Direct Construction of Imino-pyrrolidine-thione Scaffold via Isocyanide-Based Multicomponent Reaction

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A novel and efficient method has been developed for the direct construction of imino-pyrrolidine-thione scaffold via the coupling of isocyanides, heterocyclic thiols, and *gem*-dicyano olefins. Smiles rearrangement followed by intramolecular cyclization leads directly to formation of the core structure. A water-acceleration effect is observed, promoting most of the reactions to go to completion within a short reaction time.

Introduction

The pyrrolidine moiety is widely featured in a myriad of pharmacologically and biologically active compounds.[1] Pyrrolidine derivatives of thioxopyrrolidine and iminopyrrolidine have been demonstrated to be useful functional scaffolds in biologic and organic syntheses. For example, 3-hydroxymethylene-2-thioxopyrrolidine was found out to show good activity in inhibiting the growth of mutant streptococci.[2] In addition, the unique scaffold and good reactivity of thioxopyrrolidines lead to useful building blocks in the synthesis of natural cyclic tetrapyrroles.[3] On the other hand, iminopyrrolidine derivatives display biological activity as nitric oxide synthase inhibitors.[4] Nowadays, the combination of several functional groups in one molecule appears as an efficient strategy to optimize properties of pharmaceutical and bioactive compounds. Therefore, explorations on the synthesis and application of such highly functionalized compounds have drawn a great deal of attention from many chemists.

Multicomponent reactions (MCRs), where several different starting materials can be combined in one reaction, are capable of efficiently generating hundreds to millions of small organic molecules, many of which possess highly complicated structures.[5] MCRs, especially involved in isocyanides, are expected to offer great opportunities both in discovering new reactions and in synthesizing complex molecules. Among them, the Ugi four-component reaction (U-4CR) is one of the most important isocyanide-based multicomponent reactions (I-MCRs).[6] The U-4CR containing aldehydes, amides, isocyanides and nucleophiles undergoes a Ugi-Smiles coupling to yield various drug backbones effectively.[7] It should be noted that various nucleophiles, such as carboxylic acids, nitrophenol,[8] heterocyclic thiols,[9a] and even water,[10] can be all utilized in the reaction. Since Saegusa and coworkers[11] developed the first reaction between isocyanides and olefins bearing electron-withdrawing groups over thirty years ago, only couples of I-MCRs involving olefins have been reported.[12] Our continuing interest in multicomponent reactions,[13] especially in I-MCRs,[14] focuses in the introduction of such substrates into the modified U-4CR reactions. Inspired by our previous works as well as the Ugi-Smiles coupling, we report here a novel reaction to synthesize imino-pyrrolidine-thione derivatives using a one-pot condensation of *gem*-dicyano olefin **1**, isocyanide **2**, and 2-mercaptobenzothiazole **3a** (Scheme 1). The reactions proceeded efficiently in the presence of pyridine and aqueous MeCN to afford products in a good yield at ambient temperature.

Results and Discussion

Initially, 4-cholorobenzylidenemalonitrile (**1a**), *tert*-butyl isocyanide (**2a**), and 2-mercapto-benzothiazole (**3a**) were stirred in a mixture of MeCN and H_2O (V_{MeCN}/V_{H_2O} = 3:1) at room temperature for 5 h (Table 1, entry 1).[15] After standard workup and purification of the reaction mixture via silica gel column chromatography, product **4d** was obtained in 59% yield. Full characterization involving IR, ^{1}H NMR, ^{13}C NMR, and HRMS proved the identity of **4d**, and the structure was further confirmed unambiguously by single-crystal X-ray analysis (Figure 1).

It is worthwhile to note that the reaction proceeded selectively to generate the imino-pyrrolidine-thione as a single *trans* diastereomer.

Encouraged by this interesting result, we continued to focus on the optimization of reaction conditions. To activate the thiol, one equivalent of base was added to the reaction system.[12c] The results are summarized in Table 1.

As shown in Table 1, various bases were screened for their efficiency in the reaction. Among them, pyridine was proven superior to other bases, and the yield of the desired product

Scheme 1. Construction of Imino-pyrrolidine-thione Derivatives **4** via a One-Pot Condensation of *gem*-Dicyano Olefin **1**, Isocyanide **2** and 2-Mercaptobenzothiazole **3a**

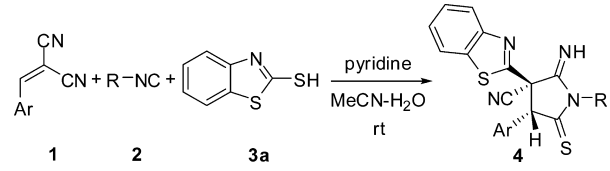

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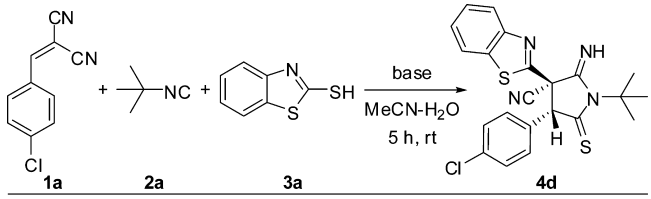
Table 1. Optimization of the Reaction Conditions[a]



entry	base	solvent	yield (%)[b]
1		MeCN/H_2O = 3:1	59
2	$MgCO_3$	MeCN/H_2O = 3:1	48
3	Na_2CO_3	MeCN/H_2O = 3:1	38
4	K_2CO_3	MeCN/H_2O = 3:1	33
5	NaOH	MeCN/H_2O = 3:1	37
6	KOH	MeCN/H_2O = 3:1	41
7	piperidine	MeCN/H_2O = 3:1	22
8	Et_3N	MeCN/H_2O = 3:1	52
9	quinoline	MeCN/H_2O = 3:1	59
10	diisopropylamine	MeCN/H_2O = 3:1	43
11	HMPA	MeCN/H_2O = 3:1	60
12	**pyridine**	**MeCN/H_2O = 3:1**	**69**
13	pyridine	MeCN/H_2O = 1:3	68
14	pyridine	MeCN/H_2O = 1:1	54
15	pyridine	H_2O	0
16	pyridine	MeCN	45
17	pyridine	MeCN	71[c]

[a] Unless otherwise noted, the reactions were carried out at room temperature for 5 h using 4-cholorobenzylidenemalonitrile **1a** (0.5 mmol), *tert*-butyl isocyanide **2a** (0.6 mmol), 2-mercaptobenzothiazole **3a** (0.5 mmol), base (0.5 mmol), and solvent (2.0 mL). [b] Isolated yield. [c] Reaction time: 16 h.

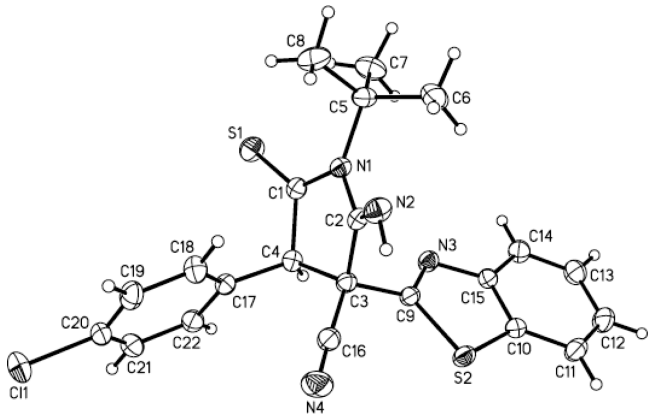
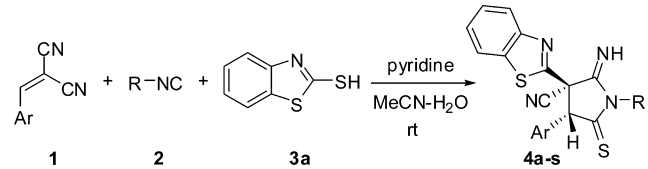


Figure 1. Crystal structure of **4d**.

