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SILVER-MEDIATED SULFENYLATION OF INDOLES AND BENZIMIDAZOLES WITH DI(HETERO)ARYL DISULFIDES

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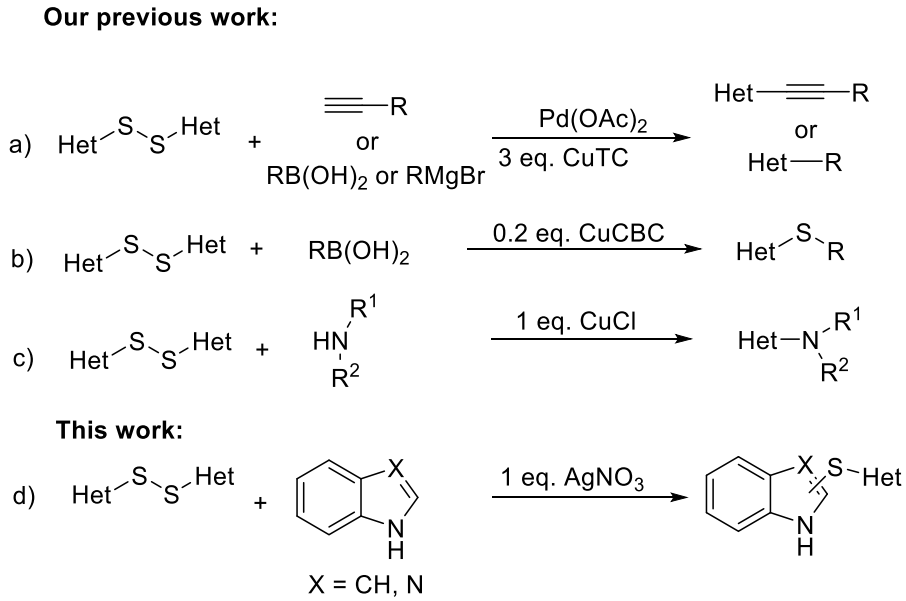
Abstract – An efficient synthesis of novel sulfenylated *N*-heterocycles derivatives via $AgNO_3$ mediated C–S coupling reaction has been developed. This reaction could be carried out under mild reaction conditions with straightforward operation and good yield. A wide range of substrates can be utilized for the C–S coupling reaction giving sulfenylated indoles and benzimidazoles, which are the importance of frameworks in medicinal and synthetic chemistry.

INTRODUCTION

Nitrogen-containing heterocyclic derivatives are widely used in the pharmaceutical, agrochemical and dye industries. For example, 3-sulfenylindoles have shown important biological activity against heart disease, allergies, cancer, HIV and obesity,[1] and sulfenylated benzimidazole derivatives have acted as proton pump inhibitor (PPIs) and used to prevent ulcers.[2] Thus, developing new methods for the synthesis of sulfenylated indole and benzimidazole derivatives has attracted much attention among many researchers.

In the past decades, there have been two significant methods to synthesize 3-sulfenylindoles, including the direct sulfenylation of an existing indole ring[3-6] and the cyclization reactions of 2-alkynylanilines[7] or *N,N*-dialkyl-2-iodoanilines.[8] In addition, a number of sulfenylating reagents were used to synthesize 3-sulfenylindoles.[9-15] Moreover, other methods for the synthesis of 3-sulfenylindoles have been developed in the presence of metal catalysts, such as $VO(acac)_2$, $MgBr_2$, $FeCl_3$, FeF_3, $CeCl_3$, CuI and $PdCl_2$.[16] However, these approaches have some shortcomings and limitations, such as harsh reaction conditions, toxic reagents and oxygen-free techniques. Therefore, it is essential for us to develop a simple and efficient strategy to synthesize 3-sulfenylindoles. Then, a few methodologies were reported for the

sulfenylation of indoles using diaryl disulfides as the sulfenylation reagents under metal free conditions.[17-19] Similarly, various sulfenylbenzimidazoles were prepared.[20] These reactions have been proved to be efficient for the synthesis of a series of substituted 3-sulfenylindoles. Nonetheless, these catalytic systems rarely refer to the cross-coupling reaction of di(hetero)aryl disulfides with indoles and benzimidazole, which lead to limit the scope of reactions substrates. Alternatively, the tetra-substituted pyrimidines have shown a wide range of pharmacological and biological properties,[21] such as calcium channel modulator, antifungal and antibacterial profiles.[22] Recently, we developed efficient C–C, C–S and C–N cross coupling of di(pyrimidin-2-yl) disulfides with arylboronic acids, alkynes, Grignard reagents and amines as the original examples on selective cleavage of the C–S and S–S bonds in disulfides (Scheme 1, a-c).[23]



Scheme 1. Cross coupling of disulfides with various nucleophiles

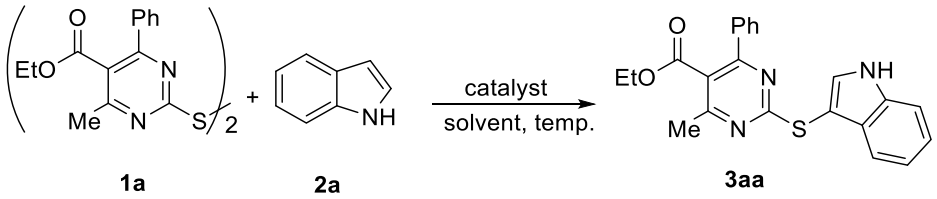
Herein, we described the C–S cross-coupling reaction of di(pyrimidin-2-yl) disulfides with indoles or benzimidazole via C–H functionalization of indoles or benzimidazole in the presence of $AgNO_3$ (Scheme 1d). This reaction carried out in high yields under mild conditions and had a wide substrate scope.

RESULTS AND DISCUSSION

Initially, we began our investigation by exploring the reaction between 1,2-di(pyrimidin-2-yl) disulfide (**1a**) and indole (**2a**) (Table 1).

When iodine or ammonium persulphate was used as catalyst in DMF at 60 °C for 8 h the desired product **3aa** was obtained in trace or 36% yields (entries 1-2). To our surprise, when silver nitrate was used as the catalyst, the desired product **3aa** was obtained in 55% yield under an air atmosphere (entry 5).

