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Synthesis of new unsymmetric *N*,*N*′-dipyridylurea derivatives by selenium and selenium dioxide-catalyzed reductive carbonylation of substituted nitropyridines

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Abstract—Without using phosgene, a series of new unsymmetric *N*,*N*′-dipyridylurea derivatives have been synthesized in moderate to good yields by the one-pot reductive carbonylation of substituted nitropyridines. These reactions utilize selenium or selenium dioxide as the catalyst, aminopyridine derivatives as co-reagents, and carbon monoxide as the carbonyl source.

1. Introduction

Pyridines are important heterocyclic compounds. Many pyridylurea derivatives containing both a peptide bond (−CONH−) and a pyridyl group possess biological activities and are widely used as insecticides, agrochemical fungicides, herbicides and plant growth regulators.[1–4] However, research concerning *N*,*N*′-dipyridylurea derivatives has mostly focused on their conformational behavior,[5,6] and the conventional method for the preparation of pyridylurea derivatives utilizes highly toxic phosgene as the carbonyl source.[5,6] This conventional process has many disadvantages. For example, the toxicity and corrosive nature of phosgene and formation of hydrogen chloride as a by-product are particularly troublesome.[7,8] Accordingly, catalytic carbonylation of organic nitro compounds has been recently investigated by several industrial and academic research groups.[9,10] The major objective of this research is to find a new catalytic process for synthesis of important chemicals that avoids the use of dangerous and corrosive phosgene. The group VIII transition metals rhodium, ruthenium and palladium have been commonly used as catalysts for this purpose.[11,12]

Additionally, non-transition metal elements and their oxides such as sulfur,[13,14] selenium[15–17] and selenium dioxide[18,19] have also been found to catalyze the synthesis of urea derivatives. These environmentally benign reactions have many advantages over the traditional phosgene routes used for synthesis of urea derivatives. However, most studies focus only on reactions of nitrobenzene derivatives, and little has been known of the reduction[20,21] and reductive carbonylation reactions of nitropyridines. In this regard, the synthesis of unsymmetric *N*,*N*′-dipyridylurea derivatives by means of such catalytic methods is even more attractive than that of symmetric ureas, because their conformational behavior can be studied as the model systems for polypeptides and proteins.[22]

2. Results and discussion

2.1. Synthesis of unsymmetric *N*,*N*′-dipyridylurea derivatives

In our previous studies,[17] we reported a series of unsymmetric phenyl ureas synthesized in a one-pot reaction sequence that combined selenium-catalyzed oxidative carbonylation of anilines with reductive carbonylation of nitrobenzene under relatively mild conditions. In this reaction, the nitrobenzene acts as both a reagent and as an oxidant, and plays an important role in the formation of a catalytic cycle. However, aliphatic nitro compounds did not function as reagents but only as oxidants.

Recently, we have found that selenium and selenium dioxide are good catalysts for the reductive carbonylation of substituted nitropyridines, using carbon monoxide and aminopyridine derivatives as co-reagents. A series of new unsymmetric *N*,*N*′-dipyridylurea derivatives **1a** have been synthesized in moderate to good yields (Table 1).

Keywords: carbonylation; reduction; selenium and compounds; ureas.
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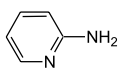
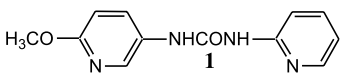
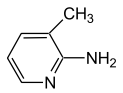
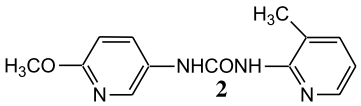
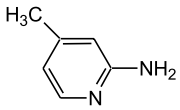
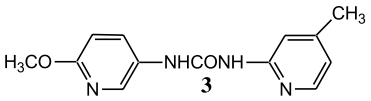
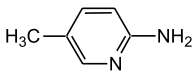
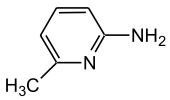
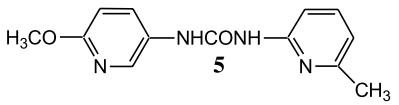
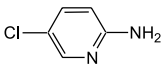
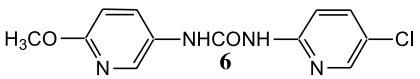
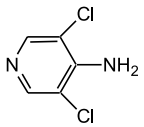
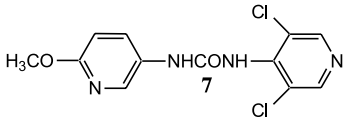
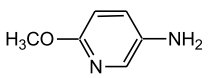
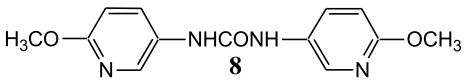
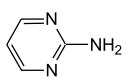
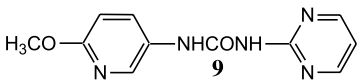
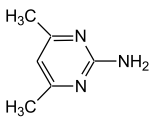
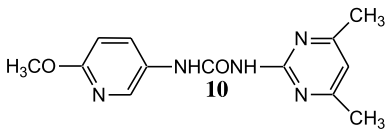
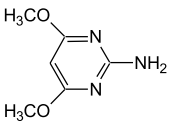
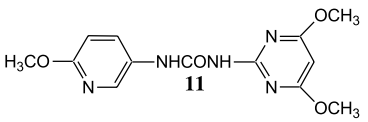
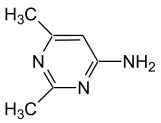
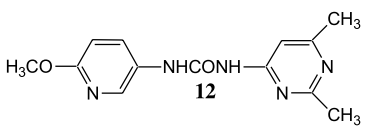
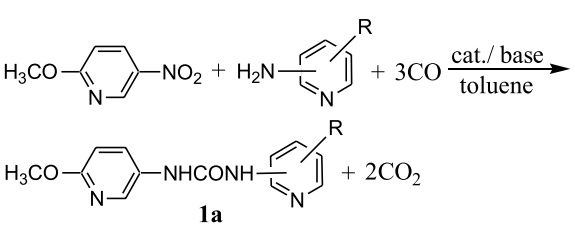
Table 1. The synthesis of unsymmetric *N*,*N*′-dipyridylurea derivatives

