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A Novel Preparation of Pyridine–Urea Hybrids and Elucidation of Their Structures

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ABSTRACT: *A mechanistically unique and serendipitously discovered reaction providing a variety of pyridine–urea hybrids via the thiophenol-initiated uracil ring opening and pyridine ring-forming process was reported. The identification process of the hybrids and the pathway through which they were formed were also briefly described.* © 2009 Wiley Periodicals, Inc. Heteroatom Chem 20:362–368, 2009; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20560

INTRODUCTION

Azaheterocycles are prominent in natural products, pharmaceutical, and functional materials. Of various azaheterocycles, pyridine structural unit occurs in many medicinally interesting natural products and substituted pyridine derivatives have been reported to show promising biological activities [1–3]. On the other hand, ureas are important components of biologically active molecules, having greater hydrogen-bonding potential than amides while being less acidic than sulfonamides [4]. Ureas have also found applications as amide bond surrogates [5], allowing for a β-sheet-like display of functionality [6], and as fluorescence probe [7], intermediate for the synthesis of hydantocidin [8], and inhibitors of Met kinase [9]. Therefore, it is of great synthetic and biological interests to develop novel and efficient methods to prepare hybrids combining both pyridine and urea moiety in one molecule with potentially synergetic biological activities.

Recently, we have an on-going program to design and synthesize nucleoside–heterocycle hybrids as potential antiviral agents that has already resulted in several antiviral lead compounds [10]. As a continuation, we were interested in the preparation of hybrids of pyrimidine nucleoside with 2-amino-6-sulfanyl-3,5-dicyano pyridines because both pyrimidine nucleoside [11] and 2-amino-4-aryl-6-sulfanyl-3,5-dicyano pyridines [12] showed diverse biological potency, especially with regard to antiviral activities. The preparation is based on literature procedures [12], involving a one-pot three-component condensation of benzylidenemalononitrile, thiophenol, and malononitrile (Scheme 1). Unexpectedly, during the preparation of such a pyrimidine nucleoside-substituted pyridine hybrid, a novel procedure leading to pyridine–urea hybrids was discovered.

RESULTS AND DISCUSSIONS

In our preparation of the pyrimidine nucleoside–pyridine hybrid, benzylidenemalononitrile (Scheme 1) is replaced by 5-(2′,2′-dicyanovinyl)-2′-deoxyuridine (**1a**; Scheme 2). Compound **1a** was prepared from the condensation of 3′,5′-diacetyl-5-formyl-2′-deoxyuridine and malononitrile; **1b**

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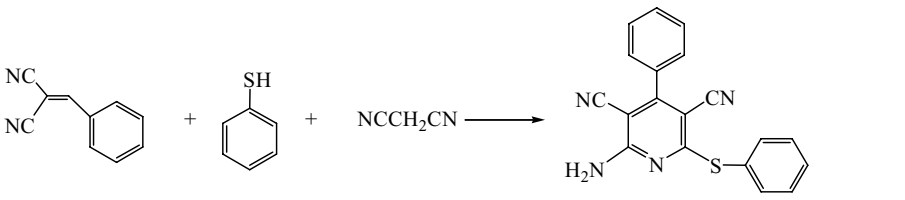


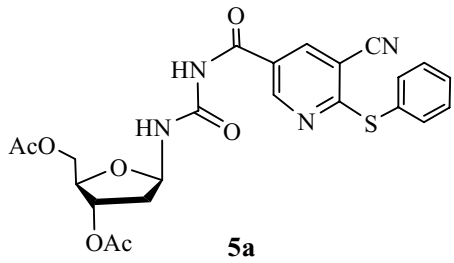
2-Amino-4-aryl-6-sulfanyl-3,5-dicyano pyridine

SCHEME 1

was prepared from 5-formyl-2′-deoxyuridine and malononitrile; **7** was prepared in a similar manner from 5-formyluracil and malononitrile. Thus, **1a**, thiophenol (**2**) and malononitrile (**3**) were mixed together and treated with triethylamine (Et_3N) in refluxing ethanol. It was then found that the desired hybrid (**4a**; Scheme 2) could be obtained but only in low yield (22%). Upon checking the reaction mixture, it turned out that the low yield of **4a** was partly due to the formation of a byproduct (**5a**). Efforts were then made to elucidate the structure of this unknown compound and the possible pathway through which it was formed.