4d could be increased to 69% (entry 12). The influence of volume ratio of MeCN and H_2O on the reaction was also investigated. A 3:1 ratio of V_{MeCN}/V_{H_2O} proved to be optimal (entries 12−14). However, the reaction could hardly occur in pure water (entry 15), and a much longer reaction time was needed when the reaction was carried out in pure MeCN (entries 16−17). This indicated that a certain amount of water could accelerate this reaction well, which might be explained through the properties of water as a solvent and especially the direct involvement of water in a bond-making step.[16a,b] This acceleration may be attributed to many factors, including the hydrophobic effect,[16c,d] enhanced hydrogen bonding in the transition state,[16e] and the high cohesive energy density of water (550.2 cal/mL at 25 °C).[16f,g]

With the optimized reaction conditions in hand, we continued to examine the substrate scope of the reaction using a wide variety of *gem*-dicyano olefins. As shown in Table 2, the *gem*-dicyano olefins bearing electron-withdrawing

Table 2. Substrate Scope Study Using Different *gem*-Dicyano Olefins and Isocyanides[a]



entry	Ar	R	time (h)	products	yield (%)[b]
1	4-$NO_2C_6H_4$	*t*-Bu	1	**4a**	92
2	3-$NO_2C_6H_4$	*t*-Bu	1	**4b**	87
3	4-FC_6H_4	*t*-Bu	4	**4c**	63
4	4-ClC_6H_4	*t*-Bu	3	**4d**	69
5	3-ClC_6H_4	*t*-Bu	2	**4e**	84
6	2-ClC_6H_4	*t*-Bu	2	**4f**	89
7	2,4-$Cl_2C_6H_3$	*t*-Bu	1	**4g**	92
8	4-BrC_6H_4	*t*-Bu	4	**4h**	93
9	3-BrC_6H_4	*t*-Bu	2	**4i**	89
10	2-BrC_6H_4	*t*-Bu	3	**4j**	81
11	2-naphthyl	*t*-Bu	2	**4k**	96
12	1-naphthyl	*t*-Bu	8	**4l**	70
13	C_6H_5	*t*-Bu	5	**4m**	73
14	4-$OCH_3C_6H_4$	*t*-Bu	24	**4n**	trace
15	4-$NO_2C_6H_4$	*c*-hexyl	3	**4o**	62
16	3-$NO_2C_6H_4$	*c*-hexyl	3	**4p**	50
17	2,4-$Cl_2C_6H_3$	*c*-hexyl	10	**4q**	72
18	3-BrC_6H_4	*c*-hexyl	3	**4r**	78
19	2-naphthyl	*c*-hexyl	4	**4s**	57

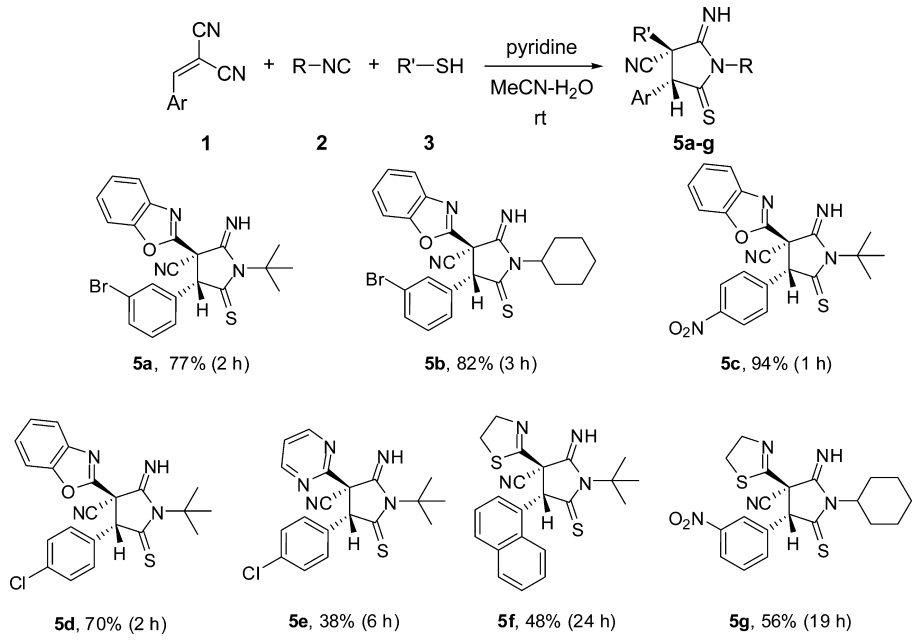
[a] The reactions were carried out at room temperature for a specific time using **1** (0.5 mmol), **2** (0.6 mmol), **3a** (0.5 mmol), pyridine (0.5 mmol), solvent (2.0 mL, V_{MeCN}:V_{H_2O} = 3:1). [b] Isolated yield.

groups gave good yields within a short reaction time (entries 1−10) and olefins containing naphthyl and phenyl group could also react well to produce the desired products in good to excellent yields (entries 11−13). Unfortunately, the electron-donating counterparts were not good substrates even upon prolonging the reaction time to 24 h (entry 14). When cyclohexyl isocyanide was used instead of *tert*-butyl isocyanide, the reactions could also proceed well to give the desired products in good yields (entries 15−19).

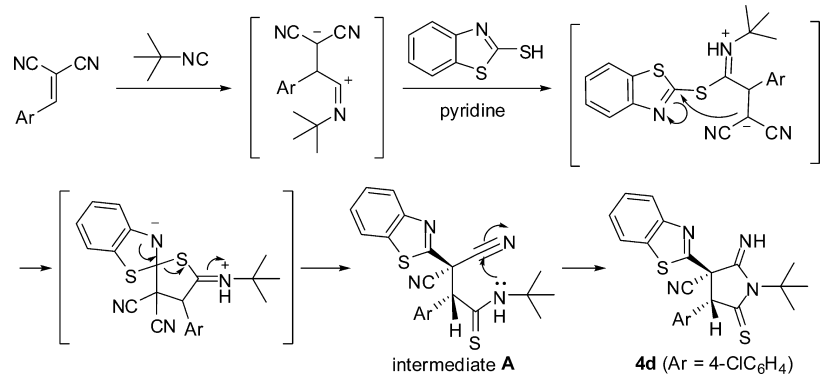
To further explore the generality of this novel multicomponent reaction, we continued to study the use of other heterocyclic thiols (Table 3). As shown in Table 3, moderate to good yields were also obtained when thiols including 2-mercaptobenzoxazole, 2-mercaptopyrimidine, and 2-thiazoline-2-thiol were used. Random combination of the three starting materials could give the final products with up to 94% yield.

