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MICROWAVE-ASSISTED SYNTHESIS OF 2-AMINOTHIOPHENE DERIVATIVES VIA IMPROVED GEWALD REACTIONS

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Abstract – In this paper, a new and efficient method was developed to prepare 2-aminothiophene derivatives through improved Gewald reaction. Thirty-one final products were synthesized under microwave radiation for 30 min with 57%-95% isolated yields. All the products could be used as building blocks in drug discovery.

2-Aminothiophenes are important organic intermediates, which are often found in drug research.[1,2] Due to the broad activities of the derivatives including anti-microbial, anti-tumor, anti-oxidation, and anti-inflammatory, it has been greatly interested in development of new 2-aminothiophenes for organic chemists and medicinal chemists.[3-5] In 2013, Davis reported a new drug candidate **CaCCinh-A01**,[6] which was used as inhibitor for treatment of glioblastoma. In addition, Ballatore studied **ATTZ-15** and **2-TCU**[7] in the next year, which were performed significant effects in neurological diseases. Recently, Sim also developed a series of 2-aminothiophene-3-carboxamide derivatives as calcium-activated chloride ion channel blockers.[8]

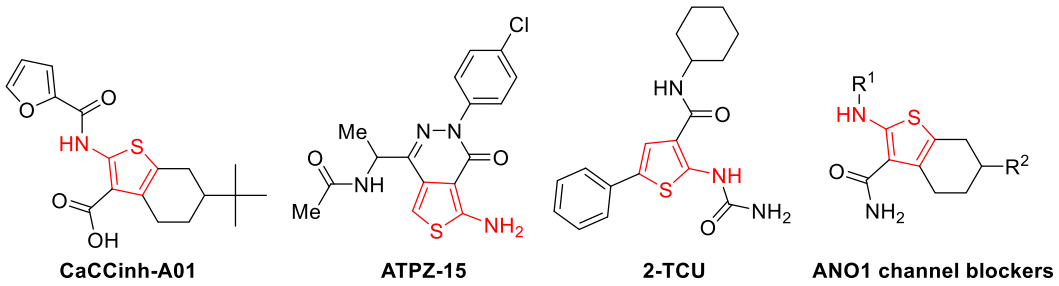


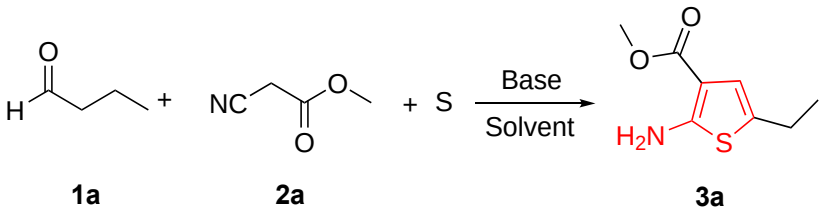
Figure 1. 2-Aminothiophene skeleton in biological compounds

The most classic method for the synthesis of 2-aminothiophene derivatives is Gewald method, which consists of α-ketones, active cyano compounds, and sulfur under base catalysis.[9] In recent years, more and more chemists are trying to develop new methods to synthesize 2-aminothiophene derivatives.[10] In 2014, Yan and co-authors developed a new type of Gewald-type reaction of double activated 2,3-diarylcyclopropane with sulfur to synthesize polysubstituted 2-aminothiophenes.[11] In 2016, Tayebee and co-authors used a new nanocomposite material of ZnO_2 to catalyze the Gewald reaction.[12]

Microwave radiation (MW) synthesis is a very powerful and novel technology. It has been proved that microwave-assisted synthesis can greatly increase the reaction rate and reduce the formation of by-products.[13-15] In 2007, Sridhar firstly reported the microwave-assisted Gewald reaction for the synthesis of 2-aminothiophene.[16] However, there are still some drawbacks for this procedure including limit of substrates and moderate yield. Based on the potential biological activities of 2-aminothiophene, we are very interested in the development of 2-aminothiophene derivatives under microwave radiation. In this paper, we will describe a newly efficient method for synthesis of 2-aminothiophenes under MW condition.

