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CHEMOSELECTIVE MULTICOMPONENT CONDENSATION OF 1,3-CYCLOHEXANEDIONE, UREA OR THIOUREA WITH ALDEHYDES: ONE-POT SYNTHESIS OF TWO FAMILIES OF FUSED HETEROBICYCLIC AND SPIRO-FUSED HETEROBICYCLIC ALIPHATIC RINGS

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Abstract- One-pot chemoselective condensation of 1,3-cyclohexanedione, urea or thiourea with aldehydes has been performed by using TMSCl as a Lewis acid in DMF/MeCN. This extended Biginelli-type reaction afforded two families of fused heterobicyclic and spiro-fused heterobicyclic compounds in excellent yields. *para*-Substituted benzaldehydes exhibited different chemical behaviors to *ortho*- or *meta*-substituted benzaldehydes and aliphatic aldehydes. The possible mechanism was discussed to account for experimental results.

INTRODUCTION

Biginelli reaction is one of the most powerful synthetic methodologies for the heterocyclic six-membered rings. 3,4-Dihydropyrimidin-2(1*H*)-ones (DHPMs) and their derivatives have attracted considerable interest due to their wide range of therapeutic and pharmacological properties, such as antiviral, antitumor, antibacterial and antiinflammatory properties.[1] The first synthesis of 3,4-dihydropyrimidin-2-(1*H*)-ones was described by Biginelli in 1893.[2] Large number of improving methods and new Biginelli-like scaffolds have been reported over the past decade.[3]

Recently, Biginelli-type reaction which used cyclic β-diketones instead of open-chain dicarbonyl compounds has attracted a synthetical interest. Spiro-fused heterocycles were synthesized by a multicomponent reaction between an aldehyde, urea or thiourea and a cyclic β-diester.[4] The scope of the extended Biginelli reaction was extended by a variety of cyclic β-diester shown in Figure 1.

We investigated 1,3-cyclohexanedione reacted with aromatic aldehydes and aliphatic aldehydes in the

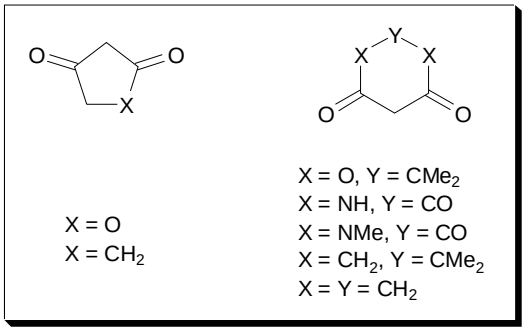


Figure 1.

reaction system TMSCl–DMF–MeCN in room temperature and found interestingly that two families of fused heterobicyclic and spiro-fused heterobicyclic compounds were formed; *para*-substituted benzaldehydes exhibited different chemical behaviors to *ortho*-, *meta*-substituted benzaldehydes and aliphatic aldehydes.

RESULTS AND DISCUSSION

We first tried to proceed the transformation by a simple mixture of 1,3-cyclohexanedione (**1**, 10 mmol), thiourea (**2a**, 12 mmol), and benzaldehyde (**3a**, 10 mmol) in the system TMSCl–DMF–MeCN (10 mmol–4 mL–8 mL, respectively). The reaction was performed in room temperature for 2-3 h. The corresponding product 1, 5-diphenyl-3-thioxo-2, 4-diazaspiro[5, 5]undecane-7, 11-dione (Figure 2, **4a**) was isolated and identified by NMR and HRMS. But under the same experimental conditions, the reaction between 1,3-cyclohexanedione (**1**), urea (**2b**), and benzaldehyde (**3a**) afforded the unexpected fused heterobicyclic compound phenyl-4,6,7,8-tetrahydro-1*H*,3*H*-quinazoline-2,5-dione (Figure 2, **5i**) in 86% isolated yield;[4-c] no spiro-fused heterobicyclic products were observed.

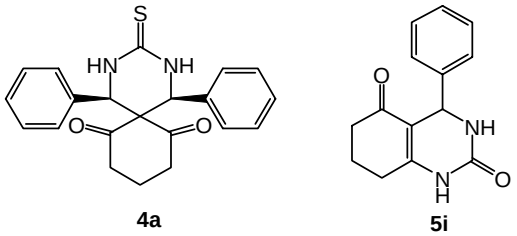
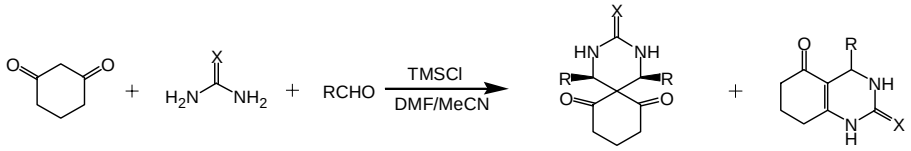


Figure 2.

For the experiment results above, series of reactions were investigated in details. Aromatic aldehydes (**3b**-**3i**) instead of benzaldehyde (**3a**) reacted with 1,3-cyclohexanedione (**1**) and thiourea (**2a**) or urea (**2b**). These reactions were carried out in DMF/MeCN at room temperature for 2-3 h in molar ratio/**1** : **2** : **3** : TMSCl = 1.0 : 1.2 : 1.0 : 1.0. A similar result was obtained with two families of fused heterobicyclic and spiro-fused heterobicyclic compounds (**4**, **5**) in excellent yields with high purities. The results were summarized in Table 1.