Entry	Substrates	Products	Products mp (°C)	Yield (%)[a]		
				Se[b]	SeO_2[c]	SeO_2[d]
1		 **1**	178–180	74	77	62
2		 **2**	173–175	79	82	67
3		 **3**	188–189	83	85	69
4		 **4**	178	86	89	71
5		 **5**	210–212	85	88	74
6		 **6**	211	66	69	52
7		 **7**	/	0	0	0
8		 **8**	228–231	70	73	59
9		 **9**	220–221	62	65	50
10		 **10**	198–201	67	68	51
11		 **11**	228–229	57	58	41
12		 **12**	163–166	69	72	58

[a] Isolated yields. Reaction conditions: substrate, 10 mmol; 2-methoxyl-5-nitropyridine, 10 mmol; CO, 3.0 MPa; toluene, 10 mL; 120–130°C; 4.0 h.
[b] Se, 0.5 mmol; Et_3N, 10 mmol.
[c] SeO_2, 0.5 mmol; Et_3N, 10 mmol.
[d] SeO_2, 0.5 mmol; Ph_3P, 1.0 mmol.



(1)

1a

It was found that reactions catalyzed by both selenium and selenium dioxide exhibit remarkable chemoselectivity, and the substituted nitropyridines can be converted into ureas in the same manner as nitrobenzene. It is worthy to note that symmetric *N*,*N*′-dipyridylurea derivatives were not detected in the crude reaction mixtures by HPLC analysis. This is in contrast to the reports of mixtures of three symmetric and

Table 2. Effects of different experimental conditions on selenium and selenium dioxide-catalyzed reaction

Entry	Temperature (°C)	Catalyst (mmol)	Base (mmol)	Yield (%)[a]	
				Se	SeO_2
1	110	0.5	TEA[b] (10)	68	67
2	130	0.5	TEA (10)	74	77
3	150	0.5	TEA (10)	73	75
4	170	0.5	TEA (10)	70	70
5	130	0.01	TEA (10)	34	30
6	130	0.05	TEA (10)	59	63
7	130	0.1	TEA (10)	75	77
8	130	1.0	TEA (10)	78	82
9	130	0.5	TEA (/)	/	/
10	130	0.5	TEA (30)	76	77
11	130	0.5	TPP[c] (1)	/	62
12	130	0.5	NMP[d] (10)	76	76
13	130	0.5	DABCO[e] (10)	77	75
14	130	0.5	DBN[f] (10)	81	80
15	130	0.5	DBU[g] (10)	81	83

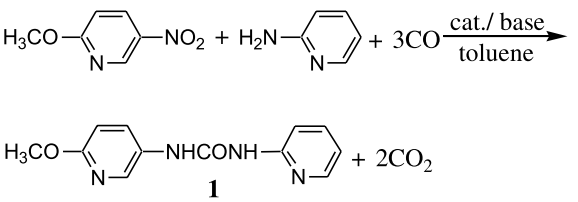
[a] Isolated yields. Reaction conditions: 2-methoxy-5-nitropyridine, 10 mmol; 2-aminopyridine, 10 mmol; base, 0–30 mmol; CO, 3.0 MPa; toluene, 10 mL; 110–170°C; 4.0 h; catalyst, Se or SeO_2, 0.01–1.0 mmol.
[b] Triethylamine.
[c] Triphenylphosphine.
[d] *N*-Methylpyrrolidine.
[e] 1,4-Diazabicyclo[2,2,2]octane.
[f] 1,5-Diazabicyclo[4,3,0]non-5-ene.
[g] 1,8-Diazabicyclo[5,4,0]undec-7-ene.

unsymmetric ureas being formed when primary amines were used as co-reagents.[15,17,23] In most case, selenium dioxide showed higher catalytic activity than selenium under the same reaction conditions. The reason that the catalytic activity of selenium dioxide was little higher than that of selenium can be presumably rationalized that selenium dioxide more readily forms the necessary reactive intermediate.

