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Chemo-, Regio-, and Stereoselective Construction of Core Skeleton of Furo[2,3-*b*]pyrrole via Multicomponent Bicyclization Reaction

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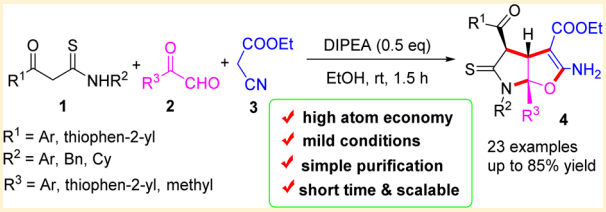
Supporting Information

ABSTRACT: An efficient and straightforward *N*-ethyldiisopropylamine (DIPEA)-catalyzed multicomponent bicyclization reaction was developed to synthesize furo[2,3-*b*]pyrrole derivatives from *β*-ketothioamides, glyoxals, and ethyl cyanacetate in EtOH at rt for 1.5 h. This was achieved via a sequential Knoevenagel condensation, Michael addition, and double cyclization, resulting in continuous formation of four chemical bonds (two C−C, two C−O, and one C−N bonds), two five-membered cycles, and three stereogenic centers in a one-pot operation.



INTRODUCTION

Furo[2,3-*b*]pyrrole core is an important privileged heterocyclic scaffold in numerous biologically active pharmacophores and natural products. For instance, compound **I** (madindoline A, MadA)[1] specifically inhibits the growth of interleukin-6 (IL-6), which can be used for the development of novel chemotherapeutic agents against multiple myeloma and cancer cachexia. Compounds **II** (aza/oxa naphthalene-8-ones)[2] show excellent antibacterial and antifungal activities. Compounds **III** (analogues of physostigmine: (−)-physovenol, (−)-physovenine, (−)-cymyl carbamate of psysovenol)[3] display distinct inhibition profiles toward HuAChE (human acetylcholinesterase) enzymes, which are considered for use as drugs for Alzheimer's disease (Figure 1). To the best of our knowledge, very few molecules of this sort have been synthesized, and there is no general strategy to prepare them.

Multicomponent reactions involving bicyclization (MBRs) have emerged as a very useful and sustainable platform in the synthesis of heterocyclic scaffolds, which provide unmatched opportunities for the expeditious increase in complexity of synthetic outcomes by simultaneous formation of two or more bonds.[4] MBRs feature high annulation efficiency, environmental friendliness, and ease of operation.[5] Thus, developing a new, environmentally benign MBR has been recognized as one of the most important topics of green chemistry.

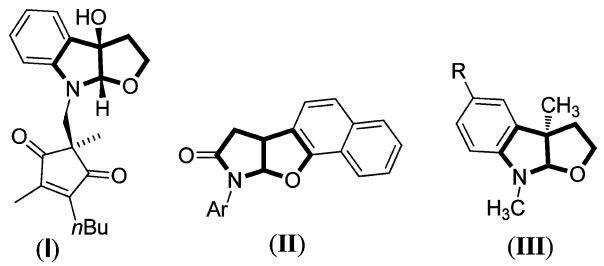


Figure 1. Representative examples of furo[2,3-*b*]pyrroles with bioactivities.

β-Ketothioamides (KTAs)[6] have proven to be fascinating and versatile synthons in the construction of heterocyclic systems. Reactions of KTAs with a variety of biselectrophilic groups have so far been applied to make five- and six-membered and fused heterocycles during the past years.[7] Recently, the groups of Singh[8] and Deng[9] reported two methods for the synthesis of pyrroles and thiophenes, respectively. Nandi[10] also developed a tandem reaction for synthesis of pyrrole and furan derivatives using the KTAs as synthons. However, the reaction of KTAs with biselectrophilic reagents for the synthesis of furo[2,3-*b*]pyrrole has not been explored. As part of our ongoing research interest in multicomponent synthesis of heterocycles by using KTAs,[11] we were interested in the straightforward construction of furo[2,3-*b*]pyrroles via MBR of *β*-aroylthioamides, glyoxals, and ethyl cyanacetate catalyzed by DIPEA in EtOH at room temperature for 1.5 h.

RESULTS AND DISCUSSION

Our study commenced by optimizing the reaction conditions with *β*-benzoylthioamide (**1a**), phenylglyoxal (**2a**), and ethyl cyanacetate (**3**) as model substrates (Table 1). The model reaction gave a complex mixture in EtOH at 40 °C for 6 h (Table 1, entry 1). When 0.5 equiv of DIPEA was added into the reaction system, the desired product **4a** was obtained in 64% yield (entry 2). Encouraged by the result, other bases such as Et_3N, DABCO (1,4-diazabicyclo[2.2.2]octane), DBU (1,8-diazabicyclo[5.4.0] undec-7-ene), DMAP (4-dimethylaminopyridine), pyridine, piperidine, *t*-BuOK, and K_2CO_3 were also screened, but no higher yield was obtained (entries 3−10).

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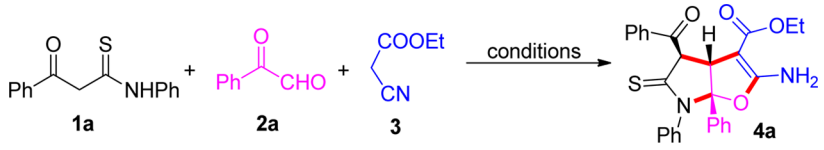
Table 1. Optimization of Reaction Conditions[a]



entry	catalyst	solvent	temp (°C)	time (h)	yield[b] (%)
1		C_2H_5OH	40	6	complex
2	DIPEA (0.5)	C_2H_5OH	40	6	64
3	Et_3N (0.5)	C_2H_5OH	40	6	10
4	DABCO (0.5)	C_2H_5OH	40	6	13
5	DBU (0.5)	C_2H_5OH	40	6	15
6	DMAP (0.5)	C_2H_5OH	40	6	26
7	pyridine (0.5)	C_2H_5OH	40	6	10
8	piperidine (0.5)	C_2H_5OH	40	6	55
9	*t*-BuOK (0.5)	C_2H_5OH	40	6	45
10	K_2CO_3 (0.5)	C_2H_5OH	40	6	complex
11	DIPEA (0.5)	C_2H_5OH	40	2	65
12	DIPEA (0.5)	C_2H_5OH	40	1.5	74
13	DIPEA (0.5)	C_2H_5OH	40	1	60
14	DIPEA (0.25)	C_2H_5OH	40	1.5	64
15	DIPEA (0.75)	C_2H_5OH	40	1.5	73
16	DIPEA (0.5)	C_2H_5OH	60	1.5	59
17	**DIPEA (0.5)**	**C_2H_5OH**	**rt**	**1.5**	**79**
18	DIPEA (0.5)	C_2H_5OH	0	1.5	45
19	DIPEA (0.5)	CH_3OH	rt	1.5	61
20	DIPEA (0.5)	TFE[c]	rt	1.5	21
21	DIPEA (0.5)	CH_3CN	rt	1.5	53
22	DIPEA (0.5)	CH_2Cl_2	rt	1.5	42
23	DIPEA (0.5)	C_2H_5OH	rt	1.5	68[d]

[a]Reaction conditions: **1a** (0.6 mmol), **2a** (0.6 mmol), **3** (0.6 mmol), solvent (2 mL). [b]Isolated yield. [c]TFE = trifluoroethanol. [d]1 mL of C_2H_5OH.