Therefore, we have discovered a novel I-MCR leading to highly substituted thioxopyrrolidines. Since the first Ugi-Smiles conversion of thiols was observed in 2006 by Kaim and co-workers,[9a] few such processes have been explored.[9b−k] On the basis of the above results, a plausible mechanism was proposed for the formation of the thioxopyrrolidine derivatives (Scheme 2) by analogy with the Ugi multicomponent condensation. The first step probably involves the reaction of *gem*-dicyano olefin with isocyanide, followed by attack of thiol on the resulting intermediate. Subsequent Ugi-Smiles-type rearrangement followed by nucleophilic addition of the amino group onto the cyano group affords the final product. According to the molecular structure of **4d**, presence of the C−S double bond and benzothiazole group indicated the possible involvement of a Ugi-Smiles-type coupling. Formation of the imino fragment might be the result of the

Table 3. Substrate Scope Study Using Various Thiols



Scheme 2. Possible Mechanism for the Formation of Product **4d**



nucleophilic addition of an amino group to the activated cyano group. To verify the hypothesis we brought forward, another experiment was carried out. When the model reaction was terminated after it had proceeded for 30 min, a Ugi-Smiles-type coupling product, which was proposed to be a key intermediate (**A**) of this reaction was isolated (16% yield) and fully characterized. Once intermediate **A** is formed in the reaction mixture, the simultaneous presence of an activated cyano group and thio-amide functional group in the intermediate triggered an intramolecular cyclization to furnish the final product. To identify the hypothesis, the intermediate **A** was stirred in the same reaction condition and the product **4d** was obtained in 70% yield after 3 h.

Conclusion

In summary, we have developed a novel and highly efficient three-component reaction involving isocyanides, various thiols and *gem*-dicyano olefins bearing electron-withdrawing groups to produce the corresponding imino-pyrrolidine-thiones. Most of the reactions are completed within short time. This is a novel and direct route for the construction of biologically relevant heterocyclic scaffolds of imino-pyrrolidine-thiones via a Ugi-Smiles-type strategy. In addition, this reaction is 100% atom economic that makes the whole reaction highly efficient. Further studies are underway to examine more thoroughly the scope and limitations of this three-component reaction system.

Experimental Section

Typical Experimental Procedure for the Synthesis of Imino-pyrrolidine-thione Derivatives 4a−s, 5a−g and the Intermediate A. To a mixture of *gem*-dicyano olefin **1** (0.5 mmol) and heterocyclic thiol **3** (0.5 mmol) in the mixed solvent of MeCN and H_2O (3:1, v/v) was added isocyanide **2** (0.6 mmol) and pyridine (0.5 mmol). The solution was stirred at room temperature for a specific as shown in Tables 2 and 3. The progress of the reaction was monitored by TLC. After completion of the reaction, 30 mL of H_2O was added to the reaction mixture and then extracted by CH_2Cl_2 (10 mL × 3). The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. The organic layer was evaporated under reduced pressure, and the residue was subjected to silica gel column chromatography using petroleum ether and ethyl acetate as eluant to afford the desired

products of **4a**−**s** and **5a**−**g**. The intermediate **A** was obtained when the reaction proceeded for 30 min.

4a: Yellow solid; mp 187−189 °C; IR (KBr) ν 3244 (NH), 2978, 1677 (C═N), 1522, 1349 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 1.91 (s, 9H, $3CH_3$), 5.24 (s, 1H, CH), 7.46 (d, J = 8.4 Hz, 2H, ArH), 7.52−7.64 (m, 2H, ArH), 7.96 (d, J = 7.8 Hz, 1H, ArH), 8.13 (d, J = 7.8 Hz, 1H, ArH), 8.28 (d, J = 8.7 Hz, 2H, ArH), 9.33 (br s, 1H, NH) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 202.5, 163.3, 160.9, 152.7, 148.4, 143.3, 135.3, 130.2, 127.7, 127.2, 124.6, 124.5, 122.2, 114.7, 65.8, 65.1, 57.7, 28.4 ppm; HRMS (*m*/*z*) calcd for $C_{22}H_{19}N_5O_2S_2$ (M^+) 449.0980, found 449.0985; Anal. Calcd for $C_{22}H_{19}N_5O_2S_2$ C 58.78, H 4.26, N 15.58; found C 59.10, H 4.31, N 15.87.

4b: Yellow solid; mp 132−134 °C; IR (KBr) ν 3259 (NH), 2979, 1672 (C═N), 1531, 1349 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 1.92 (s, 9H, $3CH_3$), 5.23 (s, 1H, CH), 7.51−7.62 (m, 4H, ArH), 7.96 (d, J = 8.1 Hz, 1H, ArH), 8.15(t, J = 7.8 Hz, 2H, ArH), 8.25−8.29 (m, 1H, ArH), 9.31 (br s, 1H, NH) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 199.7, 160.4, 158.1, 150.1, 145.8, 135.6, 132.5, 132.1, 127.8, 124.9, 124.4, 121.7, 121.6, 121.5, 119.4, 111.9, 62.9, 62.4, 54.9, 25.6 ppm; HRMS (*m*/*z*) calcd for $C_{22}H_{19}N_5O_2S_2$ (M^+) 449.0980, found 449.0978; Anal. Calcd for $C_{22}H_{19}N_5O_2S_2$ C 58.78, H 4.26, N 15.58; found C 58.73, H 4.29, N 15.52.

4c: Yellow solid; mp 123−125 °C; IR (KBr) ν 3259 (NH), 2974, 1676 (C═N), 1509, 1356 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 1.90 (s, 9H, $3CH_3$), 5.01 (s, 1H, CH), 7.09 (t, J = 8.4 Hz, 2H, ArH), 7.22−7.25 (m, 2H, ArH), 7.50 (t, J = 7.6 Hz, 1H, ArH), 7.58 (t, J = 8.0 Hz, 1H, ArH), 7.93 (d, J = 8.0 Hz, 1H, ArH), 8.11 (d, J = 8.4 Hz, 1H, ArH), 9.31 (br s, 1H, NH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 204.4, 164.7, 162.2, 153.0, 135.5, 132.8, 132.8, 130.9, 130.8, 127.2 (d, J = 35.0 Hz, C), 124.6, 122.4, 116.9 (d, J = 16.4 Hz, CH), 115.2, 66.3, 65.0, 58.6, 28.7 ppm; Assignment of CH and C in ^{13}C NMR has been confirmed by a DEPT (see Supporting Information); HRMS (*m*/*z*) calcd for $C_{22}H_{19}FN_4S_2$ (M^+) 422.1035, found 422.1040; Anal. Calcd for $C_{22}H_{19}FN_4S_2$ C 62.53, H 4.53, N 13.26; found C 62.60, H 4.64, N 13.45.

4d: Yellow solid; mp 163−165 °C; IR (KBr) ν 3249 (NH), 2980, 1674 (C═N), 1491, 1349 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 1.90 (s, 9H, $3CH_3$), 5.00 (s, 1H, CH), 7.19 (d, J = 6.0 Hz, 2H, ArH), 7.38 (d, J = 8.4 Hz, 2H, ArH), 7.51 (t, J = 7.6 Hz, 1H, ArH), 7.59 (t, J = 7.6 Hz, 1H, ArH), 7.94 (d, J = 8.0 Hz, 1H, ArH), 8.11 (d, J = 8.4 Hz, 1H, ArH), 9.31 (br s, 1H, NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ = 197.3, 151.8, 136.2, 134.8, 133.6, 130.4, 129.1, 128.0, 127.2, 126.6, 123.4, 122.9, 114.9, 114.9, 65.7, 63.8, 57.2, 27.7 ppm; HRMS (*m*/*z*) calcd for $C_{22}H_{19}ClN_4S_2$ (M^+) 438.0740, found 438.0741; Anal. Calcd for $C_{22}H_{19}ClN_4S_2$ C 60.19, H 4.36, N 12.76; found C 60.24, H 4.50, N 12.99.