Table 1. Optimization of the reaction condition[a]



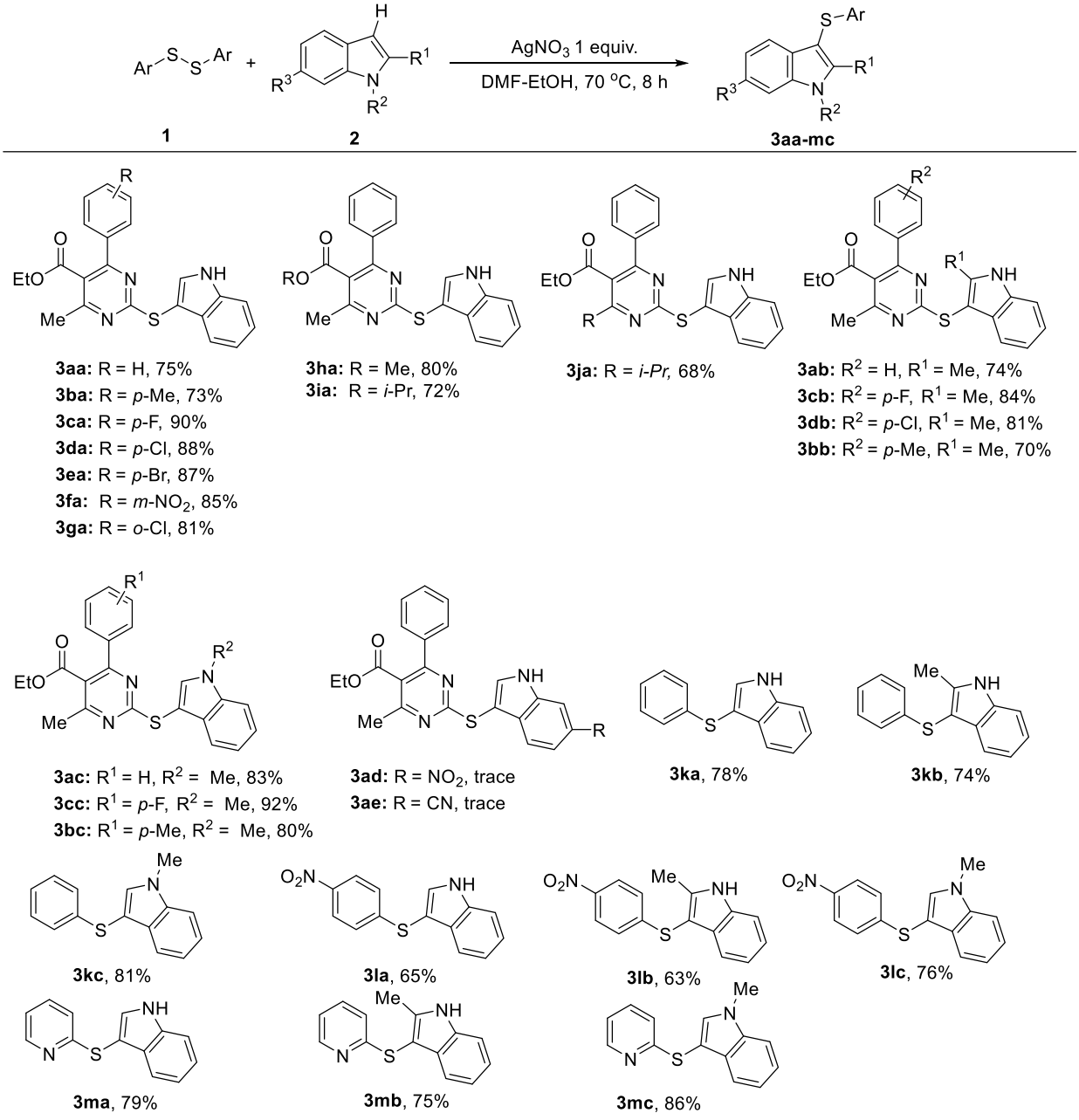
1a **2a** **3aa**

Entry	Cat.	Solvent	Temp. (°C)	Yield[b] (%)
1	I_2	DMF	60	Trace
2	$(NH_4)_2S_2O_8$	DMF	60	36
3	oxone	DMF	60	30
4	$K_2S_2O_8$	DMF	60	22
5	$AgNO_3$	DMF	60	55
6	$AgNO_3$	DMSO	60	46
7	$AgNO_3$	MeOH	60	37
8	$AgNO_3$	TFA	60	42
9	$AgNO_3$	EtOH	60	49
10	$AgNO_3$	DMF-EtOH	60	63
11	$AgNO_3$	DMF-EtOH	40	56
12	$AgNO_3$	DMF-EtOH	70	77
13	$AgNO_3$	DMF-EtOH	80	47
14	$AgNO_3$	DMF-EtOH	120	33
15[c]	$AgNO_3$	DMF-EtOH	70	49
16[d]	$AgNO_3$	DMF-EtOH	70	75
17[e]	$AgNO_3$	DMF-EtOH	70	75

[a]Reaction conditions: 1,2-di(pyrimidin-2-yl) disulfide **1a** (0.2 mmol), indole **2a** (0.3 mmol), catalyst (2 equiv.), and solvent (1 mL) under an air, 8 h. [b]Isolated yield after column chromatography. [c]Catalyst (0.5 equiv.). [d]Catalyst (1 equiv.). [e]Catalyst (1.5 equiv.)

Encouraged by this result, many solvents such as DMSO, MeOH, TFA, EtOH, DMF-EtOH were screened (entries 6-10). Obviously, DMF-EtOH in a 1:1 ratio was the best choice for this C–S coupling reaction. Then we turned our attention to examining the effect of reaction temperature (entries 11-14). Examination of various temperature indicated that 70 °C is optimal. After further optimization, the amount of $AgNO_3$ was examined (entries 15-17). Thus, the optimal reaction conditions are selected as indole **2a** (1.5 equiv.), $AgNO_3$ (1 equiv.) and DMF-EtOH (V/V 1:1) at 70 °C for 8 h under an air.

With the above optimized conditions in hand, C–S cross-coupling of various dipyrimidin-2-yl disulfides with indole was investigated and the results are summarized in Scheme 2. The reaction was found to work well and most of the functional groups were tolerated, giving the corresponding products **3aa**-**3ja** in 68-90% yields. Dipyrimidin-2-yl disulfide with Me, F, Cl, Br even NO_2 groups substituted benzene ring at 4-position, reacted smoothly, affording the desired products **3ba**-**3ga** in 73-90% yields. Various electron-withdrawing groups at C5-position on the pyrimidine ring were also smoothly converted into C–S coupled products **3ha** and **3ia** in 72 and 80% yields.

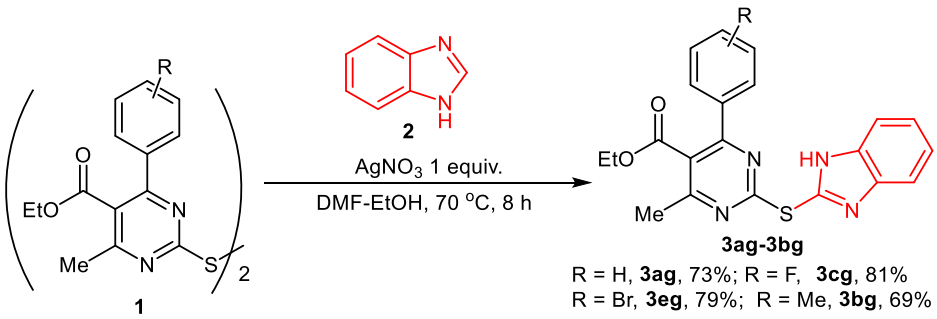


[a]Reaction conditions: 1,2-di(pyrimidin-2-yl) disulfide **1** (0.2 mmol), indole **2** (0.3 mmol), catalyst (1 equiv.), and solvent (1 mL) under an air, 8 h.