However, when the reaction time was reduced to 1.5 h, a higher yield of **4a** was obtained (entries 11−13). Next, the amount of DIPEA was investigated. It was found that reducing the amount of DIPEA could decrease the yield of **4a** to 64% (entry 14), whereas increasing the amount of DIPEA did not further improve the yield of **4a** (entry 15). Additionally, the effect of temperature on the reaction was also evaluated, and the results suggested that room temperature was the best choice, affording 79% yield of **4a** (entries 16−18). Different solvents such as CH_3OH, TFE, CH_3CN, and CH_2Cl_2 were examined, but they did not give satisfactory results (entries 19−22). Finally, decreasing the amount of solvent did not improve the yield of **4a** (entry 23). Consequently, the optimal reaction conditions were established by employing **1a**, **2a**, and **3** in a mole ratio of 1:1:1 and DIPEA (0.5 equiv) as catalyst in EtOH (c = 0.3 M) at room temperature for 1.5 h.

With the optimal conditions in hand, the substrate scope of KTAs (**1**) and glyoxals (**2**) was investigated (Table 2). As can be seen from Table 2, a wide range of KTAs (**1**) and glyoxals (**2**) were well tolerated. In most cases, the reactions proceeded smoothly to afford the corresponding furo[2,3-*b*]pyrroles (**4**) in moderate to good yields. For R^1 of KTAs (**1**), both aromatic substituents bearing electron-donating or electron-withdrawing groups and heteroaryl group such as thiophen-2-yl could transform smoothly to desired furo[2,3-*b*]pyrroles (**4a**−**4i**) in good yields, but CF_3 gave a relatively low 50% yield (**4b**). Unfortunately, however, when R^1 was an alkyl group such as methyl, no product was afforded, which may be subjected to the weak nucleophilic ability of methylene (**4j**). For R^2 of KTAs (**1**), various aromatic substituents bearing *m*- or *p*-electron-donating or electron-withdrawing groups could be tolerated well, except that *o*-Cl did not afford the desired product, which may be due to its steric hindrance (**4k**−**4r**). Delightedly, when R^2 was a benzyl (**4s**) or cyclohexyl (**4t**) group, 78 and 75% yields were provided, respectively. For substrates **2**, arylglyoxals bearing *p*-Cl (**4u**), *m*-Cl (**4v**), and *p*-methoxyl (**4x**), except for *o*-Cl (**4w**), and even heteroaryl glyoxal such as thiophen-2-yl (**4y**) and aliphatic glyoxal such as methyl (**4z**) could give smoothly furo[2,3-*b*]pyrroles in moderate to good yields. Unfortunately, however, *β*-ketothioamide of primary amine did not provide the desired product **4aa**.

Other substrates **3** such as malononitrile, 2-cyano-*N*-phenylacetamide, and phenyl acetonitrile were also explored under the standard conditions; unfortunately, the first two did not provide the desired furo[2,3-*b*]pyrroles, and the latter did not react.

The structures of all new compounds **4** were identified by their IR, ^{1}H NMR, ^{13}C NMR, and HRMS spectra and were unequivocally confirmed by X-ray diffraction analysis of monocrystal of **4a** (Figure S1 in the Supporting Information).

It is noteworthy that almost all products only need washing with EtOH rather than column chromatography or recrystallization. This easy purification makes this methodology facile, practical, and rapid to execute.

To demonstrate the practical application of the present protocol, a gram-scale experiment was carried out for the reaction of **1a** (10 mmol), **2a** (10 mmol), and **3** (10 mmol) under the optimal reaction conditions (Scheme 1). The coupling product **4a** was obtained in 71% yield. This result showed that the present method could be easily adopted for a large-scale preparation.

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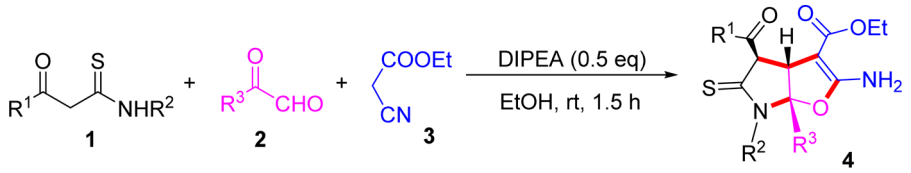
Table 2. Substrate Scope for the Synthesis of 4[a,b]



1 2 3 4

4a 79%	**4b** 50%	**4c** 67%	**4d** 63%
4e 61%	**4f** 64%	**4g** 79%	**4h** 81%
4i 78%	**4j** 0%	**4k** 46%	**4l** 61%
4m 64%	**4n** 62%	**4o** 0%.	**4p** 58%
4q 80%	**4r** 85%	**4s** 78%	**4t** 75%
4u 61%	**4v** 59%	**4w** 0%	**4x** 74%
4y 52%	**4z** 44%[c]	**4aa** 0%	

[a]Reaction conditions: **1** (0.6 mmol), **2** (0.6 mmol), **3** (0.6 mmol), solvent (2 mL). [b]Isolated yield. [c]Isolated by silica gel column chromatography.

To further demonstrate the application value of this tandem reaction, the following transformations using **4a** as a substrate were investigated (Scheme 2). When **4a** was treated with Pd/C and H_2 (1 atm) in AcOH at 35 °C for 14 h, the thiocarbonyl group was reduced to SH and the furan ring opened simultaneously to result in the formation of disulfide-tethered

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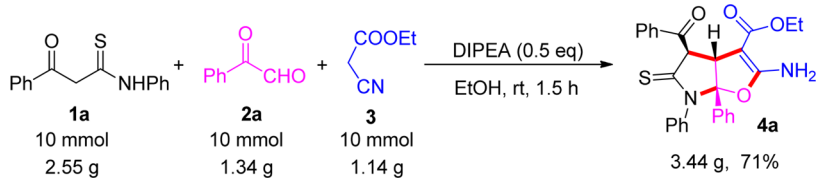
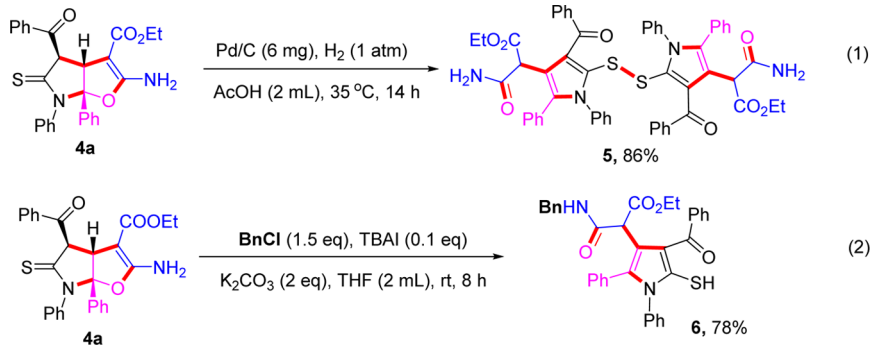
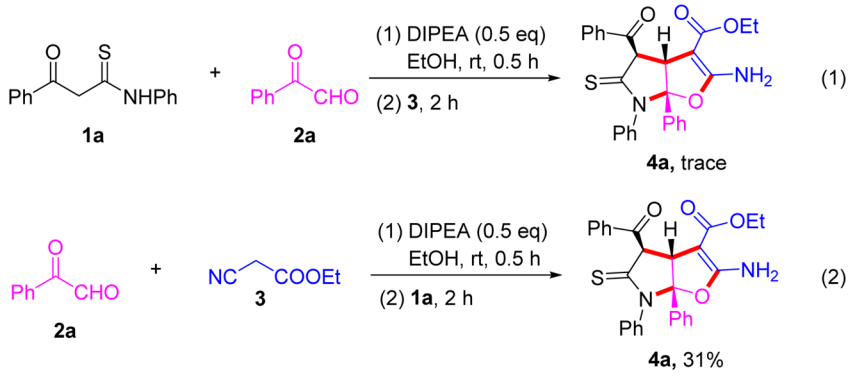
Scheme 1. Gram-Scale Synthesis of 4a