In the first place, it showed the molecular weight (MW) of **5a** is 498. Since that of **1a** and thiophenol (**2**) are 388 and 110, respectively, it is suggested that **5a** is formed from the reaction between **1a** and **2**. To confirm, a mixture of **1a** and **2** in ethanol was treated with Et_3N. As expected, it gave **5a** in high yield. With further spectra analysis, including UV, ^1H NMR, ^{13}C NMR, Cosy, HMBC, and HMQC, it was identified as a hybrid of pyridine and sugar-substituted urea as shown in Scheme 3.

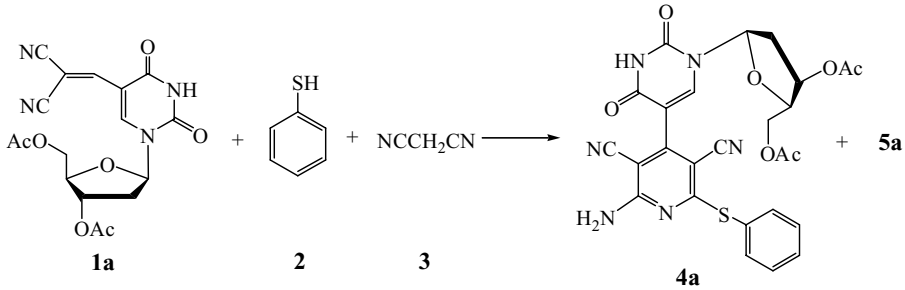
The intriguing mechanism of the reaction cascade leading to **5a** is illustrated in Scheme 4. The reaction was initiated by nucleophilic attack of thiophenol on the cyano group in **1a** to give an adduct (**A**). Within the adduct, the NH group is nucleophilic in nature and it underwent an *intramolecular* Michael addition on the sixth carbon of the uracil moiety to give an intermediate **B**. The following ring-opening process is initiated by loss of a proton attached on the fifth carbon of the uracil ring due to its relatively strong acidic nature (**C**). With the electrons transformed to N1 from C5, the C6–N1 bond broke and the disturbed pyrimidine ring opened (**D**). At the same time, a more stable pyridine ring was formed to give an acylurea derivative (**5a**), containing a five-membered sugar moiety and a pyridine ring.



5a

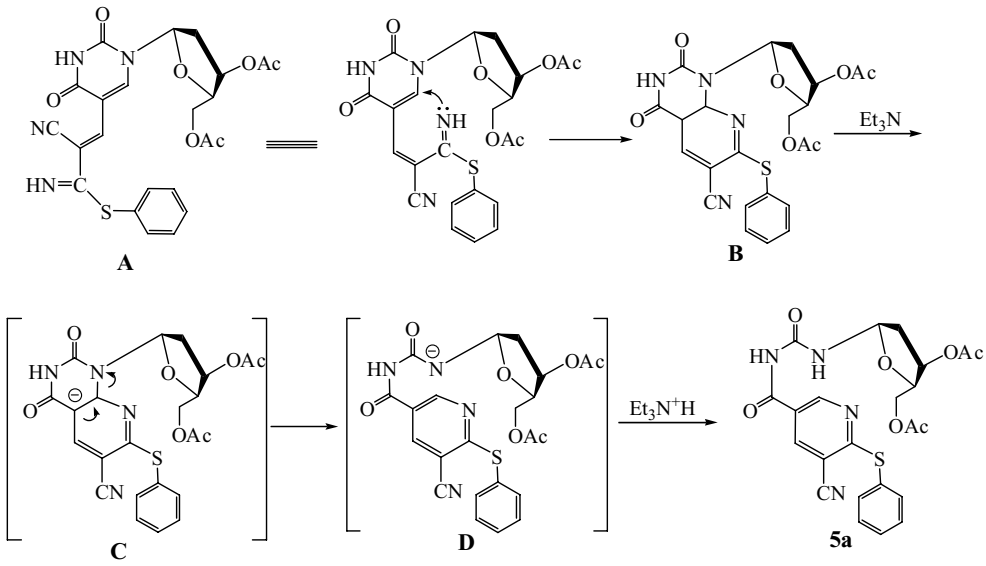
SCHEME 3

To the best of our knowledge, this is the first time such a uracil ring-opening and pyridine ring-forming cascade have ever been reported. For uracil ring opening in the reaction of 5-formyl-2′-deoxyuridine