Table 1. Multicomponent Rections between 1,3-Cyclohexanedione, Thiourea or Urea and Aldehydes.[a]



1 2 3 4 5

Run	X	**3** : R	T( )	t (h)	DMF/MeCN	**4**[b]	**5**[b]
1	S	**3a**: C_6H_5		3	1 : 2	**4a**: 77	**5a**: 21
2	S	**3b**: 4-Cl-C_6H_4		2	1 : 2	**4b**: 80	**5b**: 13
3	S	**3c**: 4- Me-C_6H_4		2	1 : 2	**4c**: 79	**5c**: 11
4	O	**3c**: 4-Me-C_6H_4		2	1 : 2	**4d**: 78	**5d**: 15
5	O	**3d**: 4-F-C_6H_4		2	1 : 2	**4e**: 70	**5e**: 23
6	O	**3e**: 4-NO_2-C_6H_4		2	1 : 2	**4f**: 69	**5f**: 25
7	S	**3d**: 4-F-C_6H_4		3	1 : 2		**5g**: 76
8	S	**3e**: 4-NO_2-C_6H_4		3	1 : 2		**5h**: 74
9	O	**3a**: C_6H_5		2	1 : 2		**5i**: 86
10	S	**3f**: 2-F-C_6H_4		2	1 : 2		**5j**: 82
11	O	**3f**: 2-F-C_6H_4		2	1 : 2		**5k**: 90
12	S	**3g**: 2-Br-C_6H_4		2	1 : 2		**5l**: 92
13	O	**3g**: 2-Br-C_6H_4		2	1 : 2		**5m**: 93
14	S	**3h**: 2-MeO-C_6H_4		2	1 : 2		**5n**: 85
15	S	**3i**: 3-NO_2-C_6H_4		3	1 : 2		**5o**: 80
16	O	**3i**: 3-NO_2-C_6H_4		2	1 : 2		**5p**: 90
17	S	**3j**: *n*-Pr	80	3	1 : 2		**5q**: 77
18	S	**3l**: *n*-Bu	80	3	1 : 2		**5r**: 80
19	S	**3m**: *i*-Bu	80	3	1 : 2		**5s**: 85
20	O	**3j**: *n*-Pr	80	3	1 : 2		**5t**: 93
21	O	**3k**: *i*-Pr	80	3	1 : 2		**5u**: 82
22	O	**3m**: *i*-Bu	80	3	1 : 2		**5v**: 86
23	O	**3n**: *n*-C_6H_{13}	80	3	1 : 2		**5w**: 83

[a]All compounds were characterized by ^{1}H-NMR, ^{13}C NMR, and MS spectroscopies. [b]Isolated yields (The yields of **4** and **5** were based on 1,3-cyclohexandione).

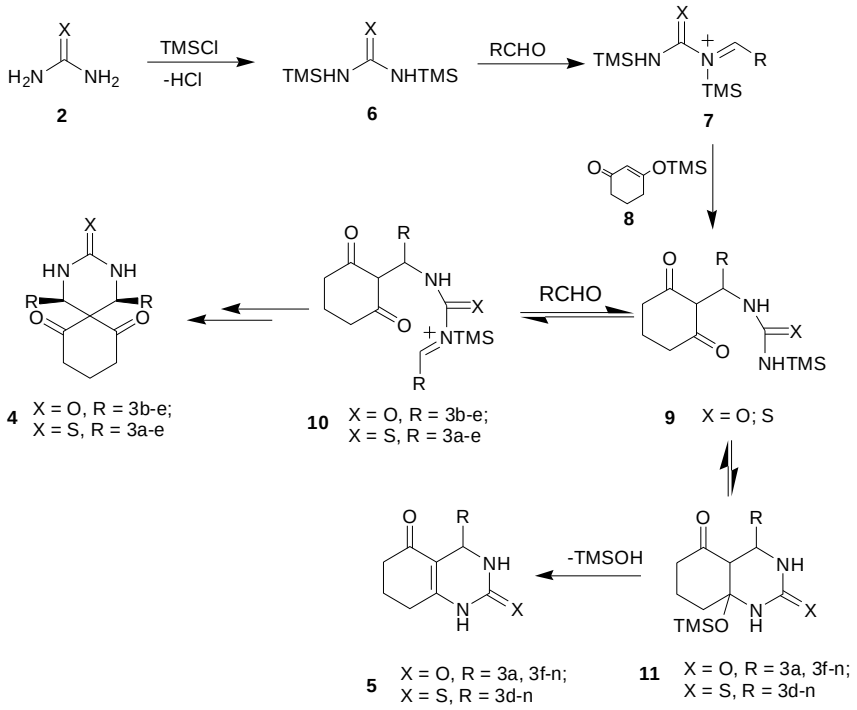
In the mentioned syntheses from Runs (1) to (6), *para*-substituted aromatic aldehydes afforded mainly spiro-fused heterobicyclic products. The stereochemistry of the aryl rings (products **4a**–**f**) was assigned *cis* based on the work of Byk.[4c] We also found these reactions were accompanied by small amounts of fused heterobicyclic compounds (**5a-f**) in yields from 11% to 25%.