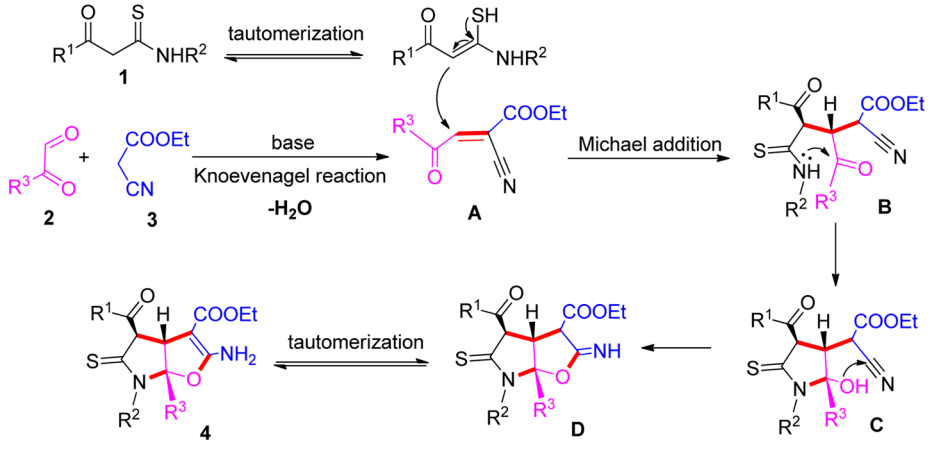
Scheme 2. Transformation Reaction Study of 4a



Scheme 3. Control Experiments



Scheme 4. Plausible Mechanism for the Formation of 4



pyrroles **5** in 86% yield (Scheme 2 (eq 1)). When a mixture of **4a** and BnCl (1.5 equiv) was stirred in THF at room temperature for 8 h, mercaptopyrrole compound **6** was formed in 78% yield. Notably, the nucleophilic substitution reaction did not occur on the S atom but on the amino group, and the furan ring opened simultaneously, then the thiocarbonyl group enolized to SH (Scheme 2 (eq 2)).

In order to gain insight into the mechanism, we carried out two control experiments (Scheme 3). First, **1a** reacted with **2a** under the standard conditions for 0.5 h, and then compound **3** was added into the reaction system for 2 h. TLC (PE/EA = 4:1) showed the reaction system was messy, and only trace product **4a** was observed (Scheme 3 (eq 1)). Next, **2a** was reacted with **3** under the same conditions for 0.5 h, and then compound **1a** was

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added. Another 2 h later, 31% yield of **4a** was obtained (Scheme 3 (eq 2)). These two results suggested that in the MBR glyoxals **2** first react with ethyl cyanacetate **3**, and successively, KTAs **1** take part in the reaction to afford products **4**.

On the basis of the above experimental results, we proposed a plausible reaction mechanism (Scheme 4). In the presence of a base, intermediates **A** are formed by the Knoevenagel reaction of glyoxals **2** with ethyl cyanacetate **3**. Meanwhile, KTAs **1** undergo a rapid keto−enol tautomerization and then a Michael addition to intermediates **A** occurred, resulting in the adducts **B**. Intermediates **B** undergo a N-cyclization to give **C**. Successively, intermediates **C** create an O-cyclization reaction[12] to provide **D**. Finally, the desired products **4** are formed via tautomerization of **D**.

CONCLUSION

In summary, we have developed a chemo-, regio-, and stereoselective three-component reaction of furo[2,3-*b*]pyrroles derivatives from KTAs, glyoxals, and ethyl cyanacetate through Knoevenagel condensation, Michael addition, and double cyclization sequence catalyzed by DIPEA at room temperature for 1.5 h. Four chemical bonds (two C−C, one C−O, and one C−N bonds), two five-membered cycles, and three stereogenic centers were formed in a one-pot operation with only losing a molecule of H_2O. Undoubtedly, this domino synthetic strategy provides a convenient and green way to construct furo[2,3-*b*]pyrrole derivatives with high atom-economy and high bond formation efficiency. This environmentally benign strategy is expected to become a useful alternative for the synthesis of furo[2,3-*b*]pyrrole derivatives.

EXPERIMENTAL SECTION

General Experimental Methods. All reagents and solvents were obtained from commercial suppliers and used without further purification unless otherwise specified. All reagents were weighed and handled in air at room temperature. Melting points were recorded on a microscopic melting apparatus and uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded at 500 and 125 MHz in $CDCl_3$. Chemical shifts are reported in δ (ppm) relative to TMS. IR spectra were recorded on a FT-IR spectrometer, and only major peaks are reported in cm^{-1}. HRMS spectra were performed on three different spectrometers with an ESI source. The X-ray single-crystal diffraction was performed on a CCD area detector. The substrates **1** were prepared according to reported procedure.[13]

General Procedure for the Synthesis of Compounds 4 (e.g., 4a). To a stirred solution of **1a** (0.6 mmol, 153.0 mg), **2a** (0.6 mmol, 80.4 mg), and **3** (0.6 mmol, 67.8 mg) in EtOH (2 mL) was added DIPEA (38.7 mg, 0.3 mmol), and then the reaction mixture was stirred at room temperature for 1.5 h. After completion of the reaction as monitored by TLC (petroleum ether/EtOAc, 4:1, v/v), amounts of solid were precipitated. The reaction mixture was filtered, washed with EtOH, and subsequently dried to give the pure product **4a**.

*Ethyl-2-amino-4-benzoyl-6,6a-diphenyl-5-thioxo-3a,5,6,6a-tetrahydro-4H-furo[2,3-b]pyrrole-3-carboxylate (**4a**):* Isolated yield 229 mg (79%); white solid; mp 192−194 °C; IR (KBr) ν 3462, 3348, 3063, 2973, 1690, 1678, 1633, 1595, 1579, 1448, 1202, 1114, 759, 709; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.71 (br, 3H), 3.90 (br, 2H), 4.43 (d, J = 3.35 Hz, 1H), 5.40 (d, J = 2.90 Hz, 1H), 5.86 (s, 2H), 7.11−7.13 (m, 2H), 7.23−7.25 (m, 1H), 7.27−7.32 (m, 3H), 7.35 (t, J = 7.50 Hz, 2H), 7.54 (t, J = 7.68 Hz, 2H), 7.63 (t, J = 7.32 Hz, 1H), 7.75 (d, J = 7.45 Hz, 2H), 8.22 (d, J = 7.60 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.8, 54.0, 59.1, 68.4, 77.9, 111.0, 126.4, 128.4, 128.6, 128.7, 128.9, 129.2, 130.1, 133.6, 136.8, 137.1, 137.5, 164.1, 166.5, 197.4, 202.9; HRMS (ESI-TOF, [M + H]$^+$) calcd for $C_{28}H_{25}N_2O_4S$, 485.1530; found, 485.1545.