Scheme 2. $AgNO_3$-mediated C–S coupling of disulfides with indoles[a]

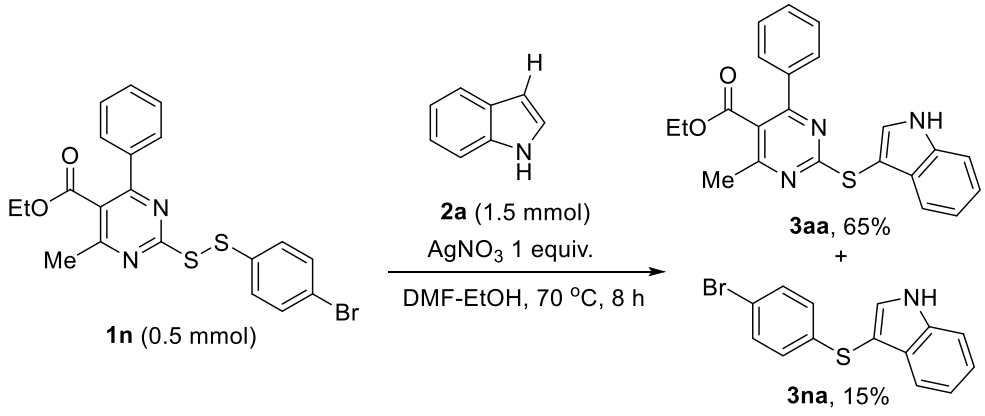
Next, various indoles were tested in the coupling reaction and C–S coupling products **3ab-3ae** were obtained in 70-92% yields. Except, the reaction of **1a** with nitro and cyano substituted indoles did result in trace of product **3ad** and **3ae**. Yet, this result was also consistent with the mechanism of the reaction. Furthermore, we explored the reaction using simple diaryl disulfides and other di(hetero)aryl disulfides. As expected, the structurally diverse sulfenyl indoles **3ka-3mc** were obtained in good yields, and the present reaction was not affected by substrates.

To further extend the scope of this protocol, we explored the reaction using benzimidazole with different dipyrimidin-2-yl disulfides. As shown in Scheme 3, benzimidazole reacted with various dipyrimidin-2-yl disulfides to afford the sulfenyl benzimidazole **3ag-3bg** in 69-81% yields. Obviously, benzimidazole proved to be suitable substrates for the reaction.



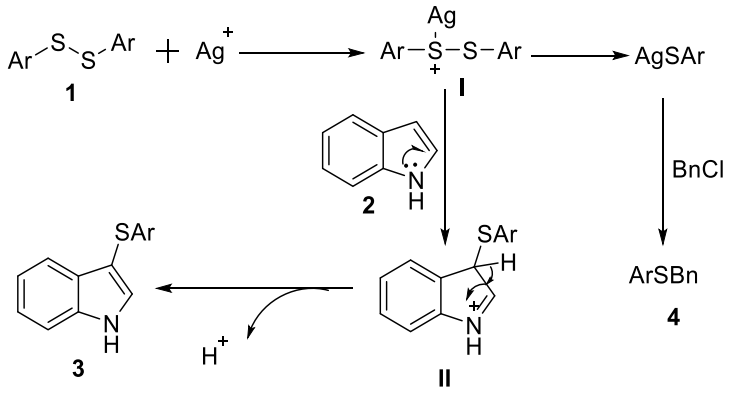
Scheme 3. Reaction of disulfides with benzimidazole

Finally, the sulfenylation reaction of unsymmetrical disulfide **1n** with indole **2a** was explored under standard conditions (Scheme 4). The yields of products **3aa** and **3na** were 65% and 15%, respectively. It demonstrated that coordination of the Ag^{+} ion with the sulfur atom which is originated in the dipyrimidyl disulfides, is easier than another sulfur atom.



Scheme 4. The C–S coupling of unsymmetric disulfide with indole

On the basis of the related literature reports,[24] a plausible reaction mechanism was proposed for this C–S cross-coupling reaction in Scheme 5. First, silver nitrate reacts with dipyrimidin-2-yl disulfide to form intermediates **I**. Then the electrophilic intermediates **I** could add onto the indole moiety to produce indole intermediate **II**, which may undergo deprotonation to give the desired product 3-sulfenylindoles **3**.



Scheme 5. The possible mechanism for the C-S coupling

In summary, we have developed an efficient protocol for the preparation of various sulfenylated indoles and benzimidazoles derivatives by using $AgNO_3$ as the catalyst in DMF-EtOH. Notably, benzimidazole reacted with various dipyrimidin-2-yl disulfides to afford the sulfenylated benzimidazoles in good yields. Given that a wide range of substrates can be utilized for the C–S coupling reaction, this simple protocol may provide a general approach to sulfenylated indoles and benzimidazoles due to the importance of frameworks in medicinal and synthetic chemistry.

EXPERIMENTAL

Infrared (IR) spectra were recorded using KBr pellets on a Nicolet Avatar 36 Fourier transform (FT)-IR spectrophotometer. ^{1}H NMR and ^{13}C NMR data analyses were performed with a Varian Mercury plus-600 instrument unless otherwise specified. $CDCl_3$ as solvent and tetramethylsilane (TMS) as the internal standard were employed. Chemical shifts were reported in units (ppm) by assigning TMS resonance in the ^{1}H NMR spectrum as 0.00 ppm. The data of ^{1}H NMR was reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet and br = broad), coupling constant (*J* values) in Hz and integration. Chemical shift for ^{13}C NMR spectra were recorded in ppm from TMS using the central peak of $CDCl_3$ (77.0 ppm) or as the internal standard. Flash chromatography was performed using 200-300 mesh silica gel with the indicated solvent system according to standard techniques. Analytical thin-layer chromatography (TLC) was performed on pre-coated, glass-backed silica gel plates. Melting points were measured with an XT-4 apparatus. High-resolution mass spectra (HRMS) (ESI) were obtained with a Bruker Daltonics APEX II 47e and Orbitrap Elite mass spectrometer. Column

chromatography was generally performed on silica gel (200-300 mesh) and TLC analyses were conducted on silica gel GF254 plates. Di(hetero)aryl disulfides[23] were prepared according to our previous method. All reagents were directly used from purchased without any further purification unless otherwise specified.