4e: Yellow solid; mp 136−137 °C; IR (KBr) ν 3245 (NH), 2975, 1674 (C═N), 1349 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 1.90 (s, 9H, $3CH_3$), 5.01 (s, 1H, CH), 7.13 (d, J = 6.3 Hz, 1H, ArH), 7.35 (d, J = 6.3 Hz, 2H, ArH), 7.49−7.62 (m, 3H, ArH), 7.94 (d, J = 7.8 Hz, 1H, ArH), 8.11 (d, J = 7.8 Hz, 1H, ArH), 9.30 (br s, 1H, NH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 203.7, 153.0, 138.7, 135.6, 135.5, 131.0, 130.5, 130.0, 129.4, 127.7, 127.3, 126.9, 125.7, 124.7, 122.4, 115.1, 66.4, 65.1, 58.3, 28.7 ppm; HRMS (*m*/*z*) calcd for $C_{22}H_{19}ClN_4S_2$ (M^+) 438.0740, found 438.0742; Anal. Calcd for $C_{22}H_{19}ClN_4S_2$ C 60.19, H 4.36, N 12.76; found C 60.48, H 4.38, N 13.00.

4f: Yellow solid; mp 145−147 °C; IR (KBr) ν 3227 (NH), 2978, 1686 (C═N), 1502, 1359 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 1.93 (s, 9H, $3CH_3$), 5.23 (s, 1H, CH), 7.10−7.12 (m, 1H, ArH), 7.33−7.36 (m, 2H, ArH), 7.46−7.60 (m, 3H, ArH), 7.95 (d, J = 8.1 Hz, 1H, ArH), 8.10 (d, J = 7.8 Hz, 1H, ArH), 9.23 (br s, 1H, NH) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 197.9, 158.2, 156.6, 147.3, 130.3, 130.1, 129.6, 125.2, 124.9, 123.0, 122.7, 122.0, 121.5, 119.0, 116.7, 109.4, 59.6, 58.3, 52.9, 23.1 ppm; HRMS (*m*/*z*) calcd for $C_{22}H_{19}ClN_4S_2$ (M^+) 438.0740, found 438.0794; Anal. Calcd for $C_{22}H_{19}ClN_4S_2$ C 60.19, H 4.36, N 12.76; found C 60.28, H 4.38, N 12.89.

4g: Yellow solid; mp 161−162 °C; IR (KBr) ν 3258 (NH), 2971, 1671 (C═N), 1478, 1350 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 1.90 (s, 9H, $3CH_3$), 5.47 (s, 1H, CH), 7.04 (d, J = 8.4 Hz, 1H, ArH), 7.32 (d, J = 8.1 Hz, 1H, ArH), 7.48−7.60 (m, 3H, ArH), 7.94 (d, J = 7.8 Hz, 1H, ArH), 8.10 (d, J = 8.1 Hz, 1H, ArH), 9.31 (s, 1H, NH) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 202.7, 163.2, 161.6, 152.7, 136.4, 136.0, 135.5, 133.6, 130.1, 129.4, 128.5, 127.4, 127.0, 124.5, 122.1, 114.7, 65.0, 63.0, 57.9, 28.4 ppm; HRMS (*m*/*z*) calcd for $C_{22}H_{18}Cl_2N_4S_2$ (MH^+) 473.0423, found 473.0415; Anal. Calcd for $C_{22}H_{18}Cl_2N_4S_2$ C 55.81, H 3.83, N 11.83; found C 56.17, H 3.97, N 11.73.

4h: Yellow solid; mp 174−176 °C; IR (KBr) ν 3248 (NH), 2976, 1673 (C═N), 1488 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 1.90(s, 9H, $3CH_3$), 5.01 (s, 1H, CH), 7.14 (d, J = 6.9 Hz, 2H, ArH), 7.49−7.62 (m, 4H, ArH), 7.94 (d, J = 7.8 Hz, 1H, ArH), 8.12 (d, J = 8.1 Hz, 1H, ArH), 9.29 (br s, 1H, NH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 203.7, 164.0, 161.8, 153.0, 139.0, 132.8, 132.4, 131.3, 127.7, 127.3, 124.7, 123.6, 122.4, 115.0, 66.4, 65.2, 58.4, 28.7 ppm; HRMS (*m*/*z*) calcd for $C_{22}H_{19}BrN_4S_2$ (M^+) 482.0235, found 482.0230; Anal. Calcd for $C_{22}H_{19}BrN_4S_2$ C 54.66, H 3.96, N 11.59; found C 54.94, H 4.02, N 11.58.

4i: Yellow solid; mp 148−150 °C; IR (KBr) ν 3247 (NH), 2924, 1675 (C═N), 1568, 1348 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 1.91 (s, 9H, $3CH_3$), 5.01 (s, 1H, CH), 7.18 (d, J = 7.2 Hz, 1H, ArH), 7.31 (d, J = 7.8 Hz, 1H, ArH), 7.42 (s, 1H, ArH), 7.50−7.62 (m, 3H, ArH), 7.95 (d, J = 7.8 Hz, 1H, ArH), 8.01 (d, J = 8.1 Hz, 1H, ArH), 9.29 (br s, 1H, NH) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 203.5, 163.8, 161.6, 152.7, 138.7, 135.3, 132.6, 132.1, 131.1, 127.5, 127.1, 124.6, 124.5, 123.4, 122.2, 114.8, 66.2, 65.0, 58.2, 28.5 ppm; HRMS (*m*/*z*) calcd for $C_{22}H_{19}BrN_4S_2$ (M^+) 482.0235, found 482.0237; Anal. Calcd for $C_{22}H_{19}BrN_4S_2$ C 54.66, H 3.96, N 11.59; found C 54.84, H 3.94, N 11.42.

4j: Yellow solid; mp 138−140 °C; IR (KBr) ν 3278 (NH), 2978, 1669 (C═N), 1494, 1359 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 1.93 (s, 9H, $3CH_3$), 5.53 (s, 1H, CH), 7.10 (d, J = 7.8 Hz, 1H, ArH), 7.26 (t, J = 7.7 Hz, 1H, ArH), 7.38 (t, J = 7.5 Hz, 1H, ArH), 7.48−7.60 (m, 2H, ArH), 7.69 (d, J = 8.1 Hz, 1H, ArH), 7.94 (d, J = 7.8 Hz, 1H, ArH), 8.10

(d, J = 7.8 Hz, 1H, ArH), 9.32 (s, 1H, NH) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 198.0, 158.1, 156.6, 147.3, 131.5, 130.1, 128.2, 125.5, 123.4, 123.1, 122.0, 121.5, 121.2, 119.0, 116.7, 109.4, 60.8, 60.0, 52.9, 23.0 ppm; HRMS (*m*/*z*) calcd for $C_{22}H_{19}BrN_4S_2$ (MH^+) 483.0307, found 483.0305; Anal. Calcd for $C_{22}H_{19}BrN_4S_2$ C 54.66, H 3.96, N 11.59; found C 54.54, H 3.90, N 11.70.