*Ethyl-2-amino-6,6a-diphenyl-5-thioxo-4-(4-(trifluoromethyl)-benzoyl)-3a,5,6,6a-tetrahydro-4H-furo[2,3-b]pyrrole-3-carboxylate (**4b**):* Isolated yield 167 mg (50%); white solid; mp 175−177 °C; IR (KBr) ν 3410, 3296, 3061, 2985, 2949, 1690, 1636, 1589, 1510, 1456, 1120, 1031, 853, 764, 696; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.73 (br, 3H), 3.92 (br, 2H), 4.46 (d, J = 3.05 Hz, 1H), 5.38 (s, 1H), 5.88 (s, 2H), 7.09−7.11 (m, 2H), 7.27−7.30 (m, 3H), 7.33 (d, J = 7.10 Hz, 1H), 7.37 (t, J = 7.42 Hz, 2H), 7.72 (d, J = 7.55 Hz, 2H), 7.81 (d, J = 8.10 Hz, 2H), 8.34 (d, J = 7.95 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.0, 53.9, 59.2, 68.8, 77.8, 111.0, 123.6 (q, $^1J_{C-F}$ = 273.4 Hz), 125.6, 126.4, 128.5, 128.7, 128.8, 129.0, 129.4, 130.4, 134.8 (q, $^2J_{C-F}$ = 32.8 Hz), 137.0, 137.4, 139.6, 164.2, 166.3, 196.4, 201.9; HRMS (ESI-TOF, [M + H]$^+$) calcd for $C_{29}H_{24}F_3N_2O_4S$, 553.14034; found, 553.13983.

*Ethyl-2-amino-4-(4-fluorobenzoyl)-6,6a-diphenyl-5-thioxo-3a,5,6,6a-tetrahydro-4H-furo[2,3-b]pyrrole-3-carboxylate (**4c**):* Isolated yield 202 mg (67%); white solid; mp 189−191 °C; IR (KBr) ν 3444, 3339, 3071, 2978, 1680, 1648, 1599, 1505, 1445, 1215, 1109, 850, 757, 697; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.76 (br, 3H), 3.93 (br, 2H), 4.44 (d, J = 3.15 Hz, 1H), 5.34 (s, 1H), 5.87 (s, 2H), 7.10−7.11 (m, 2H), 7.21 (t, J = 8.48 Hz, 3H), 7.26−7.32 (m, 3H), 7.35 (t, J = 7.35 Hz, 2H), 7.73 (d, J = 7.50 Hz, 2H), 8.26 (dd, J_1 = 7.85 Hz, J_2 = 5.50 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.9, 53.9, 59.1, 68.4, 77.8, 110.9, 115.7 (d, $^2J_{C-F}$ = 21.9 Hz), 126.4, 128.5, 128.7, 128.9, 129.3, 132.9 (d, $^3J_{C-F}$ = 8.0 Hz), 133.1, 137.1, 137.4, 164.2, 166.2 (d, $^1J_{C-F}$ = 256.3 Hz), 166.4, 195.6, 202.5; HRMS (ESI-TOF, [M + H]$^+$) calcd for $C_{28}H_{24}FN_2O_4S$, 503.1435; found, 503.1449.

*Ethyl-2-amino-4-(4-chlorobenzoyl)-6,6a-diphenyl-5-thioxo-3a,5,6,6a-tetrahydro-4H-furo[2,3-b]pyrrole-3-carboxylate (**4d**):* Isolated yield 196 mg (63%); white solid; mp 172−174 °C; IR (KBr) ν 3409, 3291, 3055, 2982, 1691, 1635, 1588, 1494, 1447, 1113, 1030, 844, 764, 695; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.78 (br, 3H), 3.94 (br, 2H), 4.44 (d, J = 3.20 Hz, 1H), 5.33 (s, 1H), 5.87 (s, 2H), 7.09−7.11 (m, 2H), 7.24−7.25 (m, 1H), 7.27−7.32 (m, 3H), 7.35 (t, J = 7.40 Hz, 2H), 7.52 (d, J = 8.45 Hz, 2H), 7.72 (d, J = 7.50 Hz, 2H), 8.17 (d, J = 8.35 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.1, 53.8, 59.2, 68.5, 77.9, 111.0, 126.5, 128.5, 128.8, 128.9, 129.3, 131.5, 135.1, 137.1, 137.5, 140.3, 164.1, 166.3, 196.0, 202.3; HRMS (ESI-TOF, [M + H]$^+$) calcd for $C_{28}H_{24}ClN_2O_4S$, 519.1140; found, 519.1148.

*Ethyl-2-amino-4-(3-chlorobenzoyl)-6,6a-diphenyl-5-thioxo-3a,5,6,6a-tetrahydro-4H-furo[2,3-b]pyrrole-3-carboxylate (**4e**):* Isolated yield 190 mg (61%); white solid; mp 171−173 °C; IR (KBr) ν 3410, 3292, 3066, 2982, 2938, 1691, 1635, 1588, 1494, 1448, 1113, 1030, 845, 764, 695; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.77 (br, 3H), 3.94 (br, 2H), 4.44 (d, J = 3.00 Hz, 1H), 5.32 (s, 1H), 5.87 (s, 2H), 7.09−7.10 (m, 2H), 7.23−7.25 (m, 1H), 7.27−7.32 (m, 3H), 7.35 (t, J = 7.40 Hz, 2H), 7.51 (d, J = 8.35 Hz, 2H), 7.72 (d, J = 7.50 Hz, 2H), 8.16 (d, J = 8.25 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.0, 53.8, 59.2, 68.4, 77.8, 110.9, 126.4, 128.5, 128.7, 128.9, 129.3, 131.5, 135.1, 137.0, 137.4, 140.3, 164.1, 166.4, 196.0, 202.3; HRMS (ESI-TOF, [M + H]$^+$) calcd for $C_{28}H_{24}ClN_2O_4S$, 519.1140; found, 519.1142.