As shown in Table 1, heterocyclic aromatic amines such as aminopyridine and aminopyrimidine react readily with substituted nitropyridines in the presence of selenium or selenium dioxide and carbon monoxide under mild conditions. The fact that 4-amino-3,5-dichloropyridine gave none of the expected product suggests that the reaction is sterically sensitive to *ortho* substituents of the aromatic amine used (Table 1, entry 7). The yields of entries 2–5 were good and higher than those of entries 1 and 6. This shows that the reactions are electronically influenced by substituents on the aromatic rings (Table 1, entries 1–6). By using this method, the symmetric *N*,*N*′-bis(6-methoxy-3-pyridyl)urea **8** (entry 8) can also be synthesized.

2.2. The carbonylation of 2-methoxy-5-nitropyridine and 2-aminopyridine

Treatment of 2-methoxy-5-nitropyridine with 2-aminopyridine in 1: 1 molar ratio, using either selenium or selenium dioxide as the catalyst in the presence of carbon monoxide led to the formation of *N*-(2-pyridyl)-*N*′-(6-methoxy-3-pyridyl)urea **1** (Eq. (2)). Parameters such as temperature, amount of catalyst, and organic bases were investigated (Table 2).



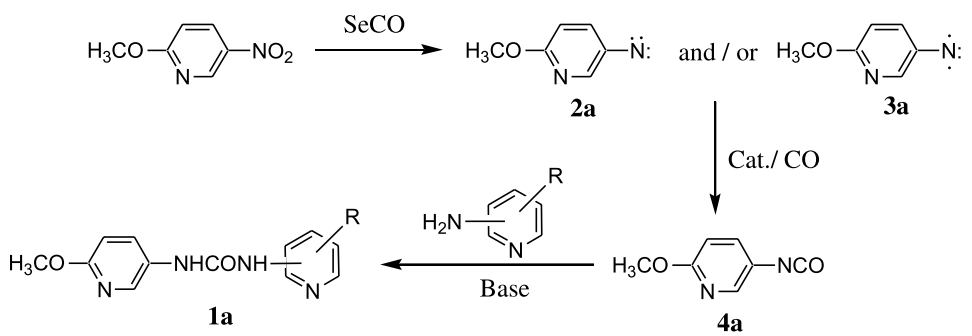
(2)

In the temperature range from 110 to 170°C, using either selenium or selenium dioxide, yields of **1** increased with temperature up to 130°C and then decreased with further increasing the reaction temperature (Table 2, entries 1–4). Decreasing yields at temperatures above 130°C can be rationalized if **1** decomposed faster than carbonylation of the remaining 2-aminopyridine. The yields of **1** also increased with increasing catalyst loading (Table 2, entries 5–8).

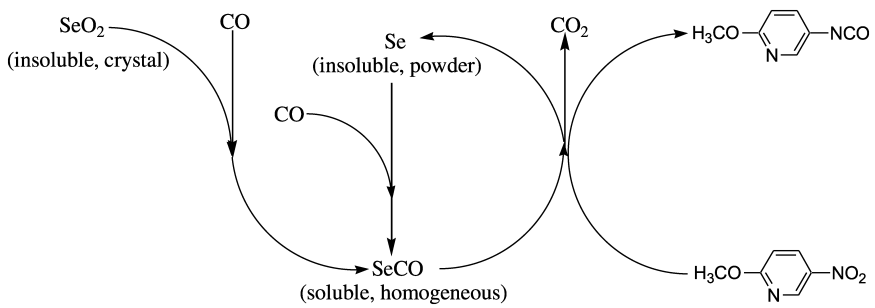
Organic bases dramatically affect formation of the product (Table 2, entries 9–15). Besides triethylamine, stronger organic bases such as 1,8-diazabicyclo[5,4,0]undec-7-ene (DBU) and 1,5-diazabicyclo[4,3,0]non-5-ene (DBN), the tertiary amine as 1,4-diazabicyclo[2,2,2]octane (DABCO) and the amide *N*-methylpyrrolidine (NMP) were all effective in the reductive carbonylation of 2-methoxy-5-nitropyridine with 2-aminopyridine. Interestingly, in the presence of triphenylphosphine (Table 2, entry 11), the selenium dioxide-catalyzed reaction afforded **1** in 62% yield, but the selenium-catalyzed reaction did not take place under the same conditions.