4k: Yellow solid; mp 199−200 °C; IR (KBr) ν 3256 (NH), 2978, 2226, 1678 (C═N), 1586, 1349 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.98 (s, 9H, $3CH_3$), 5.20 (s, 1H, CH), 7.33 (d, J = 8.1 Hz, 1H, ArH), 7.52−7.64 (m, 4H, ArH), 7.80−7.97 (m, 5H, ArH), 8.16 (d, J = 7.5 Hz, 1H, ArH), 9.37 (s, 1H, NH) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 204.5, 164.2, 162.1, 152.8, 135.4, 134.0, 133.6, 133.5, 129.7, 129.1, 128.5, 128.1, 127.5, 127.1, 127.0, 126.9, 125.0, 124.5, 122.2, 115.1, 67.2, 64.9, 58.4, 28.6 ppm; HRMS (*m*/*z*) calcd for $C_{26}H_{22}N_4S_2$ (M^+) 454.1286, found 454.1285; Anal. Calcd for $C_{26}H_{22}N_4S_2$ C 68.69, H 4.88, N 12.32; found C 68.94, H 4.95, N 11.90.

4l. Yellow solid; mp 178−179 °C; IR (KBr) ν 3219 (NH), 2986, 1683 (C═N), 1450, 1358 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.96 (s, 9H, $3CH_3$), 6.00(s, 1H, CH), 7.27 (s, 1H, ArH), 7.44−7.64 (m, 5H, ArH), 7.90−7.97 (m, 3H, ArH), 8.08 (d, J = 8.1 Hz, 1H, ArH), 8.18 (d, J = 8.1 Hz, 1H, ArH), 9.28 (br s, 1H, NH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 205.5, 153.1, 135.7, 134.4, 134.0, 132.7, 130.3, 129.7, 127.7, 127.7, 127.2, 126.8, 126.0, 125.4, 124.8, 123.1, 122.4, 121.8, 115.3, 112.5, 65.1, 62.3, 59.1, 28.8 ppm; HRMS (*m*/*z*) calcd for $C_{26}H_{22}N_4S_2$ (M^+) 454.1286, found 454.1285; Anal. Calcd for $C_{26}H_{22}N_4S_2$ C 68.69, H 4.88, N 12.32; found C 68.30, H 4.85, N 12.10.

4m: Yellow solid; mp 146−147 °C; IR (KBr) ν 3264 (NH), 2966, 1674 (C═N), 1492, 1350 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.91 (s, 9H, $3CH_3$), 5.26 (s, 1H, CH), 7.26 (s, 2H, ArH), 7.39 (d, J = 1.5 Hz, 3H, ArH), 7.48−7.60 (m, 2H, ArH), 7.93 (d, J = 7.5 Hz, 1H, ArH), 8.10 (d, J = 8.1 Hz. 1H, ArH), 9.10 (br s, 1H, NH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 204.8, 164.1, 162.3, 153.0, 137.0, 135.6, 129.8, 129.7, 128.8, 127.6, 127.2, 124.6, 122.3, 115.2, 67.3, 64.9, 58.8, 28.7 ppm; HRMS (*m*/*z*) calcd for $C_{22}H_{20}N_4S_2$ (M^+) 404.1129, found 404.1126; Anal. Calcd for $C_{22}H_{20}N_4S_2$ C 65.32, H 4.98, N 13.85; found C 65.57, H 4.93, N 13.46.

4o: White solid; mp 176−177 °C; IR (KBr) ν 3243 (NH), 2928, 1675 (C═N), 1522, 1386 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.28−1.45 (m, 3H, CH_2), 1.70−1.73 (m, 2H, CH), 1.86−1.96 (m, 3H, CH_2), 2.46−2.62 (m, 2H, CH_2), 5.02−5.11 (m, 1H, CH), 5.36 (s, 1H, CH), 7.47 (d, J = 8.7 Hz, 2H, ArH), 7.50−7.63 (m, 2H, ArH), 7.95 (d, J = 7.8 Hz, 1H, ArH), 8.12 (d, J = 8.1 Hz, 1H, ArH), 8.29 (d, J = 8.7 Hz, 2H, ArH), 9.05 (br s, 1H, NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ = 202.7, 165.3, 151.8, 142.0, 141.0, 135.3, 127.2, 126.8, 123.6, 122.4, 114.0, 106.4, 55.4, 55.0, 52.6, 25.5, 25.4, 24.8, 24.8, 23.2 ppm; HRMS (*m*/*z*) calcd for $C_{24}H_{21}N_5O_2S_2$ (M^+) 475.1137, found 475.1140; Anal. Calcd for $C_{24}H_{21}N_5O_2S_2$ C 60.61, H 4.45, N 14.73; found C 60.64, H 4.53, N 15.11.

4p: Brown solid; mp 95−98 °C; IR (KBr) ν 3230 (NH), 2932, 1670 (C═N), 1513, 1370 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.24−1.46 (m, 3H, CH_2), 1.70−1.74 (m, 2H, CH), 1.86−1.96 (m, 3H, CH_2), 2.47−2.63 (m, 2H, CH_2), 5.07 (t, J = 12.2 Hz, 1H, CH), 5.36 (s, 1H, CH), 7.53 (t, J = 7.5 Hz,1H, ArH), 7.61−7.66 (m, 3H, ArH), 7.94 (d, J = 7.8 Hz, 1H, ArH), 8.12 (d, J = 8.4 Hz, 1H, ArH), 8.16 (s, 1H, ArH), 8.26−8.29 (m, 1H, ArH), 9.05 (br s, 1H, NH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 202.1, 162.2, 161.5, 152.9, 148.7, 137.8, 135.0, 130.7, 127.7, 127.2, 124.6, 124.5, 122.2, 114.7, 65.2, 59.2, 56.0, 27.9, 26.8, 26.2, 26.0, 25.3 ppm; HRMS (*m*/*z*) calcd for $C_{24}H_{21}N_5O_2S_2$ (M^+) 475.1137, found 475.1142; Anal. Calcd for $C_{24}H_{21}N_5O_2S_2$ C 60.61, H 4.45, N 14.73; found C 60.22, H 4.06, N 14.50.

4q: Yellow solid; mp 172−174 °C; IR (KBr) ν 3292 (NH), 2932, 1673 (C═N), 1393 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.29−1.44 (m, 3H, CH_2), 1.71−1.74 (m, 2H, CH), 1.91 (s, 3H, CH_2), 2.57−2.62 (m, 2H, CH_2), 5.12 (s, 1H, CH), 5.63 (s, 1H, CH), 7.05−7.08 (m, 1H, ArH), 7.33 (s, 1H, ArH), 7.52−7.60 (m, 3H, ArH), 7.94 (t, J = 5.7 Hz, 1H, ArH), 8.11 (d, J = 6.9 Hz, 1H, ArH), 8.99 (br s, 1H, NH) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 202.6, 162.6, 152.9, 136.2, 135.3, 133.1, 130.2, 129.3, 128.5, 127.5, 127.0, 124.5, 122.1, 114.7, 62.6, 59.2, 56.0, 28.2, 26.6, 26.2, 26.0, 25.3 ppm; HRMS (*m*/*z*) calcd for $C_{24}H_{20}Cl_2N_4S_2$ (M^+) 498.0506, found 498.0506; Anal. Calcd for $C_{24}H_{20}Cl_2N_4S_2$ C 57.71, H 4.04, N 11.22; found C 57.56, H 4.12, N 11.35.