*Ethyl-2-amino-4-(4-bromobenzoyl)-6,6a-diphenyl-5-thioxo-3a,5,6,6a-tetrahydro-4H-furo[2,3-b]pyrrole-3-carboxylate (**4f**):* Isolated yield 216 mg (64%); white solid; mp 176−178 °C; IR (KBr) ν 3410, 3293, 3055, 2983, 2927, 1691, 1635, 1583, 1496, 1429, 1110, 1031, 843, 763, 694; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.78 (br, 3H), 3.94 (br, 2H), 4.44 (d, J = 3.25 Hz, 1H), 5.33 (s, 1H), 5.88 (s, 2H), 7.09−7.10 (m, 2H), 7.24−7.25 (m, 1H), 7.27−7.32 (m, 3H), 7.35 (t, J = 7.43 Hz, 2H), 7.69 (d, J = 8.40 Hz, 2H), 7.72 (d, J = 7.50 Hz, 2H), 8.09 (d, J = 8.35 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.1, 53.8, 59.2, 68.4, 77.9, 111.0, 126.4, 128.5, 128.8, 128.9, 129.1, 129.3, 131.6, 131.9, 135.6, 137.1, 137.5, 164.1, 166.3, 196.2, 202.3; HRMS (ESI-TOF, [M + H]$^+$) calcd for $C_{28}H_{24}BrN_2O_4S$, 563.0635; found, 563.0640.

*Ethyl-2-amino-4-(4-methylbenzoyl)-6,6a-diphenyl-5-thioxo-3a,5,6,6a-tetrahydro-4H-furo[2,3-b]pyrrole-3-carboxylate (**4g**):* Isolated yield 236 mg (79%); white solid; mp 174−176 °C; IR (KBr) ν 3385, 3248, 3060, 2973, 2931, 1697, 1674, 1632, 1606, 1494, 1456, 1111, 1027, 849, 758, 698; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.76 (br, 3H), 2.44 (s, 3H), 3.93 (br, 2H), 4.44 (d, J = 3.30 Hz, 1H), 5.38 (d, J = 2.75 Hz, 1H), 5.86 (s, 2H), 7.10−7.12 (m, 2H), 7.23−7.24 (m, 1H), 7.26−7.28 (m, 2H), 7.30 (d, J = 7.20 Hz, 1H), 7.32−7.36 (m, 4H), 7.75 (d, J =

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7.50 Hz, 2H), 8.11 (d, J = 8.05 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.9, 21.7, 53.9, 59.1, 68.3, 77.9, 111.0, 126.5, 128.4, 128.7, 128.8, 129.2, 129.3, 130.2, 134.2, 137.2, 137.5, 144.7, 164.1, 166.5, 196.8, 203.0; HRMS (ESI-TOF, $[M + H]^+$) calcd for $C_{29}H_{27}N_2O_4S$, 499.1686; found, 499.1698.

*Ethyl-2-amino-4-(4-methoxybenzoyl)-6,6a-diphenyl-5-thioxo-3a,5,6,6a-tetrahydro-4H-furo[2,3-b]pyrrole-3-carboxylate (**4h**):* Isolated yield 250 mg (81%); white solid; mp 194−196 °C; IR (KBr) ν 3423, 3305, 3059, 2984, 2928, 1698, 1671, 1637, 1599, 1571, 1509, 1456, 1114, 1026, 845, 761, 704; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.78 (br, 3H), 3.90 (s, 3H), 3.94 (br, 2H), 4.45 (d, J = 3.10 Hz, 1H), 5.34 (d, J = 2.20 Hz, 1H), 5.87 (s, 2H), 7.01 (d, J = 8.70 Hz, 2H), 7.11−7.12 (m, 2H), 7.23−7.24 (m, 1H), 7.26−7.30 (m, 3H), 7.34 (t, J = 7.45 Hz, 2H), 7.76 (d, J = 7.55 Hz, 2H), 8.20 (d, J = 8.65 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.0, 53.8, 55.5, 59.1, 68.2, 78.0, 111.0, 113.8, 126.5, 128.4, 128.6, 128.8, 129.2, 129.7, 132.5, 137.3, 137.6, 164.1, 166.5, 195.5, 203.2; HRMS (ESI-TOF, $[M + H]^+$) calcd for $C_{29}H_{27}N_2O_5S$, 515.1635; found, 515.1648.

*Ethyl-2-amino-6,6a-diphenyl-4-(thiophene-2-carbonyl)-5-thioxo-3a,5,6,6a-tetrahydro-4H-furo[2,3-b]pyrrole-3-carboxylate (**4i**):* Isolated yield 230 mg (78%); white solid; mp 192−194 °C; IR (KBr) ν 3461, 3348, 3077, 2975, 2930, 1690, 1662, 1632, 1504, 1492, 1450, 1116, 1023, 759, 694; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.84 (br, 3H), 3.98 (br, 2H), 4.47 (d, J = 2.80 Hz, 1H), 5.14 (s, 1H), 5.87 (s, 2H), 7.10−7.11 (m, 2H), 7.23−7.25 (m, 2H), 7.27−7.30 (m, 3H), 7.34 (t, J = 7.38 Hz, 2H), 7.73 (d, J = 7.45 Hz, 2H), 7.78 (d, J = 4.65 Hz, 1H), 8.02 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.9, 53.6, 59.1, 70.2, 77.8, 110.9, 126.4, 128.4, 128.5, 128.7, 128.9, 129.2, 135.5, 135.8, 137.2, 137.4, 143.9, 164.0, 166.4, 189.3, 202.2; HRMS (ESI-TOF, $[M + H]^+$) calcd for $C_{26}H_{23}N_2O_4S_2$, 491.10938; found, 491.10895.

*Ethyl-2-amino-4-benzoyl-6a-phenyl-5-thioxo-6-(4-(trifluoromethyl)phenyl)-3a,5,6,6a-tetrahydro-4H-furo[2,3-b]-pyrrole-3-carboxylate (**4k**):* Isolated yield 154 mg (46%); white solid; mp 194−196 °C; IR (KBr) ν 3420, 3312, 3067, 2977, 2902, 1690, 1655, 1617, 1519, 1449, 1113, 1021, 751, 712; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.73 (br, 3H), 3.92 (br, 2H), 4.44 (d, J = 3.10 Hz, 1H), 5.40 (d, J = 2.44 Hz, 1H), 5.87 (s, 2H), 7.29 (d, J = 8.25 Hz, 2H), 7.33 (d, J = 7.10 Hz, 1H), 7.38 (t, J = 7.38 Hz, 2H), 7.52−7.56 (m, 4H), 7.64 (t, J = 7.20 Hz, 1H), 7.74 (d, J = 7.45 Hz, 2H), 8.21 (d, J = 7.55 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.9, 54.3, 59.2, 68.6, 78.0, 111.0, 123.6 (q, $^1J_{C-F}$ = 272.4 Hz), 126.1, 126.4, 128.6, 128.7, 129.4, 129.5, 130.1, 130.7 (q, $^2J_{C-F}$ = 31.7 Hz), 133.8, 136.7, 137.2, 140.4, 163.9, 166.3, 197.2, 203.2; HRMS (ESI-TOF, $[M + H]^+$) calcd for $C_{29}H_{24}F_3N_2O_4S$, 553.14034; found, 553.13983.