For the reactions of urea (**2b**) shown in Table 1 (runs 7-8), *para*-substituted aromatic aldehydes carrying either electron-donating (-Me) or electron-withdrawing (-F, -NO_2) substituents yielded spiro-fused heterobicyclic aliphatic compounds (**4d**, **4e**, **4f**). But thiourea (**2a**) exhibited different behaviors to that of urea under similar conditions. *para*-Substituted aromatic aldehydes carrying electron-withdrawing (-F, -NO_2) substituents proceeded smoothly to fused heterobicyclic products (**5g**–**h**).

Interestingly, the reaction between 1,3-cyclohexanedione (**1**), benzaldehyde (**3a**), and urea (**2b**) proceeded smoothly to give fused heterocyclic scaffold product (**5i**) in yield 86%, and no other product was detected. Aromatic aldehydes carrying either electron-donating or electron-withdrawing substituents in the *ortho* or *meta* positions (**3f**-**i**) proceeded smoothly to give a family of fused bicyclical rings (products: **5j**-**p**) in good yields; no spiro-fused heterobicyclic products were detected. Thiourea (**2a**) exhibited analogue behavior to urea under similar conditions. All reactions were spontaneous under TMSCl in DMF/ MeCN at room temperature with yields ranging from 74 to 93%. This result was in agreement with the classical Biginelli reaction.

Our interest lead us attempt to extend the methodology to aliphatic aldehydes. Aliphatic aldehydes were used with similar success to *ortho*-, *meta*-substituted benzaldehydes. *n*-Butyraldehyde (**3j**), *iso*-butyraldehyde (**3k**), *n*-valeraldehyde (**3l**), *iso*-valeraldehyde (**3m**), and *n*-heptaldehyde (**3n**) afforded fused bicyclic compounds 4-alkyl-2-thioxo-2,3,4,6,7,8-hexahydro-1*H*-quinazolin-5-one (**5q**-**s**) and 4-alkyl-4,6,7,8- tetrahydro-1*H*,3*H*-quinazoline-2,5-dione (**5t**-**w**) with yields from 77 to 93% at 80 ℃ for 2-3 h (Table 1). But aliphatic aldehydes exhibited lower activity, the reactions required higher temperatures to convert into target compounds.

TMSCl shows remarkable reactivity as a Lewis acid in Biginelli reaction.[5] We assume that steric hindrances from the substituent in the *ortho* or *meta* positions have influenced on the formation of products. The nucleophilic additions are more facilitated to form key intermediate (**9**) from *N*-acyliminium ion intermediate (**7**).[6] Subsequently, two trends are presented in Scheme 1. One is



Scheme 1.

involving condensation of aldehyde with intermediate (**10**) and then nucleophilic addition to spiro-fused heterobicyclic compounds (**4**). The other is cyclization to hexahydropyrimidine (**11**) and acid-catalyzed elimination to fused heterobicyclic compounds (**5**). The steric hindrance from the substituent in the *ortho* or *meta* position hampered nucleophilic addition to furnish spiro-fused heterobicyclic compounds (**4**). For aliphatic aldehydes, ion intermediate (**10**) shows lower stability when R = alkyl, and is inclined to furnish the cyclization products (**5**).

In summary, we have studied the reactivity of 1,3-cyclohexanedione (**1**) toward the Biginelli reaction in a systematic manner. In the reaction, *para*-substituted benzaldehydes exhibited different chemical behaviors to *ortho*-, or *meta*-substituted benzaldehydes and aliphatic aldehydes by using TMSCl as a Lewis acid in DMF/MeCN. The successful reactions have expanded the synthetic scope of the multicomponent Biginelli reaction.

EXPERIMENTAL

1. General

Reagents and all solvents were analytically pure grade and were used without further purification. Anhydrous conditions were not required for the reaction. Melting points were measured on a XT-4 and were uncorrected, IR spectra were recorded as KBr pellets on a NEXUS 470 FT-IR. ^{1}H and ^{13}C-NMR spectra were recorded on Bruker AVANCE DMX-500 spectrometer at 500 and 125 MHz in DMSO, respectively, chemical shifts were given in ppm (δ), TMS as internal standard and coupling constants (J) were given in Hz, HRMS spectra were recorded with a Bruker APEX 3 system.

2. General procedures for synthesis of fused heterobicyclic (5a-f) and spiro-fused heterocyclic compounds (4a-f)

1,3-Cyclohexanedione (**1**, 1.120 g, 10 mmol), thiourea (**2a**, 0.912 g, 12 mmol) or urea (**2b**, 0.720 g, 12 mmol), aromatic aldehydes (**3a**–**e**, 10 mmol), and DMF/MeCN (4 mL/8 mL) were mixed in a flask and TMSCl (1.086 g, 10 mmol) was added dropwise at rt. The reaction mixture was stirred at rt for 2-3 h. The products (**4**) precipitated from the reaction medium, and then isolated by a filtration from the reaction mixture. The solution was poured into crashed ice with stirring. The precipitation (**5**) was filtered and washed by ethanol. The products (**4**) and (**5**) were purified by recrystallization (DMSO/H_2O).