Initially, we chose butyraldehyde **1a**, methyl cyanoacetate **2a**, and sulfur as the model reaction to screen the improved Gewald reactions. We first examined the reaction in the presence of different base (K_2CO_3, Cs_2CO_3, NaOH, Et_3N, DIEA, DBU, piperidine, pyrrolidine, KO^{t}Bu, NaO^{t}Bu) in DMF under MW for 30 min. As shown in Table 1 entries 1-10, pyrrolidine gave the highest yield of 92%. Therefore, pyrrolidine was regarded as the optimal base of the model reaction. Then we screened the different solvents including DMSO, EtOH, *i*-PrOH, THF, dioxane, DCM, NMP, toluene, MeCN (Table 1, entries 11-19). Unfortunately, the best solvent was still DMF with 92% yield. At last, we considered the influence of temperature on the reaction. The isolated yield at 25 °C, 50 °C, and 75 °C was 92%, 95%, and 94%, respectively. However, when the temperature was further increased to 100 °C, the yield is slightly reduced to 88%. We also examined the reaction under conventional thermal heating conditions and the yield of the desired product was 47% (Table 1, entry 23). As a result, the optimized condition was used pyrrolidine as base, DMF as solvent under MW in 50 °C for 30 min.

Table 1. Optimization of the Gewald reaction conditions



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

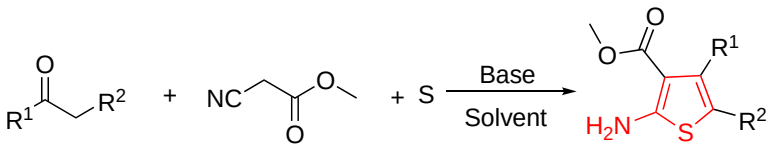
Entry	Base	Solvent	T (°C)	Yield (%)[a,b]
1	K_2CO_3	DMF	25	24
2	Cs_2CO_3	DMF	25	31
3	NaOH	DMF	25	52
4	Et_3N	DMF	25	81
5	DIEA	DMF	25	80
6	DBU	DMF	25	39
7	piperidine	DMF	25	85
8	pyrrolidine	DMF	25	92
9	KO^{t}Bu	DMF	25	29
10	NaO^{t}Bu	DMF	25	30
11	pyrrolidine	DMSO	25	81
12	pyrrolidine	EtOH	25	47
13	pyrrolidine	*i*-PrOH	25	37
14	pyrrolidine	THF	25	77
15	pyrrolidine	dioxane	25	63
16	pyrrolidine	DCM	25	69
17	pyrrolidine	NMP	25	63
18	pyrrolidine	toluene	25	29
19	pyrrolidine	MeCN	25	52
20	pyrrolidine	DMF	50	95
21	pyrrolidine	DMF	75	94
22	pyrrolidine	DMF	100	88
23	pyrrolidine	DMF	50	47[c]

[a] Reagents and conditions: **1a** (1 mmol), **2a** (1.1 mmol), S (1.1 mmol), Base (1 mmol), Solvent (3 mL), microwave, 30 min. [b] Isolated yields. [c] Reagents and conditions: **1a** (1 mmol), **2a** (1.1 mmol), S (1.1 mmol), Base (1 mmol), Solvent (3 mL), oil bath, 30 min.

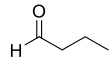
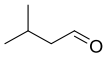
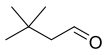
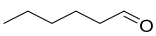
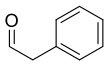
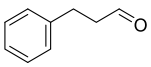
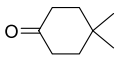
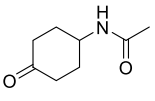
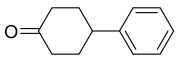
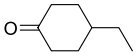
After determining the best condition, the scope of the reaction was explored with different substituted compounds **1**. As shown in Table 2 entries 1-4, aliphatic aldehydes with long chain gave the yields with 81%-95%. Otherwise, the aldehydes with benzene ring afforded the corresponding products in decreased yields of 74%-78% (Table 2, entries 5 and 6). Then we replaced aldehyde with ketone to study the effect of substitution of the Gewald reaction. Interestingly, cyclopentanone **1g** and cyclohexanone **1h** gave the desired products in 70% and 79% yield, respectively (Table 2, entries 7 and 8). Moreover, with the

expansion of ring, the yield of product **3i** was sharply increased to 91% (Table 2, entry 9). In order to further investigate the effect of substitution of cyclohexanone, compounds **1j-1m** were utilized in the Gewald reaction (Table 2, entries 10-13). Surprisingly, the yield of product **3k** reached 91% and the other yields were 77%-84%. This phenomenon indicated that electron-donating substituents at cyclohexanone moieties such as acetylamino group and benzyl group could produce higher yield.