2.3. A possible reaction pathway of carbonylation

Although a detailed study of the reaction pathway has not been performed, the present reactions can be mechanistically explained by the reaction pathway shown in Scheme 1. Initial deoxygenation of the substituted nitropyridine derivative with carbonyl selenide (SeCO), generated in situ by the reaction of elemental selenium or selenium dioxide with carbon monoxide in the presence of



Scheme 1. A possible reaction pathway for carbonylation.



Scheme 2. Selenium or selenium dioxide-catalyzed carbonylation of substituted nitropyridines.

triethylamine,[24,25] results in an intermediate(s) nitrene **2a** and/or nitrenoid **3a** which further react with carbon monoxide to form pyridyl isocyanate complex **4a**. Finally, **4a** reacts with aminopyridine derivatives to afford the desired *N*,*N*′-dipyridylurea derivative **1a**.

It is known that selenium dioxide reacts with carbon monoxide in the presence of triethylamine under very mild conditions (10°C, 0.1 MPa), to form carbonyl selenide (COSe) in the same way as dose selenium.[16,24] In our case, when selenium dioxide goes through the first catalytic cycle, the catalyst is transformed into elemental selenium due to the reduction of selenium dioxide by carbon monoxide in the catalytic system (Scheme 2). During the reaction the substituted nitropyridine also acts as an oxidant, thus playing an important role in promoting a catalytic cycle. Products **1a** as well as the catalysts can then be easily obtained by simple phase separation.

3. Conclusion

The mild reaction conditions, good yield and high chemoselectivity of products, the one-step synthesis and the replacement of noxious phosgene by carbon monoxide combine to make the present procedure very useful for the preparation of unsymmetric *N*,*N*′-dipyridylurea derivatives. In summary, we have developed a catalytic synthetic method to prepare unsymmetric *N*,*N*′-dipyridylurea derivatives by combining reductive carbonylation of a nitropyridine with the oxidative carbonylation of an aminopyridine derivative in a one-pot reaction.

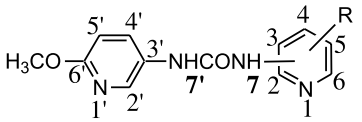
4. Experimental

4.1. General remarks

Organic solvents were all reagent grade and used without further purification. Aminopyridine derivatives, 2-methoxy-5-nitropyridine, elemental selenium (99.999%), selenium dioxide (98.0%), carbon monoxide (99.9%), triethylamine, triphenylphosphine and other organic base were all used as purchased. Purity of the products was determined by HPLC, with MeOH–H_2O as eluent. Melting points were determined on a Taike X-4 apparatus (Beijing, P. R. China) and are uncorrected. Infrared spectra were recorded on a Thermo Nicolet 470 instrument. Mass Spectra were performed on a Finnigan LCQ^{DUO} ion trap Mass Spectrometer (Finnigan MAT, San Jose, CA, USA) in ESI mode and an Applied Biosystem Mariner System 5303 in APCI mode. ^{1}H and ^{13}C NMR spectra were obtained on a Bruker DRX 400 spectrometer. Chemical shifts are reported in ppm relative to tetramethylsilane (δ-units) with dimethylsulfoxide-d_6 as solvent.

4.2. Typical procedure for the synthesis of *N*-(2-pyridyl)-*N*′-(6-methoxy-3-pyridyl)urea 1

Selenium (39.5 mg, 0.5 mmol), 2-aminopyridine (0.94 g, 10 mmol), 2-methoxy-5-nitropyridine (1.54 g, 10 mmol), triethylamine (1.01 g, 10 mmol) and toluene (10 mL) were successively introduced into a 100 mL stainless-steel autoclave. The stirring rate was kept constant for all the experiments. The reactor was sealed, flushed with 1.0 MPa of carbon monoxide three times, pressurized with 3.0 MPa carbon monoxide, and then placed in an oil bath preheated to the 130°C. After the reaction was finished, the apparatus was cooled to ambient temperature, and the remaining carbon monoxide was evacuated. The reaction mixture was filtered, and *N*-(2-pyridyl)-*N*′- (6-methoxy-3-pyridyl)urea was collected and further purified by flash chromatography (silica gel, v/v: hexane–AcOEt=5:3) in 74% yield (1.82 g).