Spiro-fused heterocyclic product (**4a**) mp 209-211 ℃; ^{1}H NMR (DMSO-d_6) δ (ppm) 8.67 (s, 2H), 7.33-7.32 (m, 6H), 7.00-6.99 (m, 4H), 4.98 (s, 2H), 1.82 (t, J = 6.1 Hz, 2H), 1.52 (t, J = 6.0 Hz, 2H), 0.51 (t, J = 6.1 Hz, 2H); ^{13}C NMR (DMSO- d_6) δ (ppm) 210.9, 206.1, 177.9, 135.9, 129.8, 129.5, 128.6, 65.9, 62.8, 43.2, 41.9; IR (KBr) 3359, 3170, 2950, 1689, 1556, 1456, 1198 cm^{-1}; HRMS: Calcd for $C_{21}H_{20}N_2O_2S$: 365.1318 $[M+H]^+$ found: 365.1310; Anal. Calcd for $C_{21}H_{20}N_2O_2S$: C, 69.20; H, 5.53; N, 7.69. Found: C, 69.32; H, 5.55; N, 7.72.

Spiro-fused heterocyclic product (**4b**) mp 219-222 ℃; ^{1}H NMR (DMSO-d_6) δ (ppm) 8.79 (s, 2H), 7.40 (t, J = 8.3 Hz, 4H), 6.95 (d, J = 8.2 Hz, 4H), 4.99 (s, 2H), 1.91 (m, 2H), 1.64 (m, 2H), 0.61 (t, J = 5.6 Hz, 2H); ^{13}C NMR (DMSO-d_6) δ (ppm) 210.7, 206.2, 194.9, 177.9, 175.4, 151.9, 143.1, 134.8, 133.0, 130.5, 129.6, 129.2, 109.6, 65.6, 52.3, 43.3, 41.9, 37.2, 26.2, 21.4, 15.0; IR (KBr) 3422, 3240, 2924, 1630, 1565, 1490, 1181 cm^{-1}; HRMS Calcd for $C_{21}H_{18}N_2O_2Cl_2S$: 455.0358 $[M+Na]^+$; found: 455.0367; Anal. Calcd for $C_{21}H_{18}N_2O_2Cl_2S$: C, 58.20; H, 4.19; N, 6.46. Found: C, 58.32; H, 4.25; N, 6.38.

Spiro-fused heterocyclic product (**4c**) mp 242-245 ℃; ^{1}H NMR (DMSO-d_6) δ (ppm) 8.56 (s, 2H), 7.12-7.10 (m, 8H), 4.92 (s, 2H), 2.51 (s, 6H), 1.92-1.83 (m, 2H), 1.54 (m, 2H), 0.55 (m, 2H); ^{13}C NMR (DMSO-d_6) δ (ppm) 211.0, 194.8, 175.3, 151.5, 141.3, 139.0, 137.6, 132.9, 130.0, 129.9, 128.4, 127.2, 110.1, 65.9, 62.9, 62.6, 52.5, 37.3, 26.2, 31.6, 21.5, 14.8; IR (KBr) 3431, 3246, 2921, 1629, 1567, 1460, 1374 cm^{-1}; HRMS Calcd for $C_{23}H_{24}N_2O_2S$: 393.1631 $[M+H]^+$; found: 393.1627; Anal. Calcd for $C_{23}H_{24}N_2O_2S$: C, 70.38; H, 6.16; N, 7.14. Found: C, 70.57; H, 6.13; N, 7.20.

Spiro-fused heterocyclic product (**4d**) mp 190-192 ℃; ^{1}H NMR (DMSO-d_6) δ (ppm) 7.15-7.14 (d, J= 7.8 Hz, 4H), 6.90 (d, J = 7.8 Hz, 4H), 5.01 (s, 2H), 2.25 (s, 6H), 1.82 (t, J = 6.1 Hz, 2H), 1.57 (t, J = 6.1 Hz, 2H), 0.56 (t, J = 6.2 Hz, 2H); ^{13}C NMR (DMSO-d_6) δ (ppm) 210.8, 206.5, 157.3, 139.2, 133.4, 130.7, 129.6, 128.3, 126.6, 66.9, 62.1, 43.3, 42.0, 21.6, 14.9; IR (KBr) 3428, 2922, 1686, 1650, 1511, 1206 cm^{-1}; HRMS Calcd for $C_{23}H_{24}N_2O_3$: 377.1860 $[M+H]^+$; found: 377.1865; Anal. Calcd for $C_{23}H_{24}N_2O_3$: C, 73.38; H, 6.43; N, 7.44. Found: C, 73.49; H, 6.38; N, 7.35.

Spiro-fused heterocyclic product (**4e**) mp 268-270 ℃; ^{1}H NMR (DMSO-d_6) δ (ppm) 7.19-7.04 (m, 8H), 5.02 (s, 2H), 1.85 (t, J=6.3 Hz, 2H), 1.63 (t, J = 6.2 Hz, 2H), 0.60 (t, J = 6.3 Hz, 2H); ^{13}C NMR (DMSO-d_6) δ (ppm) 211.2, 206.2, 164.0 and 162.0 (split), 156.4, 133.4, 130.6, 130.5, 116.5, 116.4, 67.7, 62.1, 43.4, 42.0, 15.1; IR (KBr) 3421, 3265, 2921, 1672, 1621, 1376, 1240 cm^{-1}; HRMS Calcd for $C_{21}H_{18}N_2O_3F_2$: 385.1106 $[M+H]^+$; found:385.1113; Anal. Calcd for $C_{21}H_{18}N_2O_3F_2$: C, 65.62; H, 4.72; N, 7.29. Found: C, 65.37; H, 4.79; N, 7.17.