Typical Procedure for the Preparation of Products 3. Disulfides **1** (0.2 mmol), indoles **2** (0.3 mmol), $AgNO_3$ (1 equiv, 0.2 mmol), and EtOH/DMF (v:v = 1:1) was added respectively to the an oven-dried sealed tube with a magnetic stirrer bar. The vial was sealed with a cap. The mixture was stirred at 70 °C for 8 h. And reaction progress was monitored by TLC. When the reaction time was over, the reaction mixture was cooled to room temperature. The precipitated silver mercaptide was filtered and the solvent removed at reduced pressure. The product was extracted with EtOAc (3×10 mL). The EtOAc layer was dried with anhydrous $MgSO_4$, and the solvent was then removed under vacuum. The residue was purified by column chromatography (silica gel, 200-300 mesh) using EtOAc/petroleum ether (V:V = 1:10) as eluent to afford the product **3**.

Ethyl 2-((1*H*-indol-3-yl)thio)-4-methyl-6-phenylpyrimidine-5-carboxylate (3aa): Clorless solid, mp 109-111 °C; IR (KBr): 3215(s), 2950(m), 1720(s), 1560(m), 1480(m), 1250(w) cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 8.51 (s, 1H), 7.58 (d, *J*=7.8 Hz, 1H), 7.35–7.30 (m, 3H), 7.27–7.16 (m, 5H), 7.04 (s, 1H), 4.14 (q, *J*=7.2 Hz, 2H), 2.49 (s, 3H), 1.03 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 173.01, 168.01, 165.90, 163.73, 137.26, 136.39, 130.94, 130.06, 128.82, 128.30, 128.24, 122.56, 121.41, 120.47, 119.58, 111.66, 99.39, 61.75, 22.53, 13.58; HRMS (EI) *m/z*: ($[M+H]^+$) Calcd for $C_{22}H_{20}N_3O_2S$ 390.1271; Found 390.1275.

Ethyl 2-((1*H*-indol-3-yl)thio)-4-methyl-6-(*p*-tolyl)pyrimidine-5-carboxylate (3ba): Purple solid, mp 137-139 °C; IR (KBr): 3325(s), 2980(m), 1710(s), 1578(m), 1450(m), 1238(w) cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 8.55 (s, 1H), 7.58–7.57 (m, 1H), 7.26–7.20 (m, 3H), 7.19–7.13 (m, 2H), 7.04 (d, *J*=7.8 Hz, 2H), 6.98 (d, *J*=7.2 Hz, 1H), 4.18 (q, *J*=7.2 Hz, 2H), 2.48 (s, 3H), 2.28 (s, 3H), 1.09 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 172.93, 168.23, 165.70, 163.58, 140.48, 136.43, 134.32, 131.01, 129.04, 128.84, 128.25, 122.51, 121.29, 120.43, 119.60, 111.70, 99.31, 61.76, 22.48, 21.29, 13.68; HRMS (EI) *m/z*: ($[M+H]^+$) Calcd for $C_{23}H_{22}N_3O_2S$ 404.1427; Found 404.1423.

Ethyl 2-((3a,7a-dihydro-1*H*-indol-3-yl)thio)-4-(4-fluorophenyl)-6-methylpyrimidine-5-carboxylate (3ca): Purple solid, mp 121-123 °C; IR (KBr): 3310(s), 2865(m), 1750(s), 1540(m), 1475(m), 850(w) cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 8.58 (s, 1H), 7.58 (d, *J*=7.8 Hz, 1H), 7.37–7.31 (m, 2H), 7.24 (d, *J*=6.6 Hz, 2H), 7.19–7.17 (m, 2H), 6.93 (t, *J*=8.6 Hz, 2H), 4.18 (q, *J*=7.2 Hz, 2H), 2.47 (s, 3H), 1.09 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 172.97, 168.02, 165.97, 164.72, 163.06, 162.35, 136.42, 130.79, 130.48, 130.42, 128.92, 122.70, 121.21, 120.58, 119.64, 115.46, 115.32, 111.68, 99.79, 61.86, 22.53, 13.69; HRMS (EI) *m/z*: ($[M+H]^+$) Calcd for $C_{22}H_{19}FN_3O_2S$ 408.1177; Found 408.1182.

Ethyl 2-((1*H*-indol-3-yl)thio)-4-(4-chlorophenyl)-6-methylpyrimidine-5-carboxylate (3da): Purple solid, mp 143-145 °C; IR (KBr): 3225(s), 2910(m), 1715(s), 1570(m), 1492(m), 1235(w), 835(w) cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 8.51 (s, 1H), 7.59–7.58 (m, 1H), 7.30–7.23 (m, 5H), 7.22–7.16 (m, 3H), 4.18 (q, *J*=7.2 Hz, 2H), 2.48 (s, 3H), 1.10 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 173.01, 167.93, 166.05, 162.23, 136.38, 135.67, 130.69, 129.70, 128.97, 128.51, 122.74, 121.18, 120.62, 119.68, 111.65, 100.00, 61.91, 22.56, 13.70; HRMS (EI) *m/z*: ($[M+H]^+$) Calcd for $C_{22}H_{19}ClN_3O_2S$ 424.0881; Found 424.0884.

Ethyl 2-((1*H*-indol-3-yl)thio)-4-(4-bromophenyl)-6-methylpyrimidine-5-carboxylate (3ea): Purple solid, mp 133-135 °C; IR (KBr): 3285(s), 2987(m), 1725(s), 1565(m), 1470(m), 1268(w), 680(w) cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 8.45 (s, 1H), 7.59 (d, *J*=7.8 Hz, 1H), 7.41–7.36 (m, 4H), 7.28–7.27 (m, 1H), 7.20–7.17 (m, 3H), 4.18 (q, *J*=7.2 Hz, 2H), 2.48 (s, 3H), 1.10 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 172.87, 167.99, 166.02, 162.16, 136.34, 136.20, 131.43, 130.47, 129.96, 129.13, 124.73, 122.80, 121.05, 120.67, 119.77, 111.57, 100.56, 61.88, 22.60, 13.70; HRMS (EI) *m/z*: ($[M+H]^+$) Calcd for $C_{22}H_{19}BrN_3O_2S$ 468.0376; Found 468.0372.