*Ethyl-2-amino-4-benzoyl-6-(4-fluorophenyl)-6a-phenyl-5-thioxo-3a,5,6,6a-tetrahydro-4H-furo[2,3-b]pyrrole-3-carboxylate (**4l**):* Isolated yield 184 mg (61%); white solid; mp 175−177 °C; IR (KBr) ν 3426, 3249, 3069, 2979, 2930, 1679, 1636, 1597, 1581, 1508, 1449, 1108, 1023, 776, 701; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.70 (br, 3H), 3.90 (br, 2H), 4.43 (d, J = 3.30 Hz, 1H), 5.40 (d, J = 2.10 Hz, 1H), 5.87 (s, 2H), 6.95 (t, J = 8.50 Hz, 2H), 7.08−7.11 (m, 2H), 7.31−7.33 (m, 1H), 7.37 (t, J = 7.42 Hz, 2H), 7.54 (t, J = 7.62 Hz, 2H), 7.64 (t, J = 7.25 Hz, 1H), 7.74 (d, J = 7.55 Hz, 2H), 8.21 (d, J = 7.70 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.8, 53.9, 59.2, 68.3, 77.9, 110.9, 116.0 (d, $^2J_{C-F}$ = 21.7 Hz), 126.4, 128.6, 129.4, 130.0, 130.6, 132.9, 133.7, 136.6, 137.3, 162.2 (d, $^1J_{C-F}$ = 249.7 Hz), 164.0, 166.4, 197.3, 203.1; HRMS (ESI-TOF, $[M + H]^+$) calcd for $C_{28}H_{24}FN_2O_4S$, 503.1435; found, 503.1452.

*Ethyl-2-amino-4-benzoyl-6-(4-chlorophenyl)-6a-phenyl-5-thioxo-3a,5,6,6a-tetrahydro-4H-furo[2,3-b]pyrrole-3-carboxylate (**4m**):* Isolated yield 199 mg (64%); white solid; mp 168−170 °C; IR (KBr) ν 3423, 3244, 3068, 2979, 1679, 1636, 1597, 1580, 1492, 1449, 1107, 1018, 750, 700; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.70 (br, 3H), 3.90 (br, 2H), 4.42 (d, J = 3.25 Hz, 1H), 5.38 (d, J = 2.30 Hz, 1H), 5.86 (s, 2H), 7.08 (d, J = 8.60 Hz, 2H), 7.24 (d, J = 8.55 Hz, 2H), 7.31−7.34 (m, 1H), 7.37 (t, J = 7.45 Hz, 2H), 7.54 (t, J = 7.62 Hz, 2H), 7.64 (t, J = 7.30 Hz, 1H), 7.73 (d, J = 7.60 Hz, 2H), 8.21 (d, J = 7.65 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.8, 54.0, 59.2, 68.4, 77.9, 110.9, 126.4, 128.6, 129.2, 129.4, 130.0, 133.7, 134.7, 135.6, 136.6, 137.3, 164.0, 166.4, 197.2, 203.0; HRMS (ESI-TOF, $[M + H]^+$) calcd for $C_{28}H_{24}ClN_2O_4S$, 519.1140; found, 519.1156.

*Ethyl-2-amino-4-benzoyl-6-(3-chlorophenyl)-6a-phenyl-5-thioxo-3a,5,6,6a-tetrahydro-4H-furo[2,3-b]pyrrole-3-carboxylate (**4n**):* Isolated yield 193 mg (62%); white solid; mp 181−183 °C; IR (KBr) ν 3393, 3273, 3065, 2976, 2934, 1695, 1674, 1631, 1590, 1578, 1496, 1446, 1117, 1028, 775, 738, 699, 680; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.71 (br, 3H), 3.90 (br, 2H), 4.42 (d, J = 3.30 Hz, 1H), 5.38 (s, 1H), 5.90 (s, 2H), 7.01 (d, J = 7.85 Hz, 1H), 7.17−7.24 (m, 3H), 7.32 (t, J = 7.20 Hz, 1H), 7.38 (t, J = 7.45 Hz, 2H), 7.54 (t, J = 7.58 Hz, 2H), 7.64 (t, J = 7.22 Hz, 1H), 7.74 (d, J = 7.50 Hz, 2H), 8.21 (d, J = 7.55 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.8, 54.1, 59.2, 68.4, 77.8, 110.8, 126.4, 127.3, 128.6, 128.8, 129.0, 129.4, 129.8, 130.0, 133.7, 134.4, 136.6, 137.1, 138.2, 164.0, 166.4, 197.2, 203.0; HRMS (ESI-TOF, $[M + H]^+$) calcd for $C_{28}H_{24}ClN_2O_4S$, 519.1140; found, 519.1152.

*Ethyl-2-amino-4-benzoyl-6-(4-bromophenyl)-6a-phenyl-5-thioxo-3a,5,6,6a-tetrahydro-4H-furo[2,3-b]pyrrole-3-carboxylate (**4p**):* Isolated yield 196 mg (58%); white solid; mp 179−181 °C; IR (KBr) ν 3420, 3256, 3068, 2975, 1678, 1637, 1596, 1580, 1489, 1448, 1110, 1015, 748, 695; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.70 (br, 3H), 3.90 (brs, 2H), 4.41 (d, J = 3.35 Hz, 1H), 5.39 (d, J = 2.75 Hz, 1H), 5.87 (s, 2H), 7.01 (d, J = 8.60 Hz, 2H), 7.32 (t, J = 7.25 Hz, 1H), 7.36−7.40 (m, 4H), 7.54 (t, J = 7.65 Hz, 2H), 7.64 (t, J = 7.30 Hz, 1H), 7.73 (d, J = 7.55 Hz, 2H), 8.20 (d, J = 7.70 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.8, 54.1, 59.2, 68.4, 77.8, 110.8, 122.9, 126.4, 128.6, 129.4, 130.1, 130.4, 132.2, 133.8, 136.1, 136.6, 137.2, 164.0, 166.4, 197.2, 203.0; HRMS (ESI-TOF, $[M + H]^+$) calcd for $C_{28}H_{24}BrN_2O_4S$, 563.0635; found, 563.0645.

*Ethyl-2-amino-4-benzoyl-6a-phenyl-5-thioxo-6-(p-tolyl)-3a,5,6,6a-tetrahydro-4H-furo[2,3-b]pyrrole-3-carboxylate (**4q**):* Isolated yield 239 mg (80%); white solid; mp 198−200 °C; IR (KBr) ν 3394, 3281, 3065, 2975, 2925, 1683, 1652, 1597, 1493, 1479, 1449, 1110, 1023, 834, 749, 702; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.71 (br, 3H), 2.26 (s, 3H), 3.90 (br, 2H), 4.41 (d, J = 3.30 Hz, 1H), 5.39 (d, J = 2.80 Hz, 1H), 5.86 (s, 2H), 6.99 (d, J = 8.20 Hz, 2H), 7.06 (d, J = 8.20 Hz, 2H), 7.26−7.32 (m, 1H), 7.36 (t, J = 7.50 Hz, 2H), 7.53 (t, J = 7.60 Hz, 2H), 7.62 (m, J = 7.30 Hz, 1H), 7.75 (d, J = 7.60 Hz, 2H), 8.22 (d, J = 7.70 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.8, 21.2, 53.9, 59.1, 68.4, 77.9, 111.0, 126.5, 128.4, 128.5, 129.2, 129.6, 130.1, 133.6, 134.4, 136.8, 137.6, 138.7, 164.2, 166.5, 197.4, 202.9; HRMS (ESI-TOF, $[M + H]^+$) calcd for $C_{29}H_{27}N_2O_4S$, 499.1686; found, 499.1691.