1a **2** **3** **4a**

SCHEME 2



SCHEME 4

with primary alkyl amines through a Michael addition on C6 of the pyrimidine ring, see [13]; and it provides a simple and efficient alternative for the preparation of biologically important pyridine–urea hybrids. To explore the scope and generality of this novel procedure and to get more hybrids for SAR (structure and activity relationship) study, more thiophenol substrates were tried (Scheme 5) and the results were included in Table 1.

It is noted that unsubstituted thiophenol or thiophenol with either an electron-withdrawing or electron-donating group underwent this process efficiently. Its easy going nature, high efficiency, and generality make this process a highly potential alternative for the preparation of pyridine–acylurea hybrids.

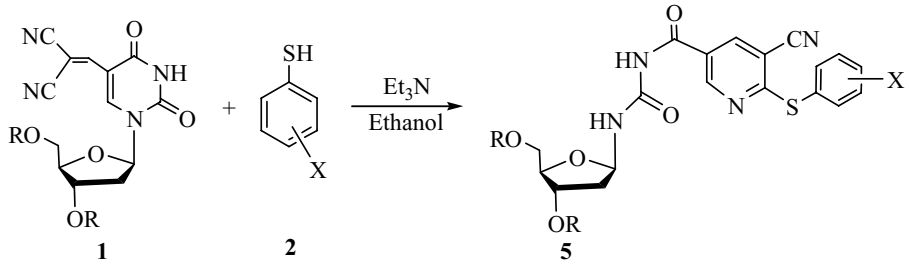
To further explore the scope of this novel sequence, uracil-5-yl-methylene malononitrile (**6**) was prepared from 5-formyluracil and was treated with thiophenol in ethanol-containing catalytic amounts of Et_3N. It successfully underwent a similar reaction and gave a pyridine-substituted acylurea derivative (**7**) with a yield of 89% (Scheme 6).

TABLE 1 Preparation of Pyridine–Urea Hybrids

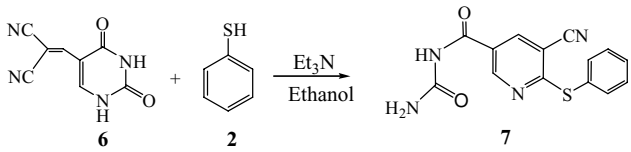
Entry	*R*	*X*	*Product*	*Reaction Time (h)*	*Yield (%)*[a]
1	Ac	H	**5a**	2	95
2	H	H	**5b**	2	92
3	Ac	4-CH_3	**5c**	2	97
4	H	4-CH_3	**5d**	2	96
5	Ac	2-Br	**5e**	2	88
6	H	2-Br	**5f**	2	84
7	Ac	4-Cl	**5g**	2	92
8	H	4-Cl	**5h**	2	90
9	Ac	4-F	**5i**	2	91
10	H	4-F	**5j**	2	86

[a]Isolated yields.

X-ray crystallography of **7** gave a solid conformation of its structure (Scheme 7). Single crystals of **7** were obtained by slow evaporation of the solvent