Table 2. Preparation of 2-aminothiophene derivatives **3**



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

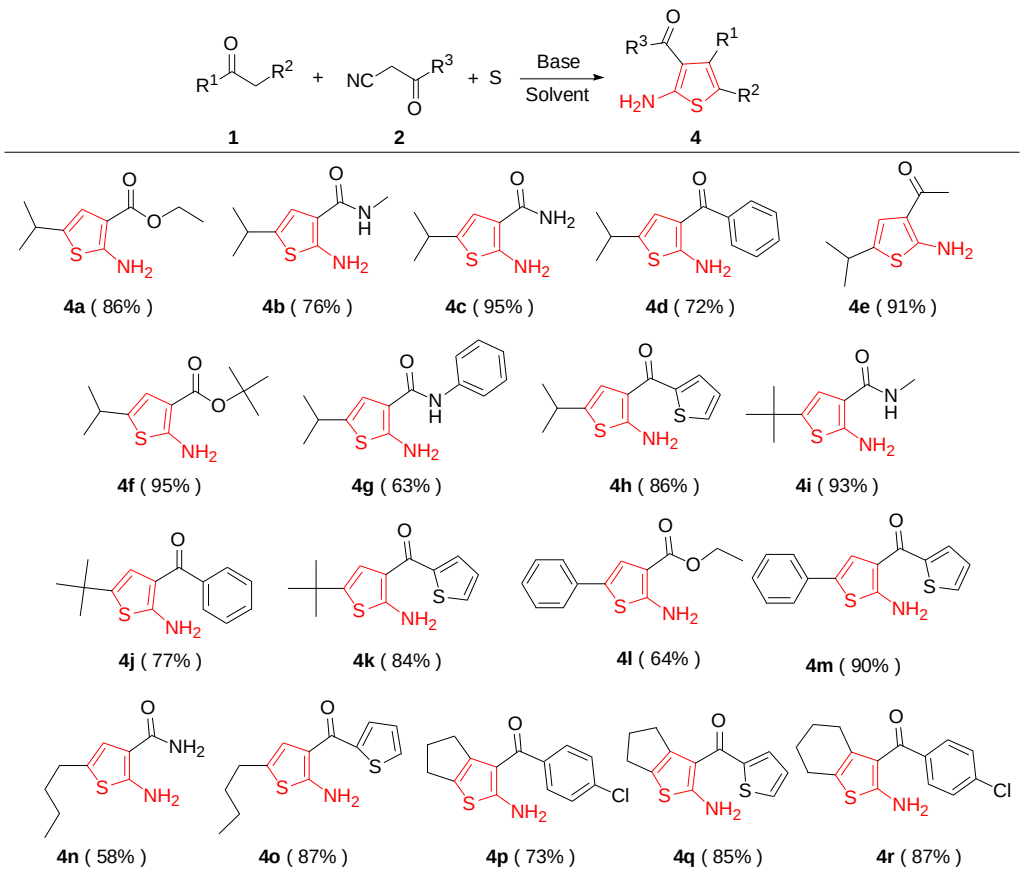
Entry	**1**		Product	Yield (%)[a,b]
1		**1a**	**3a**	95
2		**1b**	**3b**	92
3		**1c**	**3c**	93
4		**1d**	**3d**	81
5		**1e**	**3e**	78
6		**1f**	**3f**	74
7		**1g**	**3g**	70
8		**1h**	**3h**	79
9		**1i**	**3i**	91
10		**1j**	**3j**	84
11		**1k**	**3k**	91
12		**1l**	**3l**	80
13		**1m**	**3m**	77

[a] Reagents and conditions: **1** (1 mmol), **2a** (1.1 mmol), S (1.1 mmol), pyrrolidine (1 mmol), DMF (3 mL), microwave, 30 min; [b] Isolated yields.