Ethyl 2-((3a,7a-dihydro-1*H*-indol-3-yl)thio)-4-methyl-6-(3-nitrophenyl)pyrimidine-5-carboxylate (3fa): Purple soli, mp 69-71 °C; IR (KBr): 3273(s), 2978(m), 1710(s), 1578(m), 1490(m), 1350(m), 1238(w), 835(w) cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 8.51 (s, 1H), 8.20 (s, 1H), 8.15–8.14 (m, 1H), 7.62–7.58 (m, 2H), 7.41–7.33 (m, 3H), 7.29–7.25 (m, 1H), 7.20 (t, *J*=7.8 Hz, 1H), 4.22 (q, *J*=7.2 Hz, 2H), 2.52 (s, 3H), 1.13 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 173.41, 167.49, 166.53, 160.76, 148.02, 138.76, 136.35, 134.17, 130.54, 129.21, 128.89, 124.54, 123.49, 122.97, 121.26, 120.85, 119.50, 111.73, 99.99, 62.15, 22.74, 13.72; HRMS (EI) *m/z*: ($[M+H]^+$) Calcd for $C_{22}H_{19}N_4O_4S$ 435.1122; Found 435.1125.

Ethyl 4-(2-chlorophenyl)-2-((3a,7a-dihydro-1*H*-indol-3-yl)thio)-6-methylpyrimidine-5-carboxylate (3ga): Purple solid, mp 140-142 °C; IR (KBr): 3220(s), 2915(m), 1724(s), 1565(m), 1482(m), 1238(w), 843(w) cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 8.45 (s, 1H), 7.54 (d, *J*=7.8Hz, 1H), 7.26–7.24 (m, 1H), 7.20–7.12 (m, 5H), 7.06–7.00 (m, 2H), 4.02 (q, *J*=7.2 Hz, 2H), 2.58 (s, 3H), 0.88 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 173.58, 167.18, 166.21, 164.03, 137.07, 136.40, 131.99, 131.01, 130.13, 129.88, 129.26, 128.57, 126.45, 122.54, 121.96, 120.37, 119.38, 111.64, 98.81, 61.42, 23.46, 13.36; HRMS (EI) *m/z*: ($[M+H]^+$) Calcd for $C_{22}H_{19}ClN_3O_2S$ 424.0881; Found 424.0884.

Methyl 2-((1*H*-indol-3-yl)thio)-4-methyl-6-phenylpyrimidine-5-carboxylate (3ha): Purple solid, mp 129-131 °C; IR (KBr): 3218(s), 2985(m), 1713(s), 1583(m), 1475(m), 1245(w) cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 8.58 (s, 1H), 7.58 (d, *J*=7.8 Hz, 1H), 7.36–7.30 (m, 3H), 7.26 (t, *J*=7.2 Hz, 2H), 7.22–7.16 (m, 2H), 7.14–7.10 (m, 1H), 6.96–6.91 (m, 1H), 3.67 (s, 3H), 2.49 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 173.29, 168.57, 166.02, 163.67, 137.14, 136.45, 131.09, 131.07, 130.24, 128.77, 128.43, 128.24, 128.17,

122.57, 121.16, 120.49, 119.54, 111.76, 99.08, 52.53, 22.56; HRMS (EI) *m/z*: ([M+H]$^+$) Calcd for $C_{21}H_{18}N_3O_2S$ 376.1114; Found 376.1118.

Isopropyl 2-((1*H*-indol-3-yl)thio)-4-methyl-6-phenylpyrimidine-5-carboxylate (3ia): Purple solid, mp 112-114 °C; IR (KBr): 3223(s), 2965(m), 1718(s), 1570(m), 1468(m), 1265(w) cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.54 (s, 1H), 7.59 (d, *J*=7.8 Hz, 1H), 7.38–7.35 (m, 2H), 7.27–7.15 (m, 6H), 7.01 (s, 1H), 5.07–5.03 (m, 1H), 2.49 (s, 3H), 1.07 (s, 3H), 1.06 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 172.89, 167.48, 165.66, 163.63, 137.28, 136.43, 131.00, 130.01, 128.85, 128.34, 128.31, 124.10, 122.56, 121.96, 120.67, 120.46, 119.74, 111.69, 99.37, 69.71, 22.66, 22.44, 21.27; HRMS (EI) *m/z*: ([M+H]$^+$) Calcd for $C_{23}H_{22}N_3O_2S$ 404.1427; Found 404.1431.

Ethyl 2-((1*H*-indol-3-yl)thio)-4-isopropyl-6-phenylpyrimidine-5-carboxylate (3ja): Purple solid, mp 96-98 °C; IR (KBr): 3223(s), 2985(m), 1725(s), 1580(m), 1453(m), 1252(w) cm^{-1}; ^{1}H NMR (600 MHz, CDCl3): δ 8.47 (s, 1H), 7.60 (d, *J*=7.8 Hz, 1H), 7.43 (d, *J*=7.8 Hz, 2H), 7.34 (d, *J*=7.2 Hz, 1H), 7.31–7.22 (m, 5H), 7.18–7.15 (m, 1H), 4.13 (q, *J*=7.2 Hz, 2H), 3.09 (t, *J*=6.6 Hz, 1H), 1.07 (s, 3H), 1.06 (s, 3H), 1.03 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 173.35, 173.02, 168.28, 163.69, 137.59, 136.33, 130.52, 129.87, 129.22, 128.31, 128.26, 122.51, 120.73, 120.40, 119.86, 111.48, 100.55, 61.70, 33.05, 21.36, 13.59; HRMS (EI) *m/z*: ([M+H]$^+$) Calcd for $C_{24}H_{24}N_3O_2S$ 418.1584; Found 418.1588.

Ethyl 4-methyl-2-((2-methyl-1*H*-indol-3-yl)thio)-6-phenylpyrimidine-5-carboxylate (3ab): Purple solid, mp 77-79 °C; IR (KBr): 3235(s), 2975(m), 1718(s), 1590(m), 1465(m), 1248(w) cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.32 (s, 1H), 7.55–7.51 (m, 1H), 7.39 (d, *J*=7.8 Hz, 2H), 7.33 (t, *J*=7.2 Hz, 1H), 7.27 (d, *J*=7.2 Hz, 2H), 7.16–7.09 (m, 3H), 4.13 (q, *J*=7.2 Hz, 2H), 2.47 (s, 3H), 2.23 (s, 3H), 1.02 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 172.90, 168.15, 165.79, 163.78, 141.46, 137.45, 135.41, 129.94, 128.28, 128.24, 126.73, 121.70, 121.42, 120.30, 118.82, 110.83, 96.60, 61.73, 22.54, 14.07, 13.59; HRMS (EI) *m/z*: ([M+H]$^+$) Calcd for $C_{23}H_{22}N_3O_2S$ 404.1427; Found 404.1431.