SCHEME 5

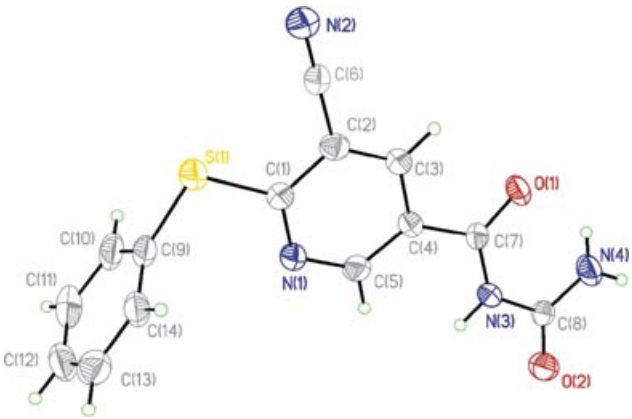


SCHEME 6

from a water–methanol (1:2 v/v) solution. Crystal data of **7**: $C_{14}H_{10}N_4O_2S$, colorless, crystal dimensions 0.32 × 0.23 × 0.05 mm, Triclinic, space group *P*-1, $a = 7.185$ (9) Å, $b = 7.718$ (9) Å, $c = 12.095$ (14) Å, $\alpha = 99.548$ (12)°, $\beta = 91.258$ (14)°, $\gamma = 93.960$ (14)°, $V = 659.4$ (14) Å^3, $M_r = 298.32$, $Z = 2$, $D_x = 1.502$ Mg m^{-3}, λ(Mo K$^{\alpha}$) = 0.71073 Å, $\mu = 0.26$ mm^{-1}, $F_{(000)} = 308$, $2.7° < \theta < 25.5°$, $R_{int} = 0.076$, $wR(F^2) = 0.252$, $S = 1.00$, largest difference peak and hole: 0.56 and −0.27e Å^{-3}. CCDC reference number 729807.

Finally, as a bonus of the above-mentioned observation, the reaction of **1a, 2**, and **3** was run again but with a different sequence of substrates addition. Thus, instead of mixing **1a**, malononitrile and thiophenol together at one time, **1a** and malononitrile was treated with Et_3N first in ethanol for about 10 min. Then thiophenol was added to the reaction mixture (Scheme 8). To our delight, it resulted in an improved reaction and gave **4a** with a yield of 33%. Through similar procedure, **4b** was obtained with a yield of 35%, which was also better than the yield (25%) obtained through the procedure shown in Scheme 2. No further optimization was attempted [12a].

In conclusion, a series of pyridine-attached acylurea derivatives were obtained through a novel uracil ring-opening and pyridine ring-forming sequence. With its high efficiency, simple procedure, and high selectivity, this novel process has the potential to be developed as a simple and efficient way to prepare novel pyridine–urea hybrids. The biological activity screen of compound **4, 5**, and **7** is currently underway, and the results will be reported in due course.



SCHEME 7

EXPERIMENTAL

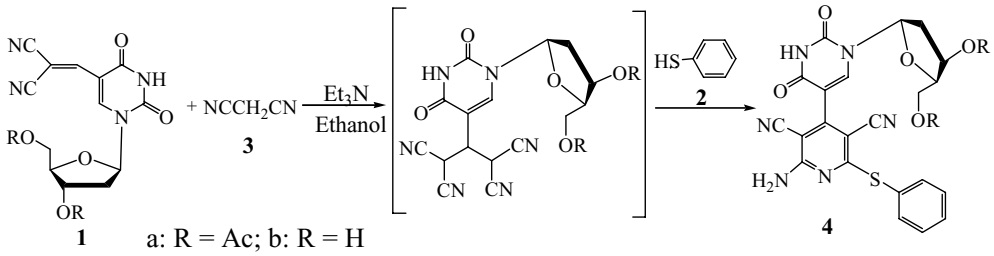
Melting points were measured by a Kofler micromelting point apparatus and were uncorrected. ^{1}H NMR spectra were determined on a Bruker AC 400 spectrometer as DMSO-d_6, CD_3OD, or $CDCl_3$ solutions. Chemical shifts (δ) were expressed in ppm downfield from the internal standard tetramethylsilane, and coupling constants J were given in hertz. Mass spectra were recorded on a Bruker Esquire 3000 mass spectrometer. The HRMS (high-resolution mass spectra) were performed on a JEOL HX 110A spectrometer.

Typical Procedure for the Preparation of **5a**

To a suspension of **1a** (0.5 mmol) and **2** (0.6 mmol) in ethanol (2 mL), Et_3N (10 μL) was added. The suspension was refluxed for 2 h. Volatiles were evaporated in vacuo, and the residue was purified on silica gel (hexane/ethyl acetate, 3:1) to yield **5a** as colorless solid. Other pyridine–urea hybrids were obtained in a similar manner.