At last, we studied the reactions of aldehydes or ketones with different cyanoacetate substitutes. Firstly, the reaction of 3,3-dimethylbutyraldehyde with various cyanocarbonyl compounds were investigated

under the optimized condition. Fortunately, the ester derivatives **4a** and **4f**, the amide derivatives **4b**, **4c**, and **4g**, the carbonyl derivatives **4d**, **4e**, and **4h** were all obtained with 63%-95% yields (Table 3). Next, we also studied the aldehydes **1c**, **1d**, **1e** with corresponding cyanoacetate substituents. The results showed that the yield of **4i**, **4j**, **4l**, and **4n** were 93%, 77%, 64%, and 58%, respectively. Furthermore, the reaction of cyanocarbonyl derivatives with **1b**, **1c**, **1d**, **1e** gave the products **4h**, **4k**, **4m**, **4o** with 86%, 84%, 90%, and 87% yield. Finally, we chose cyclopentanone **1g** and cyclohexanone **1h** to investigate the Gewald reaction. Interestingly, **1g** and **1h** successfully reacted with 2-thiophenylacetonitrile, and *p*-chlorobenzoylacetonitrile to give the satisfactory yields from 73% to 87%. All the results in Table 2 and Table 3 suggested that our protocol was a rapid and efficient method to synthesize 2-aminothiophene derivatives.

Table 3. Preparation of 2-aminothiophene derivatives **4**[a,b]



[a] Reagents and conditions: **1** (1 mmol), **2** (1.1 mmol), S (1.1 mmol), pyrrolidine (1 mmol), DMF (3 mL), microwave, 30 min; [b] Isolated yields.

In conclusion, we have successfully developed an efficient microwave-assisted Gewald method for the preparation of 2-aminothiophene derivatives. These compounds can be used to construct 2-aminothiophene compounds library and as intermediates to develop new drugs. All the compounds

were confirmed by ^{1}H NMR, ^{13}C NMR and MS. Further studies of these compounds are still ongoing in our lab.

EXPERIMENTAL

All commercial materials were used without further purification. Melting points were determined on a Kofler apparatus as uncorrected values. Analytical thin-layer chromatography was performed on precoated 250 μm layer thickness silica gel 60 F254 plates and visualized with UV light. Column chromatography was performed silica gel 300-400 mesh. IR spectra were measured on Bio-Rad FTS spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were measured on a Bruker (Avance) 400 MHz NMR instrument in DMSO-d_6 with chemical shift (δ) given in parts per million (ppm) relative to TMS as internal standard and recorded at 23 °C. The mass spectra were recorded using a liquid-mass spectrometer. Elemental analysis was determined by elemental analyzer 2400II. The microwave-assisted reaction was performed on a Discover SP microwave reactor-CEM.

A mixture of **1** (1 mmol), **2** (1.1 mmol), sulfur (1.1 mmol), corresponding base (1 mmol) and solvent (3 mL) was put into a 5 mL microwave reaction vial. The vial was irradiated in the microwave reactor at 50 °C for 30 min with the absorbance set to "very high". After cooling, the reaction mixture was extracted with EtOAc (3 × 20 mL). The combined organic phase was dried over Na_2SO_4 and concentrated under reduced pressure and the crude residue purified by flash chromatography on silica gel to give the products **3a-3m** and **4a-4r**.

2-Amino-5-ethyl-3-thiophenecarboxylic acid methyl ester (3a) Yellow solid 175 mg; 95% yield; mp 56-57 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.12 (s, 2H), 6.51 (s, 1H), 3.67 (s, 3H), 2.51 (d, J = 6.8 Hz, 2H), 1.13 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 165.1, 163.1, 126.6, 120.5, 103.1, 50.9, 22.8, 15.6. ESI-MS *m/z*: 186.0 $[M + H]^+$. Anal. Calcd for $C_8H_{11}NO_2S$: C, 51.87; H, 5.99; N, 7.56. Found C, 51.89; H, 5.97; N, 7.59.

2-Amino-5-isopropylthiophene-3-carboxylic acid methyl ester (3b) Light yellow solid 183 mg; 92% yield; mp 112-113 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.13 (s, 2H), 6.50 (d, J = 1.2 Hz, 1H), 3.68 (s, 3H), 2.89 – 2.82 (m, 1H), 1.17 (d, J = 6.8 Hz, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 165.2, 162.9, 132.2, 119.0, 103.0, 50.8, 29.2, 24.3.ESI-MS *m/z*: 200.1 $[M + H]^+$. Anal. Calcd for $C_9H_{13}NO_2S$: C, 54.25; H, 6.58; N, 7.03. Found C, 54.28; H, 6.61; N, 7.01.

2-Amino-5-*tert*-butylthiophene-3-carboxylic acid methyl ester (3c) Light yellow solid 198 mg; 93% yield; mp 187-188 °C;^{1}H NMR (400 MHz, DMSO-d_6) δ 7.12 (s, 2H), 6.48 (s, 1H), 3.68 (s, 3H), 1.23 (s, 9H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 165.2, 162.8, 136.3, 118.3, 102.8, 50.8, 33.8, 32.0. ESI-MS *m/z*: 214.1 $[M + H]^+$. Anal. Calcd for $C_{10}H_{15}NO_2S$: C, 56.31; H, 7.09; N, 6.57. Found C, 56.29; H, 7.06; N, 6.61.