Ethyl 4-(4-fluorophenyl)-6-methyl-2-((2-methyl-1*H*-indol-3-yl)thio)pyrimidine-5-carboxylate (3cb): Purple solid, mp 132-134 °C; IR (KBr): 3320(s), 2895(m), 1724(s), 1535(m), 1482(m), 865(w) cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.26 (s, 1H), 7.53 (d, *J*=7.8 Hz, 1H), 7.39–7.35 (m, 2H), 7.31–7.28 (m, 1H), 7.20–7.11 (m, 2H), 6.98–6.93 (m, 2H), 4.17 (q, *J*=7.2 Hz, 2H), 2.46 (s, 3H), 2.44 (s, 3H), 1.09 (t, *J*=7.2 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ 172.63, 164.70, 163.04, 162.17, 141.15, 135.33, 133.54, 130.50, 130.44, 130.36, 121.85, 121.01, 120.44, 118.98, 115.39, 115.25, 110.59, 61.78, 22.61, 13.69, 12.44; HRMS (EI) *m/z*: ([M+H]$^+$) Calcd for $C_{23}H_{21}FN_3O_2S$ 422.1333; Found 422.1336.

Ethyl 4-(4-chlorophenyl)-6-methyl-2-((2-methyl-1*H*-indol-3-yl)thio)pyrimidine-5-carboxylate (3db): Purple solid, mp 168-170 °C; IR (KBr): 3238(s), 2920(m), 1717(s), 1583(m), 1490(m), 1234(w), 880 (w) cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.25 (s, 1H), 7.54–7.50 (m, 1H), 7.31–7.27 (m, 3H), 7.26–7.21 (m, 3H), 7.19–7.12 (m, 2H), 4.17 (q, *J*=7.2 Hz, 2H), 2.47 (s, 3H), 2.43 (s, 3H), 1.10 (t, *J*=7.2 Hz, 3H); ^{13}C

NMR (150 MHz, $CDCl_3$): δ 172.77, 168.09, 165.92, 162.09, 141.15, 136.27, 135.86, 135.32, 130.33, 129.72, 128.47, 121.87, 121.03, 120.45, 118.96, 110.6 , 97.31, 61.83, 22.63, 13.69, 12.42; HRMS (EI) *m/z*: ($[M+H]^+$) Calcd for $C_{23}H_{21}ClN_3O_2S$ 438.1038; Found 438.1042.

Ethyl 3,4'-dimethyl-5-((2-methyl-1*H*-indol-3-yl)thio)-[1,1'-biphenyl]-2-carboxylate (3bb): Purple solid, mp 162-164 °C; IR (KBr): 3219(s), 2883(m), 1718(s), 1575(m), 1486(m), 1268(w) cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 8.25 (s, 1H), 7.55–7.50 (m, 1H), 7.29–7.26 (m, 2H), 7.15–7.11 (m, 2H), 7.08–7.05 (m, 3H), 4.17 (q, *J*=7.2 Hz, 2H), 2.46 (s, 3H), 2.29 (s, 3H), 2.19 (s, 3H), 1.08 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 172.73, 168.37, 165.54, 163.55, 141.38, 140.29, 135.41, 134.51, 130.21, 128.99, 128.23, 121.68, 121.24, 120.28, 118.87, 110.80, 96.75, 61.71, 22.51, 21.29, 13.68, 12.16; HRMS (EI) *m/z*: ($[M+H]^+$) Calcd for $C_{24}H_{24}N_3O_2S$ 418.1584; Found 418.1588.

Ethyl 4-methyl-2-((1-methyl-1*H*-indol-3-yl)thio)-6-phenylpyrimidine-5-carboxylate (3ac): Purple solid, mp 114-116 °C; IR (KBr): 2965(m), 1718(s), 1575(m), 1487(m), 1268(w) cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 7.62–7.60 (m, 1H), 7.38–7.35 (m, 3H), 7.33–7.29 (m, 3H), 7.27–7.24 (m, 2H), 7.21–7.18 (m, 1H), 4.15 (q, *J*=7.2 Hz, 2H), 3.80 (s, 3H), 2.47 (s, 3H), 1.04 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 172.84, 168.27, 165.75, 163.46, 137.46, 137.42, 134.67, 129.93, 129.92, 128.41, 128.20, 122.28, 121.23, 120.23, 120.01, 109.65, 98.45, 61.68, 33.1, 22.62, 13.61; HRMS (EI) *m/z*: ($[M+H]^+$) Calcd for $C_{23}H_{22}N_3O_2S$ 404.1427; Found 404.1432.

Ethyl 4-(4-fluorophenyl)-6-methyl-2-((1-methyl-3a,7a-dihydro-1*H*-indol-3-yl)thio)pyrimidine-5-carboxylate (3cc): Purple solid, mp 127-129 °C; IR (KBr): 2958(m), 1728(s), 1586(m), 1485(m), 1275(w), 886(w) cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 7.59–7.58 (m, 1H), 7.39 (d, *J*=7.8 Hz, 1H), 7.36–7.28 (m, 4H), 7.20–7.18 (m, 1H), 6.96–6.89 (m, 2H), 4.18 (q, *J*=7.2 Hz, 2H), 3.83 (s, 3H), 2.47 (s, 3H), 1.10 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 172.88, 168.20, 165.85, 164.72, 163.06, 162.11, 137.48, 134.62, 130.58, 130.52, 129.86, 122.32, 120.97, 120.26, 119.98, 115.36, 115.22, 109.69, 98.41, 61.78, 33.17, 22.61, 13.70; HRMS (ESI+) *m/z*: ($[M+H]^+$) Calcd for $C_{23}H_{21}FN_3O_2S$ 422.1333; Found 422.1337.

Ethyl 3,4'-dimethyl-5-((1-methyl-1*H*-indol-3-yl)thio)-[1,1'-biphenyl]-2-carboxylate (3bc): Purple solid, mp 149-151 °C; IR (KBr): 2985(m), 1712(s), 1578(m), 1498(m), 1279(w) cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 7.89–7.86 (m, 1H), 7.65–7.60 (m, 1H), 7.39–7.37 (m, 1H), 7.33–7.30 (m, 1H), 7.29–7.26 (m, 2H), 7.22–7.19 (m, 2H), 7.18–7.15 (m, 1H), 4.19 (q, *J*=7.2 Hz, 2H), 3.81 (s, 3H), 2.47 (s, 3H), 2.32 (s, 3H), 1.11 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 172.68, 168.51, 165.54, 163.23, 137.05, 134.66, 132.51, 129.96, 129.31, 128.94, 122.26, 122.02, 121.04, 120.22, 120.06, 119.80, 119.5, 109.63, 98.57, 61.69, 33.13, 22.60, 21.31, 13.71; HRMS (EI) *m/z*: ($[M+H]^+$) Calcd for $C_{24}H_{24}N_3O_2S$ 418.1584; Found 418.1587.

