3004, 2838, 1622, 1577, 1522, 1426, 1340, 1214, 1160, 1110, 1037, 835, 633, 565. ^{1}H-NMR: 3.42 (*s*, 3 H); 3.70 (*s*, 3 H); 3.71 (*s*, 3 H); 6.01 (*s*, 1 H); 6.03 (*s*, 1 H); 6.85 (*d*, *J* = 8.4, 2 H); 7.11 (*d*, *J* = 8.4, 2 H); 8.61(*s*, 1 H); 9.09 (*s*, 1 H); 9.61 (*s*, 1 H); 10.30 (*s*, 1 H); 10.66 (*s*, 1 H). ^{13}C-NMR: 55.0; 55.3; 89.9; 93.8; 107.1; 113.6; 128.1; 129.1; 129.9; 156.0; 156.2; 157.6; 158.1; 158.6; 161.0; 161.4; 180.8. Anal. calc. for $C_{20}H_{20}N_4O_4S$ (412.46): C 58.24, H 4.89, N 13.58; found: C 58.53, H 4.70, N 13.32.

1-[4-(2-Hydroxy-4-methoxyphenyl)-5-(4-methoxyphenyl)pyrimidin-2-yl]thiourea (**3c**). Yellow solid. M.p. 268.1–269.6°. IR: 3370, 3189, 2840, 1621, 1572, 1523, 1427, 1356, 1273, 1211, 1081, 1043, 843, 796, 644, 562. ^{1}H-NMR: 3.70 (*s*, 3 H); 3.74 (*s*, 3 H); 6.32 (*d*, *J* = 8.1, 1 H); 6.37 (*s*, 1 H); 6.89 (*d*, *J* = 7.5, 2 H); 6.97 (*d*, *J* = 8.1, 1 H); 7.15 (*d*, *J* = 7.5, 2 H); 8.58 (*s*, 1 H); 9.16 (*s*, 1 H); 10.10 (*s*, 1 H); 10.31 (*s*, 1 H); 10.85 (*s*, 1 H). ^{13}C-NMR: 55.0; 101.7; 105.2; 114.0; 115.9; 127.3; 128.4; 129.7; 131.7; 155.5; 157.2; 158.5; 158.6; 161.5; 162.5; 180.8. Anal. calc. for $C_{19}H_{18}N_4O_3S$ (382.44): C 59.67, H 4.74, N 14.65; found: C 59.34, H 4.92, N 14.88.

1-[4-(2-Hydroxy-4-methoxyphenyl)-5-phenylpyrimidin-2-yl]thiourea (**3d**). White solid. M.p. 254.8–255.7°. IR: 3376, 3189, 2839, 1624, 1582, 1527, 1422, 1268, 1212, 1130, 1080, 1024, 963, 851, 796, 703. ^{1}H-NMR: 3.68 (*s*, 3 H); 6.27 (*d*, *J* = 7.9, 1 H); 6.36 (*s*, 1 H); 6.93 (*d*, *J* = 8.2, 1 H); 7.14–7.29 (*m*, 5 H); 8.58 (*s*, 1 H); 9.11 (*s*, 1 H); 10.08 (*s*, 1 H); 10.28 (*s*, 1 H); 10.79 (*s*, 1 H). ^{13}C-NMR: 55.6; 102.1; 105.7; 116.3; 126.9; 127.9; 128.0; 129.0; 132.3; 136.8; 156.2; 157.7; 159.1; 162.1; 163.1; 181.3. Anal. calc. for $C_{18}H_{16}N_4O_2S$ (352.41): C 61.35, H 4.58, N 15.90; found: C 61.17, H 4.76, N 15.67.

1-[4-(2-Hydroxy-4,5,6-trimethoxyphenyl)-5-(4-methoxyphenyl)pyrimidin-2-yl]thiourea (**3e**). White solid. M.p. 233.8–234.7°. IR: 3393, 3192, 2999, 2835, 1614, 1568, 1424, 1244, 1110, 1022, 834, 736. ^{1}H-NMR: 3.43 (*s*, 3 H); 3.58 (*s*, 3 H); 3.72 (*s*, 3 H); 3.74 (*s*, 3 H); 6.25 (*s*, 1 H); 6.87 (*d*, *J* = 8.3, 2 H); 7.19 (*d*, *J* = 8.3, 2 H); 8.66 (*s*, 1 H); 9.13 (*s*, 1 H); 9.46 (*s*, 1 H); 10.30 (*s*, 1 H); 10.73 (*s*, 1 H). ^{13}C-NMR: 55.1; 55.5; 60.4; 60.5; 95.7; 111.4; 113.7; 127.7; 129.4; 129.5; 134.0; 150.7; 150.8; 154.1; 155.9; 157.6; 158.8; 160.8; 180.8. Anal. calc. for $C_{21}H_{22}N_4O_5S$ (442.49): C 57.00, H 5.01, N 12.66; found: C 57.21, H 4.79, N 12.43.