5a: Colorless solid, mp 151–152°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.13 (s, 6H, 2×CH_3), 2.18–2.48 (m, 2H, CH_2), 4.18–4.28 (m, 3H, CH, CH_2), 5.19–5.22 (m, 1H, CH), 6.05–6.11 (m, 1H, CH), 7.44–7.58 (m, 5H, Ar-H), 8.74 (d, 1H, CH, $J = 2.4$ Hz), 8.99 (d, 1H, CH, $J = 2.4$ Hz), 9.29 (d, 1H, NH, $J = 9.6$ Hz), 11.01 (br s, 1H, NH). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 21.1, 21.3, 38.4, 64.6, 75.1, 81.6, 81.8, 106.3, 114.9, 123.6, 126.9, 129.8, 130.5, 135.8, 140.1, 153.3, 155.04, 165.4, 168.4, 170.9, 171.0. IR (KBr): 3295, 2225, 1748, 1690, 1590, 1530 cm^{-1}; ESI LRMS m/z: 499 (MH^+), 521 (MNa^+). HRMS (FAB): Calcd for $C_{23}H_{23}N_4O_7S$: 499.1288 $(MH)^+$, found 499.1283.

5b: Colorless solid, mp 171–172°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.90–2.03 (m, 2H, CH_2), 3.36–3.39 (m, 2H, CH_2), 3.64–3.67 (m, 1H, OH), 4.12–4.15 (m, 1H, CH), 4.77 (t, 1H, OH, $J = 5.6$ Hz), 5.03 (d, 1H, CH, $J = 4.4$ Hz), 5.71–5.76 (m, 1H, CH), 7.47–7.61 (m, 5H, ArH), 8.70 (d, 1H, CH, $J = 2.4$ Hz), 8.78 (d, 1H, NH, $J = 9.6$ Hz), 8.88 (d, 1H, $J = 2.4$ Hz), 10.94 (br s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 41.0, 62.8, 71.8, 81.1, 87.4, 106.0, 115.6, 125.8, 127.3, 130.4, 130.9, 136.1, 142.3, 152.9, 153.1, 165.8, 166.1. IR (KBr): 3380, 3305,



a: R = Ac; b: R = H

SCHEME 8

2233, 1700, 1530 cm^{-1}; ESI LRMS *m/z*: 415 (MH^+), 437 (MNa^+). HRMS (FAB): Calcd for $C_{19}H_{19}N_4O_5S$: 415.1077 (MH^+), found 415.1093.

5c: Colorless solid, mp 161–162°C; ^1H NMR (400 MHz, DMSO-d_6) δ: 2.05 (s, 3H, CH_3), 2.08 (s, 3H, CH_3), 2.26–2.28 (m, 2H, CH_2), 2.38 (s, 3H, CH_3), 4.08–4.13 (m, 3H, CH_2, CH), 5.12–5.14 (m, 1H, CH), 5.78–5.84 (m, 1H, CH), 7.33 (d, 2H, ArH, J = 8.0 Hz,), 7.49 (d, 2H, ArH, J = 8.0 Hz), 8.72 (d, 1H, J = 2.0 Hz, CH), 8.89 (d, 1H, CH, J = 2.0 Hz), 8.93 (d, 1H, NH, J = 9.0 Hz), 11.08 (br s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 21.0, 21.2, 21.3, 37.2, 64.6, 75.4, 81.0, 81.3, 105.5, 115.3, 123.3 125.3, 130.8, 135.9, 140.7, 142.0, 152.7, 153.1, 165.8, 166.4, 170.5, 170. IR (KBr): 3294, 2226, 1746, 1687, 1592, 1528 cm^{-1}; ESI LRMS *m/z*: 513 (MH^+), 535 (MNa^+). HRMS (FAB): Calcd for $C_{24}H_{25}N_4O_7S$: 513.1445 (MH^+), found 513.1456.