4.2.1. *N*-(2-Pyridyl)-*N*′-(6-methoxy-3-pyridyl)urea 1. Colorless needle; mp 178–180°C; IR ν/cm^{-1} (KBr) 3221 (ν_{N-H}), 3012 (ν_{C-H}), 1693 ($\nu_{C=O}$), 1596, 1558, 1495, 1481, 1431 ($\nu_{C=C,C=N}$), 1383 (ν_{-CH3}), 782 (ν_{C-H}); ^{1}H, NMR (400 MHz, DMSO-d_6, 23°C) δ 3.91 (s, 3H, OC*H*$_3$), 6.73 (d, *J*=8.8 Hz, 1H, 5′-H), 6.91 (t, *J*=6.4 Hz, 1H, 5-H), 7.15 (d, *J*=8.0 Hz, 1H, 3-H), 7.62 (td, *J*=7.8, 1.2 Hz, 1H, 4-H), 7.91 (dd, *J*=8.7, 2.8 Hz, 1H, 4′-H), 8.22 (d, *J*=4.4 Hz, 1H, 6-H), 8.29 (s, 1H, 2′-H), 9.48 (s, 1H, 7′-H), 11.32 (s, 1H, 7-H); ^{13}C, NMR (400 MHz, DMSO-d_6, 23°C) δ 53.2 (O*C*H$_3$), 110.0 (C-5′), 112.2 (C-3), 116.8 (C-5), 129.2 (C-3′), 132.0 (C-4′), 138.1 (C-2′), 138.3 (C-4), 145.6 (C-6), 152.9 (C-2), 153.5 (C=O), 160.0 (C-6′); MS (ESI): *m*/*z*: 245 (15 MH$^+$), 151 (14), 125 (30), 121 (7), 95 (100%); HRMS (APCI): MH$^+$, found 245.1021, $C_{12}H_{13}N_4O_2$ requires 245.1033.

4.2.2. *N*-(3-Methyl-2-pyridyl)-*N*′-(6-methoxy-3-pyridyl)-urea 2. Colorless needle; mp 173–175°C; IR ν/cm^{-1} (KBr) 3294 (ν_{N-H}), 2955 (ν_{C-H}), 1683 ($\nu_{C=O}$), 1592, 1559, 1495 ($\nu_{C=C,C=N}$), 1461, 1379 (ν_{-CH3}), 746 (ν_{C-H}); ^{1}H, NMR (400 MHz, DMSO-d_6, 23°C) δ 2.05 (s, 3H, C*H*$_3$), 3.85 (s,

3H, OCH_3), 6.84 (d, J=8.7 Hz, 1H, 5′-H), 7.02 (t, J=6.5 Hz, 1H, 5-H), 7.64 (d, J=4.1 Hz, 1H, 4-H), 7.97 (d, J=8.8 Hz, 1H, 4′-H), 8.22 (s, 1H, 2′-H), 8.36 (d, J=8.4 Hz, 1H, 6-H), 8.66 (s, 1H, 7′-H), 11.81 (s, 1H, 7-H); ^{13}C, NMR (400 MHz, DMSO-d_6, 23°C) δ 17.0 (CH_3), 53.2 (OCH_3), 110.1 (C-5′), 117.8 (C-5), 121.4 (C-3), 129.7 (C-3′), 132.2 (C-4′), 138.1 (C-2′), 139.7 (C-4), 143.5 (C-6), 151.2 (C-2), 152.8 (C═O), 159.6 (C-6′); MS (ESI): m/z: 259 (2 MH^+), 151 (12), 135 (35), 125 (72), 110 (9), 109 (100%); HRMS (APCI): MH^+, found 259.1172, $C_{13}H_{15}N_4O_2$ requires 259.1189.

4.2.3. *N*-(4-Methyl-2-pyridyl)-*N′*-(6-methoxy-3-pyridyl)-urea 3. Colorless powder; mp 188–189°C; IR ν/cm^{-1} (KBr) 3219 (ν_{N-H}), 3019 (ν_{C-H}), 1695 ($\nu_{C=O}$), 1619, 1596, 1562, 1522, 1490 ($\nu_{C=C,C=N}$), 1459, 1382 (ν_{-CH3}), 815 (ν_{C-H}); ^{1}H, NMR (400 MHz, DMSO-d_6, 23°C) δ 2.29 (s, 3H, CH_3), 3.84 (s, 3H, OCH_3), 6.82 (d, J=8.9 Hz, 1H, 5′-H), 6.86 (d, J=5.2 Hz, 1H, 5-H), 7.25 (s, 1H, 3-H), 7.91 (dd, J=8.8, 2.8 Hz, 1H, 4′-H), 8.14 (d, J=5.2 Hz, 1H, 6-H), 8.29 (s, 1H, 2′-H), 9.46 (s, 1H, 7′-H), 10.66 (s, 1H, 7-H); ^{13}C, NMR (400 MHz, DMSO-d_6, 23°C) δ 20.9 (CH_3), 53.1 (OCH_3), 110.2 (C-5′), 111.9 (C-3), 118.7 (C-5), 129.8 (C-3′), 131.7 (C-4′), 137.6 (C-2′), 146.5 (C-6), 149.3 (C-4), 152.5 (C═O), 152.8 (C-2), 159.4 (C-6′); MS (ESI): m/z: 259 (18 MH^+), 151 (7), 135 (23), 125 (40), 110 (3), 109 (100%); HRMS (APCI): MH^+, found 259.1189, $C_{13}H_{15}N_4O_2$ requires 259.1189.