1-[4-(2-Hydroxy-4-methoxy-6-methylphenyl)-5-phenylpyrimidin-2-yl]thiourea (**3f**). White solid. M.p. 289.8–290.7°. IR: 3233, 2839, 1617, 1587, 1563, 1512, 1427, 1306, 1271, 1157, 1047, 822, 765, 702, 558. ^{1}H-NMR: 1.83 (*s*, 3 H); 3.65 (*s*, 3 H); 6.19 (*s*, 1 H); 6.21 (*s*, 1 H); 7.19–7.25 (*m*, 5 H); 8.67 (*s*, 1 H); 9.08 (*s*, 1 H); 9.47 (*s*, 1 H); 10.26 (*s*, 1 H); 10.67 (*s*, 1 H). ^{13}C-NMR: 20.0; 55.3; 99.2; 106.7; 118.3; 128.1; 128.7; 130.1; 135.9; 137.5; 156.1; 157.0; 158.7; 160.6; 164.0; 181.4. Anal. calc. for $C_{19}H_{18}N_4O_2S$ (366.44): C 62.28, H 4.95, N 15.29; found: C 62.51, H 4.60, N 15.08.

1-{4-[3-Bromo-2-hydroxy-4-(1-methylethoxy)phenyl]-5-phenylpyrimidin-2-yl}thiourea (**3g**). Yellow solid. M.p. 249.7–251.8°. IR: 3380, 3187, 2981, 1618, 1576, 1523, 1419, 1348, 1264, 1196, 1106, 1048, 845, 700, 641. ^{1}H-NMR: 1.28 (*d*, *J* = 4.6, 6 H); 4.56 (*m*, 1 H); 6.52 (*s*, 1 H); 7.23–7.34 (*m*, 6 H); 8.62 (*s*, 1 H); 9.17 (*s*, 1 H); 10.08 (*s*, 1 H); 10.25 (*s*, 1 H); 10.31 (*s*, 1 H); 10.89 (*s*, 1 H). ^{13}C-NMR: 22.1; 22.2; 71.7; 101.1; 103.4; 117.3; 128.1; 129.0; 132.6; 134.9; 136.5; 156.1; 156.3; 157.1; 159.1; 161.9; 181.3. Anal. calc. for $C_{20}H_{19}BrN_4O_2S$ (459.36): C 52.29, H 4.17, N 12.20; found: C 52.53, H 4.02, N 11.97.

1-[4-(4-Ethoxy-2-hydroxyphenyl)-5-(4-methoxyphenyl)pyrimidin-2-yl]thiourea (**3h**). Yellow solid. M.p. 262.5–263.6°. IR: 3388, 3195, 1623, 1567, 1524, 1426, 1355, 1272, 1244, 1209, 1041, 850, 800, 614. ^{1}H-NMR: 1.29 (*t*, *J* = 6.0, 3 H); 3.75 (*s*, 3 H); 3.97 (*d*, *J* = 6.5, 2 H); 6.29 (*d*, *J* = 8.0, 1 H); 6.36 (*s*, 1 H); 6.89 (*d*, *J* = 7.7, 2 H); 6.95 (*d*, *J* = 8.7, 1 H); 7.15 (*d*, *J* = 7.7, 2 H); 8.57 (*s*, 1 H); 9.10 (*s*, 1 H); 10.30 (*s*, 1 H); 10.75 (*s*, 1 H). ^{13}C-NMR: 15.0; 55.5; 63.5; 102.6; 106.0; 114.5; 116.3; 127.8; 128.9; 130.2; 132.2; 156.0; 157.8; 159.0; 159.1; 161.3; 163.0; 181.3. Anal. calc. for $C_{20}H_{20}N_4O_3S$ (396.46): C 60.59, H 5.08, N 14.13; found: C 60.41, H 5.39, N 13.97.