*Ethyl-2-amino-4-benzoyl-6-(4-methoxyphenyl)-6a-phenyl-5-thioxo-3a,5,6,6a-tetrahydro-4H-furo[2,3-b]pyrrole-3-carboxylate (**4r**):* Isolated yield 262 mg (85%); white solid; mp 174−176 °C; IR (KBr) ν 3421, 3235, 3063, 2971, 2840, 1682, 1636, 1581, 1511, 1449, 1106, 1033, 837, 742, 694; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.70 (br, 3H), 3.72 (s, 3H), 3.89 (br, 2H), 4.40 (d, J = 3.30 Hz, 1H), 5.39 (d, J = 2.35 Hz, 1H), 5.87 (s, 2H), 6.77 (d, J = 8.85 Hz, 2H), 7.02 (d, J = 8.75 Hz, 2H), 7.31 (t, J = 7.20 Hz, 1H), 7.37 (t, J = 7.48 Hz, 2H), 7.54 (t, J = 7.63 Hz, 2H), 7.63 (t, J = 7.28 Hz, 1H), 7.74 (d, J = 7.60 Hz, 2H), 8.22 (d, J = 7.65 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.8, 53.8, 55.2, 59.1, 68.3, 77.9, 111.0, 114.2, 126.4, 128.5, 128.6, 129.2, 129.6, 129.8, 130.0, 133.6, 136.7, 137.6, 159.3, 164.1, 166.5, 197.4, 203.0; HRMS (ESI-TOF, $[M + H]^+$) calcd for $C_{29}H_{27}N_2O_5S$, 515.1635; found, 515.1645.

*Ethyl-2-amino-4-benzoyl-6-benzyl-6a-phenyl-5-thioxo-3a,5,6,6a-tetrahydro-4H-furo[2,3-b]pyrrole-3-carboxylate (**4s**):* Isolated yield 233 mg (78%); white solid; mp 176−178 °C; IR (KBr) ν 3393, 3295, 3066, 2987, 2919, 1674, 1639, 1595, 1578, 1497, 1447, 1108, 1031, 757, 702; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.73 (br, 3H), 3.91 (br, 2H), 4.13 (d, J = 2.70 Hz, 1H), 4.46 (d, J = 15.20 Hz, 1H), 5.29 (d, J = 15.15 Hz, 1H), 5.38 (s, 1H), 5.61 (s, 2H), 7.16−7.22 (m, 5H), 7.38−7.45 (m, 3H), 7.52 (t, J = 7.68 Hz, 2H), 7.60−7.64 (m, 3H), 8.19 (d, J = 7.65 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.9, 48.8, 53.4, 59.1, 67.7, 77.7, 111.0, 126.5, 127.1, 127.8, 128.1, 128.5, 128.8, 129.5, 130.1, 133.6, 135.7, 136.7, 137.0, 164.1, 166.5, 197.0, 201.2; HRMS (ESI-TOF, $[M + H]^+$) calcd for $C_{29}H_{27}N_2O_4S$, 499.1686; found, 499.1695.

*Ethyl-2-amino-4-benzoyl-6-cyclohexyl-6a-phenyl-5-thioxo-3a,5,6,6a-tetrahydro-4H-furo[2,3-b]pyrrole-3-carboxylate (**4t**):* Isolated yield 221 mg (75%); white solid; mp 206−208 °C; IR (KBr) ν 3440, 3320, 2935, 2857, 1682, 1649, 1594, 1579, 1494, 1449, 1104, 1023, 750, 701; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.67 (br, 3H), 0.92−1.20 (m, 3H), 1.48−1.51 (m, 1H), 1.58−1.66 (m, 4H), 1.84−1.86 (m,

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1H), 2.14 (br, 1H), 3.85 (br, 2H), 3.98 (d, J = 3.10 Hz, 1H), 4.10 (br, 1H), 5.22 (d, J = 2.55 Hz, 1H), 5.80 (s, 2H), 7.42 (t, J = 7.12 Hz, 1H), 7.46−7.52 (m, 4H), 7.60 (t, J = 7.28 Hz, 1H), 7.77 (d, J = 7.55 Hz, 2H), 8.16 (d, J = 7.75 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.8, 25.2, 26.1, 28.9, 29.2, 54.5, 59.0, 60.1, 68.6, 77.7, 112.0, 126.4, 128.4, 129.3, 130.0, 133.4, 137.0, 138.8, 164.0, 166.5, 197.7, 200.6; HRMS (ESI-TOF, $[M + H]^+$) calcd for $C_{28}H_{31}N_2O_4S$, 491.1999; found, 491.2008.

*Ethyl-2-amino-4-benzoyl-6a-(4-chlorophenyl)-6-phenyl-5-thioxo-3a,5,6,6a-tetrahydro-4H-furo[2,3-b]pyrrole-3-carboxylate (**4u**):* Isolated yield 190 mg (61%); white solid; mp 198−199 °C; IR (KBr) ν 3446, 3345, 3069, 2980, 2936, 1680, 1642, 1597, 1579, 1493, 1448, 1106, 1015, 777, 738, 702; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.72 (br, 3H), 3.92 (br, 2H), 4.37 (d, J = 3.10 Hz, 1H), 5.40 (d, J = 2.10 Hz, 1H), 5.86 (s, 2H), 7.10−7.12 (m, 2H), 7.28−7.33 (m, 5H), 7.54 (t, J = 7.63 Hz, 2H), 7.64 (t, J = 7.30 Hz, 1H), 7.71 (d, J = 8.50 Hz, 2H), 8.21 (d, J = 7.65 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.8, 54.0, 59.2, 68.3, 77.8, 110.5, 128.0, 128.7, 128.9, 129.0, 130.1, 133.8, 135.3, 136.1, 136.6, 136.9, 163.8, 166.3, 197.4, 202.7; HRMS (ESI-TOF, $[M + H]^+$) calcd for $C_{28}H_{24}ClN_2O_4S$, 519.1140; found, 519.1136.

*Ethyl-2-amino-4-benzoyl-6a-(3-chlorophenyl)-6-phenyl-5-thioxo-3a,5,6,6a-tetrahydro-4H-furo[2,3-b]pyrrole-3-carboxylate (**4v**):* Isolated yield 183 mg (59%); white solid; mp 198−200 °C; IR (KBr) ν 3407, 3251, 2961, 2932, 1679, 1638, 1597, 1575, 1493, 1447, 1115, 1046, 780, 754, 707, 684; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.72 (br, 3H), 3.92 (br, 2H), 4.39 (d, J = 3.25 Hz, 1H), 5.40 (d, J = 2.60 Hz, 1H), 5.88 (s, 2H), 7.12−7.13 (m, 2H), 7.28−7.35 (m, 5H), 7.54 (t, J = 7.65 Hz, 2H), 7.62−7.66 (m, 2H), 7.78 (d, J = 7.75 Hz, 1H), 8.22 (d, J = 7.75 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.9, 54.0, 59.2, 68.4, 77.8, 110.2, 125.1, 126.6, 128.6, 128.7, 128.9, 129.0, 129.4, 129.9, 130.1, 133.7, 134.5, 136.6, 136.9, 139.6, 163.8, 166.3, 197.2, 202.9; HRMS (ESI-TOF, $[M + H]^+$) calcd for $C_{28}H_{24}ClN_2O_4S$, 519.1140; found, 519.1139.