4.2.4. *N*-(5-Methyl-2-pyridyl)-*N′*-(6-methoxy-3-pyridyl)-urea 4. Colorless powder; mp 178°C; IR ν/cm^{-1} (KBr) 3209 (ν_{N-H}), 3092 (ν_{C-H}), 1675 ($\nu_{C=O}$), 1611, 1579, 1545, 1492 ($\nu_{C=C,C=N}$), 1386 (ν_{-CH3}), 835 (ν_{C-H}), ^{1}H, NMR (400 MHz, DMSO-d_6, 23°C) δ 2.23 (s, 3H, CH_3), 3.84 (s, 3H, OCH_3); 6.82 (d, J=8.8 Hz, 1H, 5′-H), 7.38 (d, J=8.0 Hz, 1H, 3-H); 7.58 (d, J=7.9 Hz, 1H, 4-H), 7.91 (d, J=8.7 Hz, 1H, 4′-H), 8.11 (s, 1H, 6-H), 8.28 (s, 1H, 2′-H), 9.42 (s, 1H, 7′-H), 10.46 (s, 1H, 7-H); ^{13}C, NMR (400 MHz, DMSO-d_6, 23°C) δ 17.2 (CH_3), 53.1 (OCH_3), 110.1 (C-5′), 111.5 (C-3), 126.3 (C-5), 130.0 (C-3′), 131.7 (C-4′), 137.5 (C-2′), 139.2 (C-4), 146.3 (C-6), 150.7 (C-2), 152.6 (C═O), 159.4 (C-6′); MS (ESI): m/z: 259 (14 MH^+) 151 (6), 135 (17), 125 (36), 110 (3), 109 (100%); HRMS (APCI): MH^+, found 259.1167, $C_{13}H_{15}N_4O_2$ requires 259.1189.

4.2.5. *N*-(6-Methyl-2-pyridyl)-*N′*-(6-methoxy-3-pyridyl)-urea 5. Colorless needle; mp 210–212°C; IR ν/cm^{-1} (KBr) 3225 (ν_{N-H}), 2997 (ν_{C-H}), 1699 ($\nu_{C=O}$), 1626, 1598, 1565, 1496 ($\nu_{C=C,C=N}$), 1460, 1383 (ν_{-CH3}), 750 (ν_{C-H}); ^{1}H, NMR (400 MHz, DMSO-d_6, 23°C) δ 2.46 (s, 3H, CH_3), 3.83 (s, 3H, OCH_3), 6.82 (d, J=8.8 Hz, 1H, 5′-H), 6.87 (d, J=7.3 Hz, 1H, 3-H), 7.18 (d, J=8.0 Hz, 1H, 5-H), 7.63 (t, J=8.0 Hz, 1H, 4-H), 7.91 (dd, J=8.7, 2.6 Hz, 1H, 4′-H), 8.28 (s, 1H, 2′-H), 9.54 (s, 1H, 7′-H), 10.86 (s, 1H, 7-H); ^{13}C, NMR (400 MHz, DMSO-d_6, 23°C) δ 23.6 (CH_3), 53.1 (OCH_3), 108.7 (C-3), 110.2 (C-5′), 116.5 (C-5), 129.9 (C-3′), 131.5 (C-4′), 137.2 (C-2′), 138.9 (C-4), 152.3 (C-2), 152.5 (C═O), 155.3 (C-6), 159.4 (C-6′); MS (ESI): m/z: 259 (8 MH^+) 151 (7), 135 (63), 125 (84), 110 (6), 109 (100%); HRMS (APCI): MH^+, found 259.1172, $C_{13}H_{15}N_4O_2$ requires 259.1189.