1-{4-[4-(Benzyloxy)-2-hydroxyphenyl]-5-[4-(benzyloxy)phenyl]pyrimidin-2-yl}thiourea (**3i**). Yellow solid. M.p. 200.5–201.6°. IR: 3383, 3198, 3027, 1621, 1568, 1516, 1423, 1241, 1019, 835, 735, 697. ^{1}H-NMR: 5.05 (*s*, 2 H); 5.08 (*s*, 2 H); 6.41 (*d*, *J* = 8.5, 1 H); 6.47 (*s*, 1 H); 6.98 (*d*, *J* = 8.1, 1 H); 7.16 (*d*, *J* = 6.5, 2 H); 7.37–7.42 (*m*, 12 H); 8.58 (*s*, 1 H); 9.17 (*s*, 1 H); 10.12 (*s*, 1 H); 10.32 (*s*, 1 H); 10.85 (*s*, 1 H). ^{13}C-NMR: 69.2; 102.6; 105.9; 114.8; 116.2; 127.3; 127.7; 127.9; 128.4; 128.6; 129.8; 131.7; 136.7; 136.9; 155.5; 157.1; 157.8; 158.5; 160.6; 162.4; 180.8. Anal. calc. for $C_{31}H_{26}N_4O_3S$ (534.63): C 69.64, H 4.90, N 10.48; found: C 69.87, H 4.66, N 10.42.

1-[4-(2-Hydroxy-4-methoxyphenyl)-5-[4-methoxy-3,5-bis(1-methylethyl)phenyl]pyrimidin-2-yl}thiourea (**3j**). Yellow solid. M.p. 229.4–230.6°. IR: 3446, 3239, 2963, 1623, 1574, 1522, 1419, 1212, 1076, 1010, 791. ^{1}H-NMR: 1.05 (*d*, *J* = 4.5, 12 H); 3.18 (*m*, 2 H); 3.65 (*s*, 3 H); 3.69 (*s*, 3 H); 6.34–6.40 (*m*, 2 H); 6.93–6.97 (*m*, 3 H); 8.68 (*s*, 1 H); 9.16 (*s*, 1 H); 9.97 (*s*, 1 H); 10.33 (*s*, 1 H); 10.80 (*s*, 1 H). ^{13}C-NMR: 23.6; 25.8; 55.1; 61.9; 101.6; 105.1; 116.4; 124.4; 127.8; 131.3; 131.6; 141.0; 153.5; 155.6; 156.8; 158.2; 161.5; 162.8; 180.8. Anal. calc. for $C_{25}H_{30}N_4O_3S$ (466.60): C 64.35, H 6.48, N 12.01; found: C 64.56, H 6.29, N 12.29.

1-[4-(2-Hydroxy-4,6-dimethoxyphenyl)-5-[4-methoxy-3,5-bis(1-methylethyl)phenyl]pyrimidin-2-yl]thiourea (**3k**). White solid. M.p. 263.8–264.7°. IR: 3393, 3278, 3138, 2960, 1618, 1587, 1513, 1219, 1153, 1106, 1067, 1039, 1011, 946, 818. ^{1}H-NMR: 1.05 (*s*, 12 H); 3.16 (*s*, 2 H); 3.25 (*s*, 3 H); 3.62 (*s*, 3 H); 3.67 (*s*, 3 H); 5.96 (*s*, 1 H); 6.12 (*s*, 1 H); 6.92 (*s*, 2 H); 8.68 (*s*, 1 H); 9.10 (*s*, 1 H); 9.71 (*s*, 1 H); 10.33 (*s*, 1 H); 10.64 (*s*, 1 H). ^{13}C-NMR: 23.6; 25.7; 55.1; 55.2; 61.9; 90.0; 94.0; 107.1; 123.8; 129.9; 131.6; 140.6; 153.5; 156.0; 156.5; 157.3; 157.8; 161.2; 161.7; 180.8. Anal. calc. for $C_{26}H_{32}N_4O_4S$ (496.62): C 62.88, H 6.49, N 11.28; found: C 62.63, H 6.76, N 11.02.