*Ethyl-2-amino-4-benzoyl-6a-(4-methoxyphenyl)-6-phenyl-5-thioxo-3a,5,6,6a-tetrahydro-4H-furo[2,3-b]pyrrole-3-carboxylate (**4x**):* Isolated yield 228 mg (74%); white solid; mp 187−189 °C; IR (KBr) ν 3431, 3069, 2974, 2934, 1678, 1636, 1591, 1580, 1494, 1447, 1110, 1030, 777, 750, 705; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.74 (br, 3H), 3.80 (s, 3H), 3.93 (br, 2H), 4.41 (d, J = 3.05 Hz, 1H), 5.41 (s, 1H), 5.87 (s, 2H), 6.88 (d, J = 8.45 Hz, 2H), 7.12 (d, J = 6.75 Hz, 2H), 7.29 (t, J = 7.01 Hz, 3H), 7.55 (t, J = 7.58 Hz, 2H), 7.65 (d, J = 7.43 Hz, 1H), 7.68 (d, J = 8.54 Hz, 2H), 8.40 (d, J = 7.40 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.9, 53.9, 55.2, 59.1, 68.3, 77.9, 111.1, 113.7, 127.9, 128.6, 128.8, 128.9, 129.5, 130.0, 133.6, 136.7, 137.2, 160.0, 164.1, 166.5, 197.5, 202.6; HRMS (ESI-TOF, $[M + H]^+$) calcd for $C_{29}H_{27}N_2O_5S$, 515.1635; found, 515.1649.

*Ethyl-2-amino-4-benzoyl-6-phenyl-6a-(thiophen-2-yl)-5-thioxo-3a,5,6,6a-tetrahydro-4H-furo[2,3-b]pyrrole-3-carboxylate (**4y**):* Isolated yield 153 mg (52%); light brown solid; mp 176−178 °C; IR (KBr) ν 3442, 3339, 3077, 2975, 1692, 1677, 1634, 1595, 1579, 1491, 1447, 1113, 1018, 707; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.83 (br, 3H), 3.96−4.02 (m, 2H), 4.50 (d, J = 2.65 Hz, 1H), 5.42 (s, 1H), 5.86 (s, 2H), 7.02 (t, J = 4.40 Hz, 1H), 7.14−7.16 (m, 2H), 7.25 (d, J = 4.65 Hz, 1H), 7.32−7.34 (m, 3H), 7.54 (t, J = 7.68 Hz, 2H), 7.62−7.66 (m, 2H), 8.23 (d, J = 7.55 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.0, 54.3, 59.2, 67.9, 77.6, 109.1, 126.9, 127.5, 127.6, 128.6, 128.9, 129.0, 130.1, 133.7, 136.4, 136.9, 140.2, 163.8, 166.3, 196.9, 201.8; HRMS (ESI-TOF, $[M + H]^+$) calcd for $C_{26}H_{23}N_2O_4S_2$, 491.10938; found, 491.10907.

*Ethyl-2-amino-4-benzoyl-6a-methyl-6-phenyl-5-thioxo-3a,5,6,6a-tetrahydro-4H-furo[2,3-b]pyrrole-3-carboxylate (**4z**):* Isolated yield 112 mg (44%); white solid; mp 176−178 °C; IR (KBr) ν 3422, 3237, 3069, 2977, 2911, 1678, 1638, 1596, 1541, 1493, 1448, 1125, 1027, 778, 697; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.04 (br, 3H), 1.84 (s, 3H), 3.97 (br, 1H), 4.05−4.16 (m, 2H), 5.44 (s, 1H), 5.79 (s, 2H), 7.27−7.29 (m, 2H), 7.46−7.55 (m, 5H), 7.63 (t, J = 7.12 Hz, 1H), 8.22 (s, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.4, 23.4, 51.2, 59.2, 67.4, 78.1, 109.6, 128.7, 129.0, 129.3, 129.5, 130.1, 133.9, 136.2, 136.8, 164.3, 166.8, 197.3, 201.6; HRMS (ESI-TOF, $[M + H]^+$) calcd for $C_{23}H_{23}N_2O_4S$, 423.13730; found, 423.13733.

*Diethyl 2,2′-(Disulfanediylbis(4-benzoyl-1,2-diphenyl-1H-pyrrole-5,3-diyl))bis(3-amino-3-oxopropanoate) (**5**):* Isolated yield 41 mg (85%); yellow solid; mp 172−174 °C; IR (KBr) ν 3060, 2980, 2930, 1732, 1682, 1635, 1596, 1577, 1497, 1462, 1263, 1200, 1026, 769, 703; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.06 (t, J = 7.12 Hz, 3H), 3.87−3.88 (m, 1H), 4.05−4.07 (m, 1H), 4.45 (s, 1H), 5.56 (d, J = 6.95 Hz, 1H), 6.04 (s, 1H), 6.75−6.77 (m, 1H), 7.11 (t, J = 7.42 Hz, 1H), 7.19−7.25 (m, 4H), 7.27−7.31 (m, 3H), 7.38 (t, J = 7.65 Hz, 2H), 7.55 (t, J = 7.40 Hz, 1H), 7.71 (d, J = 7.50 Hz, 2H), 9.06 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.0, 53.6, 61.9, 117.7, 126.6, 128.2, 128.3, 128.7, 128.9, 129.3, 129.7, 130.1, 130.9, 132.4, 136.1, 140.3, 141.3, 168.7, 171.0, 194.6; HRMS (ESI-TOF, $[M + H]^+$) calcd for $C_{56}H_{47}N_4O_8S_2$, 967.2830; found, 967.2846.

*Ethyl-2-(4-benzoyl-5-mercapto-1,2-diphenyl-1H-pyrrol-3-yl)-3-(benzylamino)-3-oxopropanoate (**6**):* Isolated yield 45 mg (78%); yellow solid; mp 178−180 °C; IR (KBr) ν 3338, 3189, 3061, 3029, 2982, 2930, 1737, 1710, 1694, 1634, 1597, 1495, 1463, 1242, 1223, 1028, 915, 769, 699; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.06 (t, J = 7.07 Hz, 3H), 3.19 (dd, J_1 = 52.30 Hz, J_2 = 12.35 Hz, 2H), 3.86−3.93 (m, 1H), 3.99−4.06 (m, 1H), 4.46 (s, 1H), 5.65 (s, 1H), 6.57 (s, 1H), 6.64 (d, J = 7.32 Hz, 2H), 7.13−7.18 (m, 6H), 7.22−7.24 (m, 2H), 7.28−7.30 (m, 2H), 7.39 (br, 2H), 7.49 (t, J = 7.58 Hz, 2H), 7.60 (t, J = 7.38 Hz, 1H), 7.86 (d, J = 7.32 Hz, 2H), 8.73 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.9, 41.3, 52.4, 61.7, 117.2, 125.9, 127.2, 128.0, 128.2, 128.3, 128.8, 129.8, 130.1, 131.0, 132.5, 136.6, 137.0, 138.5, 139.6, 169.1, 171.2, 195.9; HRMS (ESI-TOF, $[M + Na]^+$) calcd for $C_{35}H_{30}N_2NaO_4S$, 597.1818; found, 597.1827.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.7b00371.

X-ray data for **4a** (CIF)

IR, ^{1}H NMR, and ^{13}C NMR spectra of all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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