4.2.6. *N*-(5-Chloro-2-pyridyl)-*N′*-(6-methoxy-3-pyridyl)-urea 6. Colorless needle; mp 211°C; IR ν/cm^{-1} (KBr) 3211 (ν_{N-H}), 3049 (ν_{C-H}), 1712 ($\nu_{C=O}$), 1622, 1598, 1557, 1484 ($\nu_{C=C,C=N}$), 1381 (ν_{-CH3}), 829 (ν_{C-H}); ^{1}H, NMR (400 MHz, DMSO-d_6, 23°C) δ 3.84 (s, 3H, OCH_3), 6.82 (d, J=8.7 Hz, 1H, 5′-H), 7.68 (d, J=8.0 Hz, 1H, 3-H), 7.85 (d, J=8.1 Hz, 1H, 4-H), 7.87 (d, J=8.7 Hz, 1H, 4′-H), 8.26 (s, 1H, 2′-H), 9.54 (s, 1H, 7′-H), 10.32 (s, 1H, 7-H); ^{13}C, NMR (400 MHz, DMSO-d_6, 23°C) δ 53.2 (OCH_3), 110.2 (C-5′), 113.1 (C-3), 123.5 (C-5), 129.7 (C-3′), 131.6 (C-4′), 137.5 (C-2′), 138.2 (C-4), 145.5 (C-6), 151.4 (C-2), 152.2 (C═O), 159.5 (C-6′); MS (ESI): m/z: 279 (13 MH^+) 151 (40), 129 (100), 125 (2%); HRMS (APCI): MH^+, found 279.0656, $C_{12}H_{12}N_4O_2Cl$ requires 279.0643.

4.2.7. *N*,*N′*-Bis(6-methoxy-3-pyridyl)urea 8. Colorless needle; mp 228–231°C; IR ν/cm^{-1} (KBr) 3283 (ν_{N-H}), 3009 (ν_{C-H}), 1638 ($\nu_{C=O}$), 1605, 1580, 1565, 1494, 1441 ($\nu_{C=C,C=N}$), 1382 (ν_{-CH3}), 821 (ν_{C-H}); ^{1}H, NMR (400 MHz, DMSO-d_6, 23°C) δ 3.82 (s, 3H, OCH_3), 6.79 (d, J=8.8 Hz, 1H, 5-H/5′-H), 7.83 (dd, J=8.8, 2.5 Hz, 1H, 4-H/4′-H), 8.21 (s, 1H, 2-H/2′-H), 8.65 (s, 1H, 7-H/7′-H); ^{13}C, NMR (400 MHz, DMSO-d_6, 23°C) δ 53.1 (OCH_3), 110.0 (C-5/C-5′), 130.5 (C-3/C-3′), 131.3 (C-4/C-4′), 137.1 (C-2/C-2′), 153.3 (C═O), 159.1 (C-6/C-6′); MS (ESI): m/z: 275 (7 MH^+) 151 (100), 125 (27), 110 (2%); HRMS (APCI): MH^+, found 275.1139, $C_{13}H_{15}N_4O_3$ requires 275.1139.

4.2.8. *N*-(2-Pyrimidyl)-*N′*-(6-methoxy-3-pyridyl)urea 9. Colorless powder; mp 220–221°C; IR ν/cm^{-1} (KBr) 3063 (ν_{N-H}), 2975 (ν_{C-H}), 1697 ($\nu_{C=O}$), 1622, 1583, 1556, 1518, 1491, 1438 ($\nu_{C=C,C=N}$), 1455, 1384 (ν_{-CH3}), 799 (ν_{C-H}); ^{1}H, NMR (400 MHz, DMSO-d_6, 23°C) δ 3.85 (s, 3H, OCH_3), 6.83 (d, J=8.7 Hz, 1H, 5′-H), 7.15 (t, J=4.8 Hz, 1H, 5-H), 7.95 (dd, J=8.8, 2.7 Hz, 1H, 4′-H), 8.36 (s, 1H, 2′-H), 8.68 (d, J=5.2 Hz, 2H, 4-H/6-H), 10.20 (s, 1H, 7′-H), 11.29 (s, 1H, 7-H); ^{13}C, NMR (400 MHz, DMSO-d_6, 23°C) δ 53.2 (OCH_3), 110.1 (C-5′), 115.1 (C-5), 129.2 (C-3′), 132.3 (C-4′), 138.3 (C-2′), 151.8 (C═O), 157.8 (C-2), 158.2 (C-4/C-6), 159.8 (C-6′); MS (ESI): m/z: 246 (22 MH^+) 151 (64), 96 (100%); HRMS (APCI): MH^+, found 246.1001, $C_{11}H_{12}N_5O_2$ requires 246.0986.