1-[4-(2-Hydroxy-4-methoxyphenyl)-5-(4-hydroxyphenyl)pyrimidin-2-yl]thiourea (**3l**). Yellow solid. M.p. 255.4–256.6°. IR: 3373, 3160, 1623, 1568, 1531, 1424, 1358, 1263, 1082, 960, 795, 613. ^{1}H-NMR: 3.71 (*s*, 3 H); 6.31 (*d*, *J* = 8.4, 1 H); 6.39 (*s*, 1 H); 6.71 (*d*, *J* = 5.3, 2 H); 6.96 (*d*, *J* = 8.6, 1 H); 7.02 (*d*, *J* = 8.0, 2 H); 8.55 (*s*, 1 H); 9.15 (*s*, 1 H); 9.55 (*s*, 1 H); 10.15 (*s*, 1 H); 10.31 (*s*, 1 H); 10.84 (*s*, 1 H). ^{13}C-NMR: 55.1; 101.7; 105.1; 115.4; 115.9; 126.7; 127.6; 129.7; 131.7; 155.3; 156.9; 157.3; 158.4; 161.5; 162.4; 180.8. Anal. calc. for $C_{18}H_{16}N_4O_3S$ (368.41): C 58.68, H 4.38, N 15.21; found: C 58.47, H 4.53, N 15.48.

1-[4-(2-Hydroxy-4-methoxyphenyl)-5-[4-hydroxy-3,5-bis(1-methylethyl)pyrimidin-2-yl]thiourea (**3m**). Yellow solid. M.p. 145.5–146.6°. IR: 3228, 2960, 1622, 1569, 1519, 1209, 1150, 1077, 844, 796, 768. ^{1}H-NMR: 1.01 (*d*, *J* = 6.6, 12 H); 3.20–3.26 (*m*, 2 H); 3.69 (*s*, 3 H); 6.33 (*d*, *J* = 8.5, 1 H); 6.40 (*s*, 1 H); 6.85 (*s*, 2 H); 6.93 (*d*, *J* = 8.5, 1 H); 8.17 (*s*, 1 H); 8.65 (*s*, 1 H); 9.12 (*s*, 1 H); 9.98 (*s*, 1 H); 10.33 (*s*, 1 H); 10.76 (*s*, 1 H). ^{13}C-NMR: 22.7; 25.9; 55.1; 101.6; 105.0; 116.6; 123.4; 126.8; 128.3; 131.3; 135.1; 150.2; 155.3; 156.9; 158.1; 161.4; 162.5; 180.8. Anal. calc. for $C_{24}H_{28}N_4O_3S$ (452.57): C 63.69, H 6.24, N 12.38; found: C 63.91, H 6.02, N 12.03.

1-[4-(2-Hydroxy-4-methoxyphenyl)-5-(4-hydroxy-3-nitrophenyl)pyrimidin-2-yl]thiourea (**3n**). Yellow solid. M.p. 254.7–255.9°. IR: 3455, 3160, 2999, 1626, 1578, 1520, 1429, 1288, 1149, 1074, 1017, 788. ^{1}H-NMR: 3.71 (*s*, 3 H); 6.35 (*s*, 1 H); 6.42 (*d*, *J* = 8.0, 1 H); 7.04 (*d*, *J* = 8.4, 1 H); 7.10 (*d*, *J* = 8.4, 1 H); 7.30 (*d*, *J* = 8.0, 1 H); 7.79 (*s*, 1 H); 8.65 (*s*, 1 H); 9.18 (*s*, 1 H); 9.96 (*s*, 1 H); 10.30 (*s*, 1 H); 10.82 (*s*, 1 H); 11.09 (*s*, 1 H). ^{13}C-NMR: 55.1; 101.6; 105.5; 116.0; 119.1; 124.8; 125.8; 127.5; 131.7; 135.2; 136.7; 151.4; 156.0; 156.5; 158.4; 161.7; 162.7; 180.8. Anal. calc. for $C_{18}H_{15}N_5O_5S$ (413.41): C 52.30, H 3.66, N 16.94; found: C 52.03, H 3.87, N 16.74.