5d: Colorless solid, mp 163–165°C; ^1H NMR (400 MHz, DMSO-d_6) δ: 1.97–2.05 (m, 2H, CH_2), 2.38 (s, 3H, CH_3), 3.36–3.41 (m, 2H, CH_2), 3.66–3.69 (m, 1H, OH), 4.14–4.15 (m, 1H, CH), 4.81 (t, 1H, J = 5.2 Hz, OH), 5.06–5.08 (m, 1H, CH), 5.73–5.79 (m, 1H, CH), 7.33 (d, 2H, J = 8.0 Hz, ArH), 7.49 (d, 2H, J = 8.0 Hz, ArH), 8.71 (d, 1H, CH, J = 2.4 Hz), 8.80 (d, 1H, NH, J = 9.2 Hz), 8.88 (d, 1H, CH, J = 2.4 Hz), 10.97 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 21.3, 40.8, 62.5, 71.6, 80.8, 87.1, 105.5, 115.3, 123.3, 125.4, 130.8, 135.9, 140.7, 142.0, 152.6, 152.9, 165.5, 166.3. IR (KBr): 3379, 3310, 2230, 1703, 1587, 1534 cm^{-1}; ESI LRMS *m/z*: 429 (MH^+), 551 (MNa^+). HRMS (FAB): Calcd for $C_{20}H_{21}N_4O_5S$: 429.1233 (MH^+), found 429.1238.

5e: Colorless solid, mp 111–112°C; ^1H NMR (400 MHz, DMSO-d_6) δ: 2.05 (s, 3H, CH_3), 2.08 (s, 3H, CH_3), 2.19–2.28 (m, 2H, CH_2), 4.08–4.12 (m, 3H, CH_2, CH), 5.12–5.14 (m, 1H, CH), 5.80–5.84 (m, 1H, CH), 7.14–7.86 (m, 4H, ArH), 8.77–8.92 (m, 3H, NH, 2 × CH), 11.09 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 23.3, 23.5, 66.8, 77.6, 83.3, 83.5, 108.1, 117.4, 127.9, 130.8, 131.6, 132.6, 135.1, 136.4, 140.7, 144.5, 155.0, 155.2, 166.9, 167.9, 172,7, 172.9. IR (KBr): 3299, 2221, 1750, 1688, 1596, 1533 cm^{-1}; ESI LRMS *m/z*: 577 (MH^+), 599 (MNa^+). HRMS (FAB): Calcd for $C_{23}H_{22}BrN_4O_7S$: 577.0393 (MH^+), found 577.0399.

5f: Colorless solid, mp 113–115°C; ^1H NMR (400 MHz, DMSO-d_6) δ:1.99–2.08 (m, 2H, CH_2), 3.65–3.68 (m, 1H, OH), 4.05–4.09 (m, 3H, CH_2, CH), 4.81 (m, 1H, OH), 5.12–5.14 (m, 1H, CH), 5.73–5.77 (m, 1H, CH), 7.47–7.88 (m, 4H, ArH), 8.78 (d, 1H, CH, J = 2.4 Hz), 8.80 (d, 1H, NH, J = 9.2 Hz), 8.89 (d, 1H, CH, J = 2.4 Hz), 11.00 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 40.8, 62.3, 71.7, 80.8, 87.1, 105.9, 115.2, 125.8, 129.4, 130.4, 132.9, 134.2, 138.5, 142.2, 152.6, 152.8, 164.6, 165.5. IR (KBr): 3376, 3310, 2225, 1700, 1588, 1534 cm^{-1}; ESI LRMS *m/z*: 493 (MH^+), 515 (MNa^+). HRMS (FAB): Calcd for $C_{19}H_{18}BrN_4O_5S$: 493.0182 (MH^+), found 493.0163.