3-(Phenylthio)-1*H*-indole[17] **(3ka):** White solid, mp 147-149 °C; IR (KBr): 3230(s), 1585(m), 1465(m), 1268(w) cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 8.36 (s, 1H), 7.63 (d, *J*=7.8 Hz, 1H), 7.47 (d, *J*=6.0 Hz, 1H), 7.43 (d, *J*=7.8 Hz, 1H), 7.30–7.27 (m, 1H), 7.20–7.16 (m, 3H), 7.13–7.12 (m, 2H), 7.08–7.05 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 139.22, 136.48, 130.67, 129.09, 128.70, 125.86, 124.78, 123.05, 120.91, 119.66, 111.58, 102.82; HRMS (EI) *m/z*: ($[M+H]^+$) Calcd for $C_{14}H_{12}NS$ 226.0685; Found 226.0688.

2-Methyl-3-(phenylthio)-1*H*-indole[17] **(3kb):** Purple solid, mp 113-115 °C; IR (KBr): 3224(s), 2975(m), 1578(m), 1480(m), 1230(w) cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 8.14 (s, 1H), 7.61 (d, *J*=7.8 Hz, 1H), 7.34 (d, *J*=7.8 Hz, 1H), 7.26–7.22 (m, 1H), 7.21–7.16 (m, 3H), 7.11–7.06 (m, 3H), 2.50 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 141.22, 139.38, 135.47, 130.31, 128.75, 125.54, 124.58, 122.21, 120.73, 118.98, 110.75, 99.26, 12.14; HRMS (EI) *m/z*: ($[M+H]^+$) Calcd for $C_{15}H_{14}NS$ 240.0841; Found 240.0845.

1-Methyl-3-(phenylthio)-1*H*-indole[17] **(3kc):** Purple solid, mp 88-90 °C; IR (KBr): 2865(m), 1586(m), 1463(m), 1248(w) cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 7.63–7.62 (m, 1H), 7.40–7.39 (m, 1H), 7.34 (s, 1H), 7.31–7.29 (m, 1H), 7.19–7.14 (m, 3H), 7.12–7.10 (m, 2H), 7.07–7.03 (m, 1H), 3.85 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 139.66, 137.54, 135.03, 129.83, 128.63, 125.72, 124.64, 122.55, 120.48, 119.74, 109.69, 100.54, 33.13; HRMS (EI) *m/z*: ($[M+H]^+$) Calcd for $C_{15}H_{14}NS$ 240.0841; Found 240.0847.

3-((4-Nitrophenyl)thio)-1*H*-indole[17] **(3la):** Yellow solid, mp 117-119 °C; IR (KBr): 3236(s), 1583(m), 1468(m), 1380(m), 1279(w), 845(w) cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 8.61 (s, 1H), 8.02–7.99 (m, 2H), 7.55–7.49 (m, 3H), 7.32 (t, *J*=7.6 Hz, 1H), 7.21–7.19 (m, 1H), 7.13 (d, *J*=8.4 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 149.74, 144.92, 136.57, 131.14, 128.42, 125.08, 123.84, 123.56, 121.42, 119.21, 111.91, 100.72; HRMS (EI) *m/z*: ($[M+H]^+$) Calcd for $C_{14}H_{11}N_2O_2S$ 271.0536; Found 271.0540.

2-Methyl-3-((4-nitrophenyl)thio)-1*H*-indole (3lb): Yellow solid, mp 141-143 °C; IR (KBr): 3232(s), 2868(m), 1588(m), 1470(m), 1385(m), 1289(w), 855(w) cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 8.49 (s, 1H), 8.05–7.95 (m, 2H), 7.46 (d, *J*=7.8 Hz, 1H), 7.40 (d, *J*=8.4 Hz, 1H), 7.27–7.21 (m, 1H), 7.16 (t, *J*=7.2 Hz, 1H), 7.11–7.09 (m, 2H), 2.52 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 150.02, 144.71, 141.78, 135.56, 129.51, 124.88, 123.87, 122.64, 121.08, 118.47, 111.05, 96.75, 12.08; HRMS (EI) *m/z*: ($[M+H]^+$) Calcd for $C_{15}H_{13}N_2O_2S$ 285.0692; Found 285.0695.

1-Methyl-3-((4-nitrophenyl)thio)-1*H*-indole (3lc): Yellow solid, mp 145-147 °C; IR (KBr): 2875(m), 1585(m), 1460(m), 1383(m), 1275(w), 850(w) cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 7.98 (d, *J*=8.4 Hz, 2H), 7.53–7.52 (m, 1H), 7.47–7.42 (m, 1H), 7.39–7.32 (m, 2H), 7.21–7.19 (m, 1H), 7.14–7.10 (m, 2H), 3.89 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 150.17, 144.79, 137.63, 135.37, 129.12, 124.93, 123.78, 123.03, 121.00, 119.24, 110.08, 97.74, 33.31; HRMS (EI) *m/z*: ($[M+H]^+$) Calcd for $C_{15}H_{13}N_2O_2S$ 285.0692; Found 285.0697.

3-(Pyridin-2-ylthio)-1*H*-indole (3ma): Purple solid, mp 123-125 °C; IR (KBr): 3230(s), 1580(m), 1470(m), 1280(w) cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 9.16 (s, 1H), 8.41–8.37 (m, 1H), 7.61 (d, *J*=7.8 Hz, 1H), 7.47–7.46 (m, 1H), 7.42–7.40 (m, 1H), 7.35–7.33 (m, 1H), 7.28–7.23 (m, 1H), 7.18–7.16 (m, 1H), 6.97–6.92 (m, 1H), 6.79 (d, *J*=8.4 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 162.76, 149.03, 136.71, 136.68, 131.34, 128.82, 123.04, 120.94, 119.95, 119.37, 119.33, 111.84, 100.81; HRMS (EI) *m/z*: ($[M+H]^+$) Calcd for $C_{13}H_{11}N_2S$ 227.0637; Found 227.0641.

2-Methyl-3-(pyridin-2-ylthio)-1*H*-indole (3mb): Purple solid, mp 82-84 °C; IR (KBr): 3238(s), 2892(m), 1586(m), 1475(m), 1283(w) cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 8.80 (s, 1H), 8.41–8.40 (m, 1H), 7.54 (d, *J*=7.8 Hz, 1H), 7.38–7.29 (m, 2H), 7.21–7.17 (m, 1H), 7.15–7.11 (m, 1H), 6.96–6.90 (m, 1H), 6.66 (d, *J*=7.8 Hz, 1H), 2.50 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 162.79, 149.12, 141.61, 136.65, 135.66, 129.91, 122.23, 120.74, 119.46, 119.15, 118.75, 110.87, 97.80, 12.14; HRMS (EI) *m/z*: ($[M+H]^+$) Calcd for $C_{14}H_{13}N_2S$ 241.0794; Found 241.0798.