Spiro-fused heterocyclic product (**4f**) mp 218-221 ℃; ^{1}H NMR (DMSO-d_6) δ (ppm) 8.22-8.18 (m, 4H), 7.32-7.29 (m, 6H), 5.22 (s, 2H), 1.92 (t, J = 6.0 Hz, 2H), 1.65 (t, J = 5.5 Hz, 2H), 0.56 (t, J = 6.0 Hz, 2H); ^{13}C NMR (DMSO-d_6) δ (ppm) 210.7, 205.6, 156.1, 148.5, 144.5, 130.0, 128.6, 124.7, 57.3, 52.5, 43.2, 41.9, 15.2; IR (KBr) 3244, 2921, 1686, 1523, 1350 cm^{-1}; HRMS Calcd for $C_{21}H_{18}N_4O_7$: 439.1248 $[M+H]^+$; found: 439.1255; Anal. Calcd for $C_{21}H_{18}N_4O_7$: C, 57.53; H, 4.14; N, 12.78. Found: C, 57.72; H, 4.07; N, 12.90.

3. General procedures for synthesis of fused heterobicyclic compounds (5g-w)

1,3-cyclohexanedione (**1**, 1.120 g, 10 mmol), thiourea (**2a**, 0.912 g, 12 mmol) or urea (**2b**, 0.720 g, 12 mmol), aldehydes (**3e**–**n**, 10 mmol), and DMF/MeCN (4 mL/8 mL) were mixed in a flask and TMSCl (1.086 g, 10 mmol) was added dropwise at rt. The resulting reaction mixture was stirred at 80 ℃ for 3 h,

cooled into rt, and then poured into crashed ice with stirring. The precipitation was isolated by filtered through a Buechner funnel and washed with ethanol, and then dried to give the crystalline powder. Purification by recrystallization (DMSO/H_2O) gave the products **(5g-w)**

Fused heterocyclic product (**5g**) mp 278-280 °C; ^{1}H NMR (DMSO-d_6) δ (ppm) 10.63 (s, 1H), 9.68 (s, 1H), 7.24 (t, J = 7.9 Hz, 2H), 7.17-7.14 (m, 2H), 5.18 (s, 1H), 2.55-2.50 (m, 2H), 2.31-2.20 (m, 2H), 1.94-1.81 (m, 2H); ^{13}C NMR (DMSO-d_6) δ (ppm) 195.0, 175.4, 163.4 and 161.5 (split), 151.8, 140.5, 133.4, 129.5, 117.5, 116.4, 109.9, 52.3, 37.3, 26.3, 21.5; IR (KBr) 3432, 3248, 2921, 1625, 1454, 1180 cm^{-1}; HRMS Calcd for $C_{14}H_{13}N_2OFS$: 299.0625 $[M+Na]^+$; found: 299.0635; Anal. Calcd for $C_{14}H_{13}N_2OFS$: C, 60.85; H, 4.74; N, 10.14. Found: C, 61.02; H, 4.81; N, 10.05.

Fused heterocyclic product (**5h**) mp 261-263°C; ^{1}H NMR (DMSO-d_6) δ (ppm) 10.76 (s, 1H), 9.78 (s, 1H), 8.21 (d, J = 8.6 Hz, 2H), 7.48 (d, J = 8.6 Hz, 2H), 5.33 (d, J = 2.5 Hz, 1H), 2.52 (m, 2H), 2.32-2.20 (m, 2H), 1.95-1.92 (m, 1H), 1.82-1.80 (m, 1H); ^{13}C NMR (DMSO-d_6) δ (ppm) 194.9, 175.7, 152.3, 151.2, 147.8, 128.7, 124.8, 109.1, 52.6, 37.2, 26.3, 21.4; IR (KBr) 3429, 3180, 2953, 1635, 1566, 1348, 1176 cm^{-1}; HRMS Calcd for $C_{14}H_{13}N_3O_3S$: 304.0750 $[M+H]^+$; found: 304.0746; Anal. Calcd for $C_{14}H_{13}N_3O_3S$: C, 55.43; H, 4.32; N, 13.85. Found: C, 55.60; H, 4.38; N, 13.78.

Fused heterocyclic product (**5i**) mp 282-285 °C; ^{1}H NMR (DMSO-d_6) δ (ppm) 9.49 (s, 1H), 7.77 (s, 1H), 7.31-7.17 (m, 5H), 5.17 (d, J = 2.6 Hz, 1H), 2.49-2.43 (m, 2H), 2.27-2.19 (m, 2H), 1.92-1.90 (m, 1H), 1.81-1.79 (m, 1H); ^{13}C NMR (DMSO-d_6) δ (ppm) 194.2, 155.4, 152.8, 145.6, 129.3, 128.9, 127.2, 109.5, 52.7, 37.4, 26.8, 21.8; IR (KBr) 3431, 3232, 2953, 1697, 1607, 1379, 1243, 1190 cm^{-1}; HRMS Calcd for $C_{14}H_{14}N_2O_2$: 265.0947 $[M+Na]^+$; found: 265.0943; Anal. Calcd for $C_{14}H_{14}N_2O_2$: C, 69.41; H, 5.82; N, 11.56. Found: C, 69.53; H, 5.79; N, 11.48.