5g: Colorless solid, mp 143–144°C; ^1H NMR (400 MHz, DMSO-d_6) δ: 2.04 (s, 3H, CH_3), 2.05 (s, 3H, CH_3), 2.26–2.28 (m, 2H, CH_2), 4.08–4.12 (m, 3H, CH, CH_2), 5.12–5.14 (m, 1H, CH), 5.80–5.82 (m, 1H, CH), 7.59–7.66 (m, 4H, ArH), 8.75 (d, 1H, CH, J = 2.4 Hz), 8.92 (d, 1H, CH, J = 2.4 Hz), 8.94 (d, 1H, NH, J = 9.2 Hz), 11.10 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 21.0, 21.2, 37.2, 64.6, 75.4, 81.0, 81.3, 105.8, 115.2, 125.6, 126.0, 130.2, 135.8, 137.7, 142.1, 152.7, 153.0, 165.5, 165.7, 170.5, 170.7. IR (KBr): 3280, 2225, 1748, 1690, 1533 cm^{-1}; ESI LRMS *m/z*: 533 (MH^+), 555 (MNa^+). HRMS (FAB): Calcd for $C_{23}H_{22}ClN_4O_7S$: 533.0898 (MH^+), found 533.0899.

5h: Colorless solid, mp 177–179°C. ^1H NMR (400 MHz, DMSO-d_6) δ: 1.98–2.08 (m, 2H, CH_2), 3.36–3.41 (m, 2H, CH_2), 3.67–3.69 (m, 1H, OH), 4.14–4.15 (m, 1H, CH), 4.81 (t, 1H, J = 5.2 Hz, OH), 5.06–5.08 (m, 1H, CH), 5.73–5.79 (m, 1H, CH), 7.60 (d, 2H, J = 8.0 Hz, ArH), 7.65 (d, 2H, J = 8.0 Hz, ArH), 8.74 (d, 1H, CH, J = 2.4 Hz), 8.80 (d, 1H, J = 9.2 Hz, NH), 8.91 (d, 1H, CH, J = 2.4 Hz,), 10.97 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 62.5, 73.0, 80.8, 87.6, 105.5, 115.3, 123.3, 125.4, 130.8, 135.9, 140.7, 142.0, 152.6, 152.9, 165.5, 166.3. IR (KBr): 3377, 3318, 2229, 1702, 1588, 1534 cm^{-1}; ESI LRMS *m/z*: 449 (MH^+), 471 (MNa^+). HRMS (FAB): Calcd for $C_{19}H_{18}ClN_4O_5S$: 449.0687 (MH^+), found 449.0673.

5i: Colorless solid, mp 143–144°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.05 (s, 3H, CH_3), 2.08 (s, 3H, CH_3), 2.26–2.28 (m, 2H, CH_2), 4.08–4.12 (m, 3H, CH, CH_2), 5.12–5.14 (m, 1H, CH), 5.78–5.84 (m, 1H, CH), 7.36–7.70 (m, 4H, ArH), 8.74–8.93 (m, 3H, NH, 2 × CH), 11.08 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 23.3, 23.5, 39.4, 66.8, 77.6, 83.2, 83.5, 107.8, 117.5, 119.5, 119.7, 124.8, 127.7, 140.7, 140.8, 144.3, 154.9, 155.2, 167.9, 168.1, 172.7, 172.9. IR (KBr): 3300, 2226, 1736, 1680, 1534 cm^{-1}; ESI LRMS *m/z*: 517 (MH^+), 539 (MNa^+). HRMS (FAB): Calcd for $C_{23}H_{22}FN_4O_7S$: 517.1194 (MH^+), found 517.1199.

5j: colorless solid, mp 177–178°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.94–2.03 (m, 2H, CH_2), 3.37–3.39 (m, 2H, CH_2), 3.67–3.68 (m, 1H, OH), 4.15–4.16 (m, 1H, CH), 4.82 (t, 1H, J = 5.2 Hz, OH), 5.07–5.08 (m, 1H, CH), 5.73–5.78 (m, 1H, CH), 7.36–7.70 (m, 4H, ArH), 8.73 (d, 1H, CH, J = 2.0 Hz), 8.81 (d, 1H, NH, J = 9.2 Hz,), 8.90 (d, 1H, CH, J = 2.0 Hz), 10.98 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 62.5, 71.6, 80.8, 87.1, 105.6, 115.3, 117.2, 117.5, 122.6, 125.6, 138.5, 138.6, 142.0, 152.7, 152.8, 162.5, 165.0, 165.5, 165.8. IR (KBr): 3385, 3300, 2228, 1705, 1588, 1530 cm^{-1}; ESI LRMS *m/z*: 433 (MH^+), 455 (MNa^+). HRMS (FAB): Calcd for $C_{19}H_{18}FN_4O_5S$: 433.0983 (MH^+), found 433.0996.