4r: White solid; mp 179−181 °C; IR (KBr) ν 3263 (NH), 2931, 2853, 1670 (C═N), 1375 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.33−1.45 (m, 3H, CH_2), 1.70−1.73 (m, 2H, CH), 1.85−1.95 (m, 3H, CH_2), 2.47−2.62 (m, 2H, CH_2), 5.02−5.11 (m, 1H, CH), 5.13 (s, 1H, CH), 7.18 (d, J = 7.8 Hz, 1H, ArH), 7.30 (t, J = 7.8 Hz, 1H, ArH), 7.42 (s, 1H, ArH), 7.49−7.62 (m, 3H, ArH), 7.93 (d, J = 7.8 Hz, 1H, ArH), 8.10 (d, J = 8.4 Hz, 1H, ArH), 9.02 (br s, 1H, NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ = 203.3, 152.0, 139.1, 135.4, 134.8, 132.0, 131.7, 131.5, 127.2, 126.8, 126.5, 123.4, 122.8, 122.1, 65.0, 57.8, 55.4, 27.3, 26.0, 25.6, 25.3, 24.8 ppm; HRMS (*m*/*z*) calcd for $C_{24}H_{21}BrN_4S_2$ (M^+) 508.0391, found 508.0391; Anal. Calcd for $C_{24}H_{21}BrN_4S_2$ C 56.58, H 4.15, N 11.00; found C 57.33, H 4.26, N 11.11.

4s: Yellow solid; mp 153−154 °C; IR (KBr) ν 3230 (NH), 2929, 1669 (C═N), 1374 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.31−1.47 (m, 3H, CH_2), 1.72−1.76 (m, 2H, CH), 1.87−1.97 (m, 3H, CH_2), 2.53−2.70 (m, 2H, CH_2), 5.09−5.17 (m, 1H, CH), 5.31 (s, 1H, CH), 7.30 (s, 1H, ArH), 7.49−7.62 (m, 4H, ArH), 7.78 (s, 1H, ArH), 7.82−7.93 (m, 4H, ArH), 8.13 (d, J = 8.1 Hz, 1H, ArH), 9.07 (br s, 1H, NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ = 203.9, 161.3, 152.0, 134.8, 134.1, 132.8, 132.8, 129.1, 128.4, 128.1, 127.7, 127.2, 126.9, 126.9, 126.5, 124.7, 123.4, 122.9, 66.3, 57.9, 55.6, 27.4, 26.0, 25.6, 25.4, 24.8 ppm; HRMS (*m*/*z*) calcd for $C_{28}H_{24}N_4S_2$ (M^+) 480.1442, found 480.1443; Anal. Calcd for $C_{28}H_{24}N_4S_2$ C 69.97, H 5.03, N 11.66; found C 69.93, H 5.35, N 11.29.

5a: Yellow solid; mp 159−160 °C; IR (KBr) ν 3233 (NH), 2979, 1684 (C═N), 1565, 1452, 1347 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.90 (s, 9H, $3CH_3$), 5.01 (s, 1H, CH), 7.20 (d, J = 7.8 Hz, 1H, ArH), 7.32 (d, J = 7.8 Hz, 1H, ArH), 7.45−7.56 (m, 4H, ArH), 7.63 (d, J = 7.8 Hz, 1H, ArH), 7.83 (d, J = 6.9 Hz, 1H, ArH), 9.44 (s, 1H, NH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 203.2, 162.0, 151.9, 140.7,

138.5, 133.0, 132.5, 131.3, 130.5, 127.4, 126.2, 125.9, 123.6, 121.6, 113.4, 111.7, 65.3, 64.3, 54.3, 28.7 ppm; HRMS (*m*/*z*) calcd for $C_{22}H_{19}BrN_4OS$ (M^+) 466.0463, found 466.0464; Anal. Calcd for $C_{22}H_{19}BrN_4OS$ C 56.54, H 4.10, N 11.99; found C 56.46, H 3.95, N 11.97.

5b: Yellow solid; mp 110−111 °C; IR (KBr) ν 3252 (NH), 2929, 1672 (C═N), 1368 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 1.24−1.44 (m, 3H, CH_2), 1.62−1.73 (m, 2H, CH), 1.86−1.95 (m, 3H, CH_2), 2.47−2.70 (m, 2H, CH_2), 5.02−5.10 (m, 1H, CH), 5.19 (s, 1H, CH), 7.20 (d, J = 7.5 Hz, 1H, ArH), 7.31 (t, J = 7.8 Hz, 1H, ArH), 7.42−7.51 (m, 3H, ArH), 7.55 (d, J = 7.8 Hz, 1H, ArH), 7.63 (d, J = 8.1 Hz, 1H, ArH), 7.82 (d, J = 6.9 Hz, 1H, ArH), 9.21 (s, 1H, NH) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 202.6, 151.7, 140.3, 137.7, 132.9, 132.1, 131.1, 127.2, 127.2, 126.0, 123.5, 121.4, 113.1, 111.6, 63.1, 59.1, 52.3, 27.8, 26.9, 26.2, 26.0, 25.3 ppm; HRMS (*m*/*z*) calcd for $C_{24}H_{21}BrN_4OS$ (M^+) 492.0619, found 492.0618; Anal. Calcd for $C_{24}H_{21}BrN_4OS$ C 58.42, H 4.29, N 11.35; found C 58.06, H 4.30, N 11.26.

5c: Yellow solid; mp 195−196 °C; IR (KBr) ν 3231 (NH), 2977, 1679 (C═N), 1523, 1350 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 1.91 (s, 9H, $3CH_3$), 5.51 (s, 1H, CH), 7.51 (d, J = 7.5 Hz, 4H, ArH), 7.65 (d, J = 6.9 Hz, 1H, ArH), 7.85 (d, J = 6.9 Hz, 1H, ArH), 8.29 (d, J = 8.7 Hz, 2H, ArH), 9.49 (s, 1H, NH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 202.3, 170.8, 151.9, 148.7, 143.1, 140.6, 130.5, 127.6, 126.3, 124.8, 121.6, 113.2, 111.7, 105.4, 65.4, 63.9, 53.8, 28.6 ppm; HRMS (*m*/*z*) calcd for $C_{22}H_{19}N_5O_3S$ (M^+) 433.1209, found 433.1211; Anal. Calcd for $C_{22}H_{19}N_5O_3S$ C 60.96, H 4.42, N 16.16; found C 60.94, H 4.43, N 16.16.

5d: Yellow solid; mp 191−193 °C; IR (KBr) ν 3234 (NH), 2935, 1675 (C═N), 1561, 1344 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 1.89 (s, 9H, $3CH_3$), 5.03 (s, 1H, CH), 7.22(d, J = 8.4 Hz, 2H, ArH), 7.40 (d, J = 8.4 Hz, 2H, ArH), 7.45−7.49 (m, 2H, ArH), 7.63 (d, J = 8.4 Hz, 1H, ArH), 7.82 (d, J = 6.6 Hz, 1H, ArH), 9.35 (br s, 1H, NH) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 203.7, 164.0, 161.8, 153.0, 139.0, 132.8, 132.4, 131.3, 127.7, 127.3, 124.7, 123.6, 122.4, 115.0, 66.4, 65.2, 58.4, 28.7 ppm; HRMS (*m*/*z*) calcd for $C_{22}H_{19}ClN_4OS$ (M^+) 422.0968, found 422.0965; Anal. Calcd for $C_{22}H_{19}ClN_4OS$ C 62.48, H 4.53, N 13.25; found C 62.50, H 4.68, N 13.46.