Fused heterocyclic product (**5j**) mp 286-288 °C; ^{1}H NMR (DMSO-d_6) δ (ppm) 10.60 (s, 1H), 9.60 (s, 1H), 7.38-7.12 (m, 4H), 5.39 (s, 1H), 2.57-2.49 (m, 2H), 2.26-2.14 (m, 2H), 1.95-1.91 (m, 1H), 1.82-1.80 (m, 1H); ^{13}C NMR (DMSO-d_6) δ (ppm) 194.6, 175.1, 161.6 and 159.6 (split), 151.9, 131.0, 130.7, 130.4, 125.4, 116.6, 108.5, 48.4, 37.2, 26.2, 21.5; IR (KBr) 3429, 3273, 2921, 1621, 1566, 1460, 1178 cm^{-1}; HRMS Calcd for $C_{14}H_{13}N_2OFS$: 277.0805 $[M+H]^+$; found: 277.0805; Anal. Calcd for $C_{14}H_{13}N_2OFS$: C, 60.85; H, 4.74; N, 10.14. Found: C, 61.01; H, 4.80; N, 10.21.

Fused heterocyclic product (**5k**) mp 278-281°C; ^{1}H NMR (DMSO-d_6) δ (ppm) 9.54 (s, 1H), 7.70 (s, 1H), 7.29-7.10 (m, 4H), 5.39 (s, 1H), 2.48-2.46 (m, 2H), 2.25-2.12 (m, 2H), 2.07-1.82 (m, 2H); ^{13}C NMR (DMSO-d_6) δ (ppm) 193.9, 161.7 and 159.7 (split), 155.9, 152.2, 132.1, 130.2, 130.1 125.3, 116.5, 107.5, 48.3, 37.7, 26.8, 21.8; IR (KBr) 3431, 3229, 2923, 1695, 1604, 1378, 1193 cm^{-1}; HRMS Calcd for $C_{14}H_{13}N_2O_2F$: 283.0852 $[M+Na]^+$; found: 283.0847; Anal. Calcd for $C_{14}H_{13}N_2O_2F$: C, 64.61; H, 5.03; N, 10.76. Found: C, 64.32; H, 5.01; N, 10.73.

Fused heterocyclic product (**5l**) mp 289-292 °C; ^{1}H NMR (DMSO-d_6) δ (ppm) 10.63 (s, 1H), 9.56 (s, 1H), 7.56 (d, J = 8.0 Hz, 1H), 7.36-7.17 (m, 3H), 5.55 (d, J = 2.2 Hz, 1H), 2.59-2.49 (m, 2H), 2.24-2.16 (m, 2H), 2.07-1.84 (m, 2H); ^{13}C NMR (DMSO-d_6) δ (ppm) 194.5, 174.9, 152.1, 142.7, 133.7, 130.8, 130.5, 129.2, 123.4, 109.3, 53.8, 37.3, 26.2, 21.5; IR (KBr) 3422, 3156, 2995, 1617, 1559, 1458, 1374, 1174 cm^{-1}; HRMS Calcd for $C_{14}H_{13}N_2OBrS$: 337.0005 $[M+H]^+$; found: 337.0001; Anal. Calcd for $C_{14}H_{13}N_2OBrS$: C, 49.86; H, 3.89; N, 8.31. Found: C, 48.98; H, 3.79; N, 8.28.

Fused heterocyclic product (**5m**) mp 240-243 °C; ^{1}H NMR (DMSO-d_6) δ (ppm) 9.58 (s, 1H), 7.63 (s, 1H), 7.55 (t, J = 9.2 Hz, 1H), 7.33-7.30 (m, 1H), 7.26-7.24 (m, 1H), 7.19-7.07 (m, 1H), 5.54 (d, J = 1.6 Hz, 1H), 2.51-2.48 (m, 2H), 2.21-2.13 (m, 2H), 1.93-1.86 (m, 2H); ^{13}C NMR (DMSO-d_6) δ (ppm) 193.9, 162.6, 156.2, 151.9, 143.7, 133.7, 130.2, 129.2, 123.4, 108.3, 53.6, 36.8, 31.8, 21.8; IR (KBr) 3411, 3297, 2945, 1658, 1619, 1358, 1176 cm^{-1}; HRMS Calcd for $C_{14}H_{13}N_2O_2Br$: 320.9339 $[M+H]^+$; found: 320.9345; Anal. Calcd for $C_{14}H_{13}N_2O_2Br$: C, 52.36; H, 4.08; N, 8.72. Found: C, 52.44; H, 4.09; N, 8.78.