Procedure for the Preparation of Compound **7**

To a suspension of **6** (0.5 mmol) and **2** (0.6 mmol) in ethanol (2 mL), TEA (10 μL) was added. The suspension was refluxed for 2 h. Volatiles were evaporated in vacuo, and the residue was purified on silica gel (hexane/ethyl acetate, 3:1) to yield **7** as colorless solid.

7: Colorless solid, ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.52–7.85 (m, 7H, ArH, NH_2), 8.73 (d, 1H, CH, J = 2.0 Hz), 8.91 (d, 1H, CH, J = 2.0 Hz), 10.74 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 105.8, 115.3, 125.7, 127.1, 130.2, 130.6, 135.9, 142.4, 152.6, 154.0, 165.3, 165.7. IR (KBr): 3381, 3333, 3215, 2235, 1729, 1678, 1583 cm^{-1}; ESI LRMS *m/z*: 299 (MH^+), 321 (MNa^+). HRMS (FAB): Calcd for $C_{14}H_{11}N_4O_2S$: 299.0603 (MH^+), found 299.0611.

Typical Procedure for the Preparation of **4a**

To a suspension of **1a** (0.5 mmol) and malononitrile (0.6 mmol) in ethanol (5 mL), Et_3N (10 μL) was added. The mixture was stirred for 0.2 h. Then thiophenol (0.6 mmol) was added, and the solution was refluxed for another 1.8 h. Volatiles were evaporated in vacuo, and the residue was purified on silica gel (hexanes/ethyl acetate, 2:1) to yield **4a** as colorless solid. **4b** was ALSO obtained in a similar manner.

4a: Colorless solid, mp 166–167°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.99 (s, 3H, CH_3), 2.07 (s, 3H, CH_3), 2.43–2.49 (m, 2H, CH_2), 4.22–4.25 (m, 3H, CH_2, CH), 5.21–5.23 (m, 1H, CH), 6.23–6.26 (m, 1H, CH), 7.49–7.58 (m, 5H, ArH), 7.77 (br s, 2H, NH_2), 8.17 (s, 1H, CH), 12.00 (br s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 20.5, 20.6, 37.0, 37.0, 64.4, 74.8, 82.7, 85.6, 85.7, 89.3, 89.4, 95.4, 95.5, 109.5, 115.1, 115.3, 115.4, 115.7, 127.7, 129.8, 130.2, 135.7, 142.9, 142.9, 150.5, 151.6, 160.5, 166.9, 167.0, 170.6, 170.7. IR (KBr): 3434, 3332, 3223, 3069, 2217, 1745, 1690, 1550 cm^{-1}; ESI LRMS *m/z*: 563 (MH^+), 585 (MNa^+). HRMS (FAB): Calcd for $C_{26}H_{23}N_6O_7S$: 563.1349 (MH^+), found 563.1353.

4b: Colorless solid, mp >250°C; ^{1}H NMR (400 MHz, CD_3OD) δ: 2.25–2.41 (m, 2H, CH_2), 3.72–3.84 (m, 2H, CH_2), 3.95–3.96 (m, 1H, CH), 4.43–4.47 (m, 1H, CH), 6.32–6.36 (m, 1H, CH), 7.46–7.58 (m, 5H, ArH), 8.59 (s, 1H, CH). ^{13}C NMR (100 MHz, CD_3OD) δ: 41.1, 61.3, 70.6, 70.6, 85.9, 88.1, 108.3, 108.4, 114.5, 114.7, 114.8, 115.0, 127.6, 129.3, 129.8, 135.6, 143.0, 143.1, 150.2, 150.9, 151.0, 160.2, 161.0, 167.8, 167.9. IR (KBr): 3455, 3195, 3047, 2216, 1711, 1683, 1554 cm^{-1}; ESI LRMS *m/z*: 479 (MH^+), 501 (MNa^+). HRMS (FAB): Calcd for $C_{22}H_{19}N_6O_5S$: 479.1138 (MH^+), found 479.1125.

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