4.2.9. *N*-(4,6-Dimethyl-2-pyrimidyl)-*N′*-(6-methoxy-3-pyridyl)urea 10. Colorless powder; mp 198–201°C; IR ν/cm^{-1} (KBr) 3281 (ν_{N-H}), 2949 (ν_{C-H}), 1700 ($\nu_{C=O}$), 1638, 1602, 1565, 1492 ($\nu_{C=C,C=N}$), 1380 (ν_{-CH3}), 839 (ν_{C-H}); ^{1}H, NMR (400 MHz, DMSO-d_6, 23°C) δ 2.51 (s, 6H, CH_3), 3.83 (s, 3H, OCH_3), 6.79 (d, J=8.8 Hz, 1H, 5′-H), 6.90 (s, 1H, 5-H), 7.80 (d, J=8.7 Hz, 1H, 4′-H), 8.19 (s, 1H, 2′-H), 8.64 (s, 1H, 7′-H), 11.75 (s, 1H, 7-H); ^{13}C, NMR (400 MHz, DMSO-d_6, 23°C) δ 23.4 (CH_3), 53.1 (OCH_3), 110.2 (C-5′), 113.8 (C-5), 129.6 (C-3′), 131.5 (C-4′), 137.2 (C-2′), 153.3 (C═O), 157.4 (C-2), 159.6 (C-6′), 167.6 (C-4/C-6); MS (ESI): m/z: 274 (18 MH^+), 150 (3), 125 (4) 124 (100%); HRMS (APCI): MH^+, found 274.1300, $C_{13}H_{16}N_5O_2$ requires 274.1298.

4.2.10. *N*-(4,6-Dimethoxy-2-pyrimidyl)-*N′*-(6-methoxy-3-pyridyl)urea 11. Colorless flakes; mp 228–229°C; IR ν/cm^{-1} (KBr) 3271 (ν_{N-H}), 3112 (ν_{C-H}), 1700 ($\nu_{C=O}$), 1606, 1564, 1577, 1552 ($\nu_{C=C,C=N}$), 1459, 1378 (ν_{-CH3}), 812 (ν_{C-H}); ^{1}H, NMR (400 MHz, DMSO-d_6, 23°C) δ 3.83 (s, 3H, C$_{6'}$–OCH_3), 3.94 (s, 6H, C$_4$–OCH_3/C$_6$–OCH_3),

5.90 (s, 1H, 5-H), 6.83 (d, J=8.4 Hz, 1H, 5′-H), 7.92 (d, J=8.3 Hz, 1H, 4′-H), 8.27 (s, 1H, 2′-H), 10.04 (s, 1H, 7′-H), 11.00 (s, 1H, 7-H); ^{13}C, NMR (400 MHz, DMSO-d_6, 23°C) δ 53.2 ($C_{6'}-OCH_3$), 54.4 (C_4-OCH_3/C_6-OCH_3), 82.8 (C-5), 110.1 (C-5′), 129.3 (C-3′), 131.2 (C-4′), 137.9 (C-2′), 151.7 (C=O), 156.9 (C-2), 159.8 (C-6′), 171.3 (C-4/C-6); MS (ESI): m/z: 306 (14 MH^+), 182 (8), 156 (100), 125 (6%); HRMS (APCI): MH^+, found 306.1179, $C_{13}H_{16}N_5O_4$ requires 306.1197.

4.2.11. *N*-(2,6-Dimethyl-4-pyrimidyl)-*N*′-(6-methoxy-3-pyridyl)urea 12. Colorless powder; mp 163–166°C; IR ν/cm^{-1} (KBr) 3284 (ν_{N-H}), 2947 (ν_{C-H}), 1703 ($\nu_{C=O}$), 1601, 1559, 1493 ($\nu_{C=C,C=N}$), 1381 (ν_{-CH3}), 746 (ν_{C-H}); ^{1}H, NMR (400 MHz, DMSO-d_6, 23°C) δ 2.34 (s, 3H, C_6-CH_3), 2.50 (s, 3H, C_2-CH_3), 3.83 (s, 3H, OCH_3), 6.78 (s, 1H, 5-H), 6.84 (d, J=8.8 Hz, 1H, 5′-H), 7.95 (d, J=8.7 Hz, 1H, 4′-H), 8.27 (s, 1H, 2′-H), 10.21 (s, 1H, 7′-H), 11.73 (s, 1H, 7-H); ^{13}C, NMR (400 MHz, DMSO-d_6, 23°C) δ 24.8 (C_6-CH_3), 26.3 (C_2-CH_3), 54.1 (OCH_3), 104.7 (C-5), 111.0 (C-5′), 130.3 (C-3′), 132.5 (C-4′), 138.0 (C-2′), 152.9 (C=O), 158.4 (C-4), 159.3 (C-6′), 166.8 (C-6), 168.0 (C-2); MS (ESI): m/z: 274 (10 MH^+), 151 (4), 150 (12), 125 (15), 124 (100%); HRMS (APCI): MH^+, found 274.1305, $C_{13}H_{16}N_5O_2$ requires 274.1298.

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