Fused heterocyclic product (**5n**) mp 278-280 °C; ^{1}H NMR (DMSO-d_6) δ(ppm) 10.49 (s, 1H), 9.18 (s, 1H), 7.24 (t, J = 7.45 Hz, 1H), 7.00 (t, J = 8.7 Hz, 2H), 6.86 (t, J = 7.3 Hz, 1H), 5.43 (s, 1H), 3.79 (s, 3H), 2.59-2.46 (m, 2H), 2.47-2.17 (m, 2H), 1.94-1.87 (m, 2H); ^{13}C NMR (DMSO-d_6) δ(ppm) 194.6, 175.2, 157.9, 152.3, 131.0, 130.4, 128.9, 121.1, 112.4, 108.3, 56.5, 49.0, 37.3, 26.2, 21.6; IR (KBr) 3366, 3169, 2924, 1606, 1555, 1461, 1375, 1175 cm^{-1}; HRMS Calcd for $C_{15}H_{16}N_2O_2S$: 311.0825 $[M+Na]^+$; found: 311.0825; Anal. Calcd for $C_{15}H_{16}N_2O_2S$: C, 52.36; H, 4.08; N, 8.72. Found: C, 52.44; H, 4.15; N, 8.87.

Fused heterocyclic product (**5o**) mp 255-257 °C; ^{1}H NMR (DMSO-d_6) δ(ppm) 9.65 (s, 1H), 8.10(t, J=8.0 Hz, 2H), 7.92 (s, 1H), 7.70-7.61 (m, 2H), 5.33 (d, J = 2.0 Hz, 1H), 2.52-2.18 (m, 4H), 1.94-1.80 (m, 2H); ^{13}C NMR(DMSO-d_6) δ (ppm) 194.4, 156.2, 152.4, 148.7, 147.6, 134.0, 131.1, 123.2, 121.9, 108.4, 52.4, 37.1, 26.8, 21.6; IR (KBr) 3431, 3254, 2925, 1705, 1618, 1530, 1349, 1191 cm^{-1}; HRMS Calcd for $C_{14}H_{13}N_3O_3S$: 304.0750 $[M+H]^+$; found: 304.0759; Anal. Calcd for $C_{14}H_{13}N_3O_3S$: C, 55.43; H, 4.32; N, 13.85. Found: C, 55.60; H, 4.46; N, 13.75.

Fused heterocyclic product (**5p**) mp 289-292 °C; ^{1}H NMR (DMSO-d_6) δ(ppm) 10.78 (s, 1H), 9.82 (s, 1H), 8.44-8.06(m, 4H), 5.35 (s, 1H), 2.54-2.51 (m, 2H), 2.32-2.24 (m, 2H), 1.96-1.82 (m, 2H); ^{13}C NMR (DMSO-d_6) δ(ppm) 197.4, 166.5,151.3, 147.5, 135.6, 130.6, 123.7, 122.4, 115.4, 37.2, 32.4, 27.4, 20.8; IR (KBr) 3425, 2922, 1671, 1532, 1351 cm^{-1}; HRMS Calcd for $C_{14}H_{13}N_3O_4$: 310.0798 $[M+Na]^+$; found: 310.0791; Anal. Calcd for $C_{14}H_{13}N_3O_4$: C, 58.53; H, 4.56; N, 14.63. Found: C, 58.39; H, 4.68; N, 14.77.

Fused heterocyclic product (**5q**) mp: 223-226 °C; ^{1}H NMR (DMSO-d_6) δ (ppm) 10.31 (s, 1H), 9.25 (s, 1H), 4.15 (s, 1H), 2.40 (t, J = 4.8 Hz, 2H), 2.24 (t, J = 5.6 Hz, 2H), 1.91-1.80 (m, 2H), 1.39-1.17 (m, 4H), 0.82 (t, J = 7.2 Hz, 3H); ^{13}C NMR (DMSO-d_6) δ (ppm) 195.1, 176.0, 152.0, 109.6, 49.6, 39.3, 37.4, 26.2, 21.7, 17.5, 14.8; IR (KBr) 3255, 3131, 2924, 1657, 1621, 1400, 1184 cm^{-1}; HRMS Calcd for $C_{11}H_{16}N_2OS$:

225.1056 $[M+H]^+$; found: 225.1059; Anal. Calcd for $C_{11}H_{16}N_2OS$: C, 58.90; H, 7.19; N, 12.49. Found: C, 58.67; H, 7.02; N, 12.73.

Fused heterocyclic product (**5r**) mp 227-229 °C; ^{1}H NMR (DMSO-d_6) δ (ppm) 10.32 (s, 1H), 9.26 (s, 1H), 4.15 (d, J = 2.9Hz, 1H), 2.52-2.23 (m, 4H), 1.90-1.89 (m, 2H), 1.40-1.14 (m, 6H), 0.84-0.77 (m, 3H); ^{13}C NMR (DMSO-d_6) δ (ppm) 195.1, 175.9, 152.0, 109.5, 49.7, 37,3, 36.6, 26.3, 23.0, 21.3, 21.0, 14.9; IR (KBr) 3252, 3180, 2924, 1646, 1625, 1401, 1181 cm^{-1}; HRMS Calcd for $C_{12}H_{18}N_2OS$: 239.1213 $[M+H]^+$; found: 239.1220; Anal. Calcd for $C_{12}H_{18}N_2OS$: C, 60.47; H, 7.61; N, 11.75. Found: C, 60.64; H, 7.75; N, 11.66.