5e: Yellow solid; mp 161−163 °C; IR (KBr) ν 3257 (NH), 2964, 1676 (C═N), 1566, 1491, 1408 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 1.86 (s, 9H, $3CH_3$), 5.06 (s, 1H, CH) 7.21 (d, J = 8.1 Hz, 2H, ArH), 7.37 (d, J = 8.1 Hz, 2H, ArH), 7.43 (t, J = 5.0 Hz, 1H, ArH), 8.86 (d, J = 4.8 Hz, 2H, ArH), 9.31 (br s, 1H, NH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 205.5, 163.0, 158.9, 136.2, 135.4, 132.3, 130.5, 129.9, 121.9, 116.0, 65.0, 64.7, 61.5, 28.8 ppm; HRMS (*m*/*z*) calcd for $C_{19}H_{18}ClN_5S$ (M^+) 383.0971, found 383.0970; Anal. Calcd for $C_{19}H_{18}ClN_5S$ C 59.44, H 4.73, N 18.24; found C 59.60, H 4.86, N 18.45.

5f: Yellow solid; mp 170−171 °C; IR (KBr) ν 3237 (NH), 2973, 1675 (C═N), 1355 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 1.96 (s, 9H, $3CH_3$), 3.53 (t, J = 8.6 Hz, 2H, CH_2), 4.40 (t, J = 8.7 Hz, 2H, CH_2), 4.87 (s, 1H, CH), 7.21 (d, J = 8.4 Hz, 1H, ArH), 7.49−7.52 (m, 2H, ArH), 7.72 (s, 1H, ArH), 7.81−7.88 (m, 3H, ArH), 9.29 (br s, 1H, NH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 204.1, 164.0, 161.8, 158.8, 153.0, 135.8, 135.5, 135.4, 132.3, 130.4, 130.0, 127.8, 127.3, 124.7, 122.4, 115.2, 66.4, 65.2, 58.5, 28.7 ppm; HRMS (*m*/*z*) calcd for $C_{22}H_{22}N_4S_2$ (M^+) 406.1286, found 406.1285; Anal. Calcd for $C_{22}H_{22}N_4S_2$ C 64.99, H 5.45, N 13.78; found C 64.86, H 5.46, N 13.65.

5g: Yellow solid; mp 226−227 °C; IR (KBr) ν 3310 (NH), 2938, 2185, 1658 (C═N), 1603, 1528 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 1.19−1.27 (m, 1H, CH_2), 1.44−1.46 (m, 2H, CH_2), 1.78−1.96 (m, 7H, CH_2), 3.36 (s, 2H, CH_2), 4.38 (s, 2H, CH_2), 5.17 (br s, 1H, NH), 5.57 (s, 2H, CH), 7.53−7.58 (m, 1H, ArH), 7.87 (s, 1H, ArH), 8.20 (d, J = 6.9 Hz, 1H, ArH), 8.35 (s, 1H, ArH); ^{13}C NMR (100 MHz, DMSO-d_6) δ = 203.1, 168.9, 147.1, 140.6, 135.5, 129.4, 123.5, 122.8, 116.9, 112.3, 79.2, 64.4, 33.6, 26.9, 26.9, 25.7, 25.5, 25.4 ppm; HRMS (*m*/*z*) calcd for $C_{20}H_{21}N_5O_2S_2$ (M^+) 427.1137, found 427.1134; Anal. Calcd for $C_{20}H_{21}N_5O_2S_2$ C 56.18, H 4.95, N 16.38; found C 56.35, H 4.66, N 16.60.

A: Yellow solid; mp 177−178 °C; IR (KBr) ν 3250 (NH), 2950, 2245(CN), 1560, 1491, 1350 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 1.90 (s, 9H, CH_3), 5.02 (s, 1H, CH), 7.19 (d, J = 8.4 Hz, 2H, ArH), 7.38 (d, J = 8.7 Hz, 2H, ArH), 7.49−7.62 (m, 3H, ArH and NH), 7.94 (d, J = 8.1 Hz, 1H, ArH), 8.11 (d, J = 8.1 Hz, 1H, ArH) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 204.0, 153.0, 150.8, 135.8, 133.0, 130.6, 127.7, 127.3, 124.7, 124.0, 122.4, 115.1, 102.1, 66.5, 65.1, 58.4, 28.7 ppm; HRMS (*m*/*z*) calcd for $C_{22}H_{19}ClN_4S_2$ (M^+) 438.0740, found 438.0740; Anal. Calcd for $C_{22}H_{19}ClN_4S_2$ C 60.19, H 4.36, N 12.76; found C 60.45, H 4.21, N 12.89.

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Supporting Information Available. Detailed experimental procedure, compound characterization data, ^1H and ^{13}C NMR spectra, and crystallographic data. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) Remy, D. C.; Sam, W. A. V.; Lotti, V. J. *J. Med. Chem.* **1972**, *15*, 1198.
(2) (a) Hashimoto, K.; Yanagi, K.; Fukushima, K.; Uda, Y. *Int. J. Antimicrob. Agents* **2001**, *17*, 97–102. (b) Uda, Y.; Hayashi, H.; Takahashi, A.; Shimizu, A. *LWT—Food Sci. Technol.* **2000**, *33*, 37–43.
(3) (a) Montforts, F.-P.; Gerlach, B.; Hoper, F. *Chem. Rev.* **1994**, *94*, 327–347. (b) David, O.; Blot, J.; Bellec, C.; Fargeau-Bellassoued, M.-C.; Haviari, G.; Célérier, J. P.; Lhommet, G.; Gramain, J.-C.; Gardette, D. *J. Org. Chem.* **1999**, *64*, 3122–3131.
(4) (a) Moore, W. M.; Webber, R. K.; Fok, K. F.; Jerome, G. M.; Connor, J. R.; Manning, P. T.; Wyatt, P. S.; Misko, T. P.; Tjoeng, F. S.; Currie, M. G. *J. Med. Chem.* **1996**, *39*, 669–672. (b) Hagen, T. J.; Bergmanis, A. A.; Kramer, S. W.; Fok, K. F.; Schmelzer, A. E.; Pitzele, B. S.; Swenton, L.; Jerome,

G. M.; Kornmeier, C. M.; Moore, W. M.; Branson, L. F.; Connor, J. R.; Manning, P. T.; Currie, M. G.; Hallinan, E. A. *J. Med. Chem.* **1998**, *41*, 3675–3683. (c) Shankaran, K.; Donnelly, K. L.; Shah, S. K.; Guthikonda, R. N.; MacCoss, M.; Humes, J. L.; Pacholok, S. G.; Grant, S. K.; Kelly, T. M.; Wong, K. K. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 4539.

(5) *Multicomponent Reactions*; Zhu, J., Bienayme, H., Eds.; Wiley-VCH: Weinheim, Germany, 2005.