1-Methyl-3-(pyridin-2-ylthio)-1*H*-indole (3mc): Purple solid, mp 129-131 °C; IR (KBr): 2890(m), 1585(m), 1473(m), 1275(w) cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 8.41–8.40 (m, 1H), 7.62 (d, *J*=8.4 Hz, 1H), 7.40 (d, *J*=8.4 Hz, 1H), 7.36–7.28 (m, 3H), 7.20–7.18 (m, 1H), 6.93–6.91 (m, 1H), 6.74–6.73 (m, 1H), 3.84 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 163.07, 149.19, 137.64, 136.51, 135.30, 129.54, 122.72, 120.68, 119.66, 119.58, 119.16, 109.89, 99.17, 33.21; HRMS (EI) *m/z*: ($[M+H]^+$) Calcd for $C_{14}H_{13}N_2S$ 241.0794; Found 241.0799.

Ethyl 2-((1*H*-benzo[*d*]imidazol-2-yl)thio)-4-methyl-6-phenylpyrimidine-5-carboxylate (3ag): White solid, mp 124-126 °C; IR (KBr): 3218(s), 2948(m), 1715(s), 1568(m), 1489(m), 1253(w) cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 9.16 (s, 1H), 8.67–8.60 (m, 1H), 7.85 (d, *J*=7.8 Hz, 1H), 7.78–7.71 (m, 2H), 7.58–7.49 (m, 3H), 7.44–7.35 (m, 2H), 4.22 (q, *J*=7.2 Hz, 2H), 2.73 (s, 3H), 1.09 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 167.92, 157.56, 165.66, 155.04, 145.06, 142.04, 137.31, 131.87, 130.56, 128.69, 128.37, 124.73, 123.93, 122.57, 120.46, 115.84, 62.00, 22.90, 13.63; HRMS (EI) *m/z*: ($[M+H]^+$) Calcd for $C_{21}H_{19}N_4O_2S$ 391.1223; Found 391.1227.

Ethyl 5-((1*H*-benzo[*d*]imidazol-2-yl)thio)-4'-fluoro-3-methyl-[1,1'-biphenyl]-2-carboxylate (3cg): Yellow solid, mp 100-102 °C; IR (KBr): 3223(s), 2959(m), 1725(s), 1570(m), 1480(m), 1255(m), 850(w) cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 9.16 (s, 1H), 8.61 (d, *J*=7.8 Hz, 1H), 7.86 (d, *J*=7.8 Hz, 1H), 7.79–7.76 (m, 2H), 7.44–7.37 (m, 2H), 7.24–7.21 (m, 2H), 4.26 (q, *J*=7.2 Hz, 2H), 2.73 (s, 3H), 1.15 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 168.04, 167.48, 165.11, 164.38, 163.41, 155.03, 142.00, 130.57, 130.51, 124.77, 123.99, 122.40, 120.53, 115.96, 115.81, 115.75, 62.10, 22.90, 13.73; HRMS (EI) *m/z*: ($[M+H]^+$) Calcd for $C_{21}H_{18}FN_4O_2S$ 409.1129; Found 409.1133.

Ethyl 2-((1*H*-benzo[*d*]imidazol-2-yl)thio)-4-(4-bromophenyl)-6-methylpyrimidine-5-carboxylate (3eg): White solid, mp 147-149 °C; IR (KBr): 3232(s), 2948(m), 1717(s), 1576(m), 1482(m), 1258(m),

650(w) cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 9.14 (s, 1H), 8.60 (d, *J*=7.2 Hz, 1H), 7.87–7.84 (m, 1H), 7.69–7.66 (m, 2H), 7.64 (d, *J*=8.4 Hz, 2H), 7.42–7.38 (m, 2H), 4.26 (q, *J*=7.2 Hz, 2H), 2.73 (s, 3H), 1.16 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 168.21, 167.31, 164.44, 155.08, 141.96, 136.16, 131.97, 129.94, 125.37, 124.79, 124.02, 122.38, 120.55, 115.74, 62.16, 22.93, 13.73; HRMS (EI) *m/z*: ($[M+H]^+$) Calcd for $C_{21}H_{18}BrN_4O_2S$ 469.0328; Found 469.0331.

Ethyl 5-((1*H*-benzo[*d*]imidazol-2-yl)thio)-3,4'-dimethyl-[1,1'-biphenyl]-2-carboxylate (3bg): Yellow solid, mp 75-77 °C; IR (KBr): 3238(s), 2942(m), 1734(s), 1573(m), 1488(m), 1252(w) cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 9.16 (s, 1H), 8.65 (d, *J*=8.4 Hz, 1H), 7.85 (d, *J*=7.2 Hz, 1H), 7.68 (d, *J*=8.4 Hz, 2H), 7.41–7.38 (m, 2H), 7.33 (d, *J*=7.8 Hz, 2H), 4.26 (q, *J*=7.2 Hz, 2H), 2.71 (s, 3H), 2.46 (s, 3H), 1.15 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 167.78, 167.66, 165.47, 155.02, 142.06, 141,07, 134.41, 129.42, 129.13, 128.38, 128.31, 124.67, 123.87, 122.38, 120.44, 115.85, 61.98, 22.85, 21.46, 13.71; HRMS (EI) *m/z*: ($[M+H]^+$) Calcd for $C_{22}H_{21}N_4O_2S$ 405.1380; Found 405.1383.

3-((4-Bromophenyl)thio)-1*H*-indole (3na): White solid, mp 84-86 °C; IR (KBr): 3234(s), 1571(m), 1473(m), 1252(m), 680(w) cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 8.45 (s, 1H), 7.56–7.44 (m, 3H), 7.28–7.25 (m, 3H), 7.18–7.15 (m, 1H), 6.96–6.94 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 138.52, 136.48, 131.59, 130.89, 130.85, 130.67, 128.81, 127.36, 123.19, 121.04, 119.48, 118.26, 111.62, 102.30; HRMS (EI) *m/z*: ($[M+H]^+$) Calcd for $C_{14}H_{11}BrNS$ 303.9790; Found 303.9793.

Ethyl 2-((4-bromophenyl)disulfanyl)-4-methyl-6-phenylpyrimidine-5-carboxylate (1n): Yellow oil; IR (KBr): 2985(m), 1712(s), 1583(m), 1460(m), 1250(m), 680(w) cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 7.60–7.58 (m, 1H), 7.49–7.45 (m, 4H), 7.43–7.39 (m, 3H), 7.35–7.26 (m, 1H), 4.18 (q, *J*=7.2 Hz, 2H), 2.58 (s, 3H), 1.05 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 169.88, 167.67, 166.50, 164.23, 137.03, 135.82, 132.56, 131.95, 131.15, 130.43, 129.37, 128.57, 128.52, 128.48, 128.41, 122.81, 121.93, 61.95, 22.64, 13.62; HRMS (EI) *m/z*: ($[M+H]^+$) Calcd for $C_{20}H_{18}BrN_2O_2S_2$ 460.9988; Found 460.9992.

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