Fused heterocyclic product (**5s**) mp 220-223 °C; ^{1}H NMR (DMSO-d_6) δ (ppm) 10.36 (s, 1H), 9.34 (s, 1H), 4.15 (t, J = 3.8 Hz, 1H), 2.42 (m, 2H), 2.24-2.22 (m, 2H), 1.91-1.63 (m, 3H), 1.32-1.28 (m, 1H), 1.10-1.06 (m, 1H), 0.87-0.83 (m, 6H); ^{13}C NMR (DMSO-d_6) δ (ppm) 196.7, 177.7, 153.6, 112.5, 49.5, 48.2, 39.1, 28.0, 26.3, 25.5, 24.8, 23.4; IR (KBr) 3243, 2951, 1624, 1575, 1462, 1179 cm^{-1}; HRMS Calcd for $C_{12}H_{18}N_2OS$: 239.1213 $[M+H]^+$; found: 239.1218; Anal. Calcd for $C_{12}H_{18}N_2OS$: C, 60.47; H, 7.61; N, 11.75. Found: C, 60.32; H, 7.74; N, 11.59.

Fused heterocyclic product (**5t**) mp 250-253 °C; ^{1}H NMR (DMSO-d_6) δ (ppm) 10.31 (s, 1H), 9.25 (s, 1H), 4.15 (s, 1H), 2.39-2.35 (m, 2H) , 2.23-2.20 (m, 2H), 1.91-1.80 (m, 2H), 1.39-1.17 (m, 4H), 0.83 (t, J = 7.2Hz, 3H); ^{13}C NMR (DMSO-d_6) δ (ppm) 195.1, 155.5, 153.3, 109.1, 49.2, 37.3, 26.8, 21.6, 17.5, 14.8; IR (KBr) 3427, 3244, 2929, 1715, 1634, 1380, 1184 cm^{-1}; HRMS Calcd for $C_{11}H_{16}N_2O_2$: 231.1104 $[M+Na]^+$; found: 231.1105; Anal. Calcd for $C_{11}H_{16}N_2O_2$: C, 63.44; H, 7.74; N, 13.45. Found: C, 63.52; H, 7.82; N, 13.56.

Fused heterocyclic product (**5u**) mp 246-249 °C; ^{1}H NMR (DMSO-d_6) δ (ppm) 9.18 (s, 1H), 7.27 (s, 1H), 3.98 (s, 1H), 2.36-2.22 (m, 4H), 1.91-1.66 (m, 3H), 0.80 (d, J = 6.6 Hz, 3H), 0.69 (d, J = 6.5 Hz, 3H); ^{13}C NMR (DMSO-d_6) δ (ppm) 194.5, 156.0, 153.7, 108.2, 54.5, 37.4, 34.5, 26.8, 21.8, 19.5, 16.6; IR (KBr) 3436, 3247, 2961, 1703, 1612, 1386, 1250, 1192 cm^{-1}; HRMS Calcd for $C_{11}H_{16}N_2O_2$: 231.1104 $[M+Na]^+$; found: 231.1100; Anal. Calcd for $C_{11}H_{16}N_2O_2$: C, 63.44; H, 7.74; N, 13.45. Found: C, 63.32; H, 7.68; N, 13.61.

Fused heterocyclic product (**5v**) mp 264-267 °C; ^{1}H NMR (DMSO-d_6) δ (ppm) 10.37 (s, 1H), 9.34 (s, 1H), 4.15 (t, J = 3.8 Hz, 1H), 2.42 (s, 2H), 2.23 (t, J = 6.0 Hz, 2H), 1.91-1.80 (m, 1H), 1.79 (d, J = 6.2 Hz, 1H), 1.66-1.63 (m, 1H), 1.32-1.28 (m, 1H), 1.10-1.06 (m, 1H), 0.85 (q, J = 6.4 Hz, 6H); ^{13}C NMR (DMSO-d_6) δ (ppm) 196.7, 177.7, 153.6, 112.5, 49.5, 18.3, 39.1, 28.0, 26.3, 25.5, 24.8, 23.5; IR (KBr) 3211, 2802, 1706, 1631, 1405, 1243, 1190 cm^{-1}; HRMS Calcd for $C_{12}H_{18}N_2O_2$: 223.1441 $[M+H]^+$; found: 223.1447; Anal. Calcd for $C_{12}H_{18}N_2O_2$: C, 64.84; H, 8.16; N, 12.60. Found: C, 64.96; H, 8.19; N, 12.73.

Fused heterocyclic product (**5w**) mp 189-191 °C; ^{1}H NMR (DMSO-d_6) δ (ppm) 9.18 (s, 1H), 7.29 (s, 1H), 4.10 (s, 1H), 2.49-2.19 (m, 4H), 1.90-1.79 (m, 2H), 1.34-1.29 (m, 10H), 0.84 (t, J = 12.6 Hz, 3H); ^{13}C

NMR (DMSO-d_6) δ (ppm) 194.3, 155.4, 153.2, 109.1, 49.3, 37.4, 37.3, 32.2, 29.6, 26.7, 24.3, 23.0, 21.9, 14.9; IR (KBr) 3432, 3250, 2923, 1715, 1639, 1384, 1191 cm^{-1}; HRMS Calcd for $C_{14}H_{22}N_2O_2$: 251.1754 $[M+H]^+$; found: 251.1751; Anal. Calcd for $C_{14}H_{22}N_2O_2$: C, 67.17; H, 8.86; N, 11.19. Found: C, 67.33; H, 8.80; N, 11.08.

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