(6) (a) Ugi, I.; Meyr, R.; Fetzer, U.; Steinbruckner, C. *Angew. Chem.* **1959**, *71*, 386. (b) Ugi, I.; Steinbruckner, C. *Angew. Chem.* **1960**, *72*, 267. (c) Domling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3168–3210. (d) Domling, A. *Chem. Rev.* **2006**, *106*, 17–89.

(7) (a) Guery, S.; Schmitt, M.; Bourguignon, J.-J. *Synlett* **2002**, 2003–2006. (b) Armour, D. R.; Bell, A. S.; Edwards, P. J.; Ellis, D.; Hepworth, D.; Lewis, M. L.; Smith, C. R. Preparation of heterocyclylcarboxamides as oxytocin inhibitors. Patent WO 2004020414, 2004. (c) Lin, X. P.; Wenwei, L.; Xiaomin, Z. *Synthesis* **2002**, 1017–1026. (d) Rossen, K.; Sager, J.; DiMichele, L. M. *Tetrahedron Lett.* **1997**, *38*, 3183–3186. (e) Floyd, C. D.; Harnett, L. A.; Miller, A.; Patel, S.; Saroglou, L.; Whittaker, M. *Synlett* **1996**, 637–639. (f) Thormann, M.; Almstetter, M. Method of preparation of bioisosteres of actinonin of interest as metalloproteinase inhibitors. Patent WO 2004099124, 2004. (g) Li, Y.; Zhang, X.; Chu, S.; Yu, K.; Guan, H. *Carbohydr. Res.* **2004**, *339*, 873. (h) Zhang, X. R.; Li, Y. X.; Chu, S. D.; Yu, K. Y.; Guan, H. S. *Chin. Chem. Lett.* **2003**, *14*, 1130. (i) Bradley, H.; Fitzpatrick, G.; Glass, W. K.; Kunz, H.; Murphy, P. V. *Org. Lett.* **2001**, *3*, 2629–2632.

(8) Kaïm, L. E.; Grimaud, L.; Oble, J. *Angew. Chem., Int. Ed.* **2005**, *117*, 8175–8178.

(9) (a) Kaïm, L. E.; Gizolme, M.; Grimaud, L.; Oble, J. *Org. Lett.* **2006**, *8*, 4019–4021. (b) Kaïm, L. E.; Gizolme, M.; Grimaud, L.; Oble, J. *J. Org. Chem.* **2007**, *72*, 4169–4180. (c) Kaïm, L. E.; Grimaud, L.; Oble, J. *J. Org. Chem.* **2007**, *72*, 5835–5838. (d) Kaïm, L. E.; Gizolme, M.; Grimaud, L. *Org. Lett.* **2006**, *8*, 5021–5023. (e) Kaïm, L. E.; Grimaud, L.; Vieu, E. *Org. Lett.* **2007**, *9*, 4171–4173. (f) Kaïm, L. E.; Gizolme, M.; Grimaud, L. *Org. Lett.* **2008**, *10*, 3417–3419. (g) Coffinier, D.; Laurent El Kaïm, L. E.; Grimaud, L. *Org. Lett.* **2009**, *11*, 995–997. (h) Kaïm, L. E.; Grimaud, L.; Oble, J.; Wagschal, S. *Tetrahedron. Lett.* **2009**, *50*, 1741–1743. (i) Barthelon, A.; Santos, A. D.; Kaïm, L. E.; Grimaud, L. *Tetrahedron. Lett.* **2008**, *49*, 3208–3211. (j) Kaïm, L. E.; Gizolme, M.; Grimaud, L. *Synlett* **2007**, 465. (k) Dai, W. M.; Li, H. M. *Tetrahedron* **2007**, *63*, 12866–12876.

(10) Subhas, C. P.; Benjamin, L. *Angew. Chem., Int. Ed.* **2008**, *47*, 3622–3625.

(11) Saegusa, T.; Ito, Y.; Tomita, S.; Kinoshita, H.; Takaishi, N. *Tetrahedron* **1971**, *27*, 27–31.

(12) (a) Mironov, M. A.; Mokrushin, V. S.; Maltsev, S. S. *Synlett* **2003**, 943–946. (b) Nair, V.; Rajeev, S.; Menon, R. S.; Beneesh, P. B.; Sreekumar, V.; Bindu, S. *Org. Lett.* **2004**, *6*, 767–769. (c) Maltsev, S. S.; Mironov, M. A.; Bakulev, V. A. *Mendeleev Commun.* **2006**, *16*, 201–202. (d) Mironov, M. A.; Ivantsova, M. N.; Mokrushin, V. S. *Synlett* **2006**, 615–617. (e) Paulvannan, K. *Tetrahedron Lett.* **1999**, *40*, 1851–1854.

(13) (a) Zhu, S. L.; Ji, S. J.; Su, X. M.; Liu, Y. *Tetrahedron Lett.* **2008**, *49*, 1777–1781. (b) Zhu, S. L.; Ji, S. J.; Liu, Y. *Tetrahedron Lett.* **2008**, *49*, 2578–2582. (c) Zhu, S. L.; Ji, S. J.; Zhang, Y. *Tetrahedron* **2007**, *63*, 9365–9372. (d) Wu, X. J.; Jiang, R.; Wu, B.; Su, X. M.; Xu, X. P.; Ji, S. J. *Adv. Synth. Catal.* **2009**, *351*, 3150–3156. (e) Zhao, K.; Xu, X. P.; Zhu, S. L.; Shi, D. Q.; Zhang, Y.; Ji, S. J. *Synthesis* **2009**, 2697–2708. (f) Wu, X. J.; Xu, X. P.; Su, X. M.; Ji, S. J. *Eur. J. Org. Chem.* **2009**, 4963–4970. (g) Shen, Z. L.; Ji, S. J.; Wang, S. Y.; Zeng, X. F. *Tetrahedron* **2005**, *61*, 10552. (h) Shen, Z. L.; Xu, X. P.; Ji, S. J. *J. Org. Chem.* **2010**, *75*, 1162–1167.

(14) (a) Sun, C.; Ji, S. J.; Liu, Y. *Tetrahedron Lett.* **2007**, *48*, 8987–8989. (b) Sun, C.; Ji, S. J.; Liu, Y. *J. Chin. Chem. Soc.* **2008**, *55*, 292–296.

(15) This reaction condition was referenced from a similar reaction for the syntheses of propionamides and succinimides, see: Mironov, M. A.; Ivantsova, M. N.; Mokrushin, V. S. *Synlett* **2006**, 615–617.

(16) (a) Pirrung, M. C.; Sarma, K. D. *J. Am. Chem. Soc.* **2004**, *126*, 444–445. (b) Mironov, M. A.; Ivantsova, M. N.; Tokareva, M. I.; Mokrushin, V. S. *Tetrahedron Lett.* **2005**, *46*, 3957–3960. (c) Breslow, R. *Acc. Chem. Res.* **1991**, *24*, 159–164. (d) Otto, S.; Engberts, J. B. F. N. *Org. Biomol. Chem.* **2003**, *1*, 2809–2820. (e) Chandrasekhar, J.; Shariffskul, S.; Jorgensen, W. L. *J. Phys. Chem. B* **2002**, *106*, 8078–8085. (f) Lubineau, A.; Augé, J. *Top. Curr. Chem.* **1999**, *206*, 20–39. (g) Lubineau, A.; Auge, J.; Queneau, Y. *Synthesis* **1994**, 742–760.

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