1-[4-(5-Bromo-2-hydroxy-4-methoxyphenyl)-5-(3,5-dibromo-4-hydroxyphenyl)pyrimidin-2-yl]thiourea (**3o**). Yellow solid. M.p. 228.4–229.7°. IR: 3423, 3301, 3227, 1608, 1576, 1512, 1417, 1307, 1260, 1211, 1046, 878, 739. ^{1}H-NMR: 3.80 (*s*, 3 H); 6.49 (*s*, 1 H); 7.38–7.45 (*m*, 3 H); 8.64 (*s*, 1 H); 9.18 (*s*, 1 H); 10.08 (*d*, 2 H); 10.23 (*s*, 1 H); 10.86 (*s*, 1 H). ^{13}C-NMR: 56.2; 99.5; 100.8; 111.7; 117.2; 125.4; 130.3; 132.1; 134.1; 150.1; 156.0; 156.1; 157.3; 158.3; 161.4; 180.8. Anal. calc. for $C_{18}H_{13}Br_3N_4O_3S$ (605.10): C 35.73, H 2.17, N 9.26; found: C 35.97, H 2.01, N 9.57.

2-Amino-4-(2,4-dihydroxyphenyl)-5-(4-methoxyphenyl)pyrimidine. Yellow solid. M.p. 208.7–209.5°. IR: 3474, 3366, 2925, 2361, 1587, 1539, 1435, 1206, 1169, 1135, 835. ^{1}H-NMR: 3.76 (*s*, 3 H); 5.95 (*d*, 1 H); 6.21(*s*, 1 H); 6.74–6.92 (*m*, 5 H); 7.11 (*d*, 2 H); 8.13 (*s*, 1 H); 9.66 (*s*, 1 H); 12.27 (*s*, 1 H). ^{13}C-NMR: 55.0; 103.2; 106.1; 111.9; 114.1; 120.5; 129.9; 130.3; 131.8; 158.2; 160.0; 160.5; 160.6; 161.8. Anal. calc. for $C_{17}H_{15}N_3O_3$ (309.32): C 66.01, H 4.89, N 13.58; found: C 66.31, H 4.53, N 13.37.

X-Ray Crystal Structure of **3a** (see *Table 3* and *Fig.*)[1]). Diffraction data were collected on a *Bruker Smart-1000 CCD* diffractometer with graphite-monochromated MoK_α radiation (λ 0.71073 Å) using the ($\omega - 2\theta$) scan technique. The structure was solved by direct methods and refined on F^2 by full matrix least-squares with the SHELXL-97 program. All non-H-atoms were refined anisotropically. All H-atoms were treated using a riding model. The crystal used for the diffraction study showed no decomposition during data collection. In the crystal structure of **3a**, an ^{i}PrO group (C(19), C(20), C(19′), C(20′)) was disordered 0.50 and 0.50 occupied positions, so the bond lengths C(19)–C(20) and C(19′)–C(20′) were restrained in the refinement.

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[1]) The crystallographic data have been deposited with the *Cambridge Crystallographic Data Centre* as deposition No. CCDC-757075. Copies of the data can be obtained free of charge *via* http://www.ccdc.cam.ac.uk/data_request/cif.

Table 3. *Crystallographic Data of Compound* **3a**

Crystallized from	EtOH
Empirical formula	$C_{20}H_{20}N_4O_2S$
M_r [g/mol]	380.46
Crystal color, shape	colorless, block
Crystal dimensions [mm]	$0.38 \times 0.26 \times 0.14$
Temp. [K]	296(2)
Crystal system	monoclinic
Space group	$P2_1/c$
Z	4
Unit cell parameters:	
a [Å]	14.406(3)
b [Å]	16.114(3)
c [Å]	8.6911(18)
β [°]	106.674(4)
V [Å^3]	1932.7(7)
D_x [g cm^{-3}]	1.342
Absorption coefficient [mm^{-1}]	0.192
θ Range for data collection [°]	2.53 – 25.04
Limiting indices	$-10 \le h \le 17$; $-19 \le k \le 17$; $-10 \le l \le 10$
Reflections collected	9540
Independent reflections	3391 [R(int) = 0.0580]
Absorption correction	none
Completeness to θ_{max}	98.9%
Data/restraints/parameters	3391/0/264
Goodness-of-fit on F^2	1.010
Final R indices [$I > 2\sigma(I)$]	$R_1 = 0.0507$, $wR_2 = 0.1158$
R indices (all data)	$R_1 = 0.1179$, $wR_2 = 0.1285$
Largest difference peak and hole [e Å^{-3}]	0.204, −0.196

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