2-Amino-5-butylthiophene-3-carboxylic acid methyl ester (3d) Light yellow solid 172 mg; 81% yield; mp 69-70 °C;^{1}H NMR (400 MHz, DMSO-d_6) δ 7.12 (s, 2H), 6.50 (s, 1H), 3.67 (s, 3H), 2.53 – 2.50 (m, 2H), 1.53 – 1.40 (m, 2H), 1.35 – 1.56 (m, 2H), 0.88 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 165.1, 163.2, 125.0, 121.3, 103.1, 50.9, 33.0, 29.0, 21.9, 14.1. ESI-MS *m/z*: 214.1 $[M + H]^+$. Anal. Calcd for $C_{10}H_{15}NO_2S$: C, 56.31; H, 7.09; N, 6.57. Found C, 56.32; H, 7.11; N, 6.54.

2-Amino-5-phenylthiophene-3-carboxylic acid methyl ester (3e) Light yellow oil 181 mg; 78% yield; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.50 (s, 2H), 7.45 (dd, J = 8.4, 1.2 Hz, 2H), 7.34 (dd, J = 10.4, 4.8 Hz, 2H), 7.25 (s, 1H), 7.19 (t, J = 7.2 Hz, 1H), 3.74 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 165.1, 163.9, 134.2, 129.4, 126.7, 124.4, 122.7, 121.5, 105.1, 51.2. ESI-MS *m/z*: 234.0 $[M + H]^+$. Anal. Calcd for $C_{12}H_{11}NO_2S$: C, 61.78; H, 4.75; N, 6.00. Found C, 61.79; H, 4.72; N, 6.03.

2-Amino-5-benzyl-thiophene-3-carboxylic acid methyl ester (3f) Yellow solid 182 mg; 74% yield; mp 79-80 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.31 – 7.29 (m, 2H), 7.24 (s, 2H), 7.22 (s, 1H), 7.16 (s, 2H), 6.56 (s, 1H), 3.86 (s, 2H), 3.67 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 165.13 (s), 163.96 (s), 140.65 (s), 128.92 (s), 128.87 (s), 126.82 (s), 124.19 (s), 122.44 (s), 103.07 (s), 50.91 (s), 35.51 (s). ESI-MS *m/z*: 248.2 $[M + H]^+$. Anal. Calcd for $C_{13}H_{13}NO_2S$: C, 63.13; H, 5.30; N, 5.66. Found C, 63.12; H, 5.33; N, 5.64.

2-Amino-5,6-dihydro-4*H*-cyclopenta[*b*]thiophene-3-carboxylic acid methyl ester (3g) Light yellow solid 138 mg; 70% yield; mp 168-169 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.21 (s, 2H), 3.67 (s, 3H), 2.69 (dd, J = 7.6, 6.4 Hz, 2H), 2.62 (dd, J = 10.4, 4.0 Hz, 2H), 2.27 – 2.18 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 168.5, 165.5, 141.9, 119.6, 99.7, 50.8, 30.9, 28.9, 27.1. ESI-MS m/z: 198.2 $[M + H]^+$. Anal. Calcd for $C_9H_{11}NO_2S$: C, 54.80; H, 5.62; N, 7.10. Found C, 54.82; H, 5.59; N, 7.11.

2-Amino-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylic acid methyl ester (3h) Light yellow solid 166 mg; 79% yield; mp 129-130 °C;^{1}H NMR (400 MHz, DMSO-d_6) δ 7.21 (s, 2H), 3.67 (s, 3H), 2.58 (t, J = 5.6 Hz, 2H), 2.42 (t, J = 5.6 Hz, 2H), 1.75 – 1.56 (m, 4H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 165.8, 163.4, 131.8, 115.9, 102.9, 50.7, 26.9, 24.4, 23.3, 22.8. ESI-MS *m/z*: 212.1 $[M + H]^+$. Anal. Calcd for $C_{10}H_{13}NO_2S$: C, 56.85; H, 6.20; N, 6.63. Found C, 56.87; H, 6.21; N, 6.61.

2-Amino-5,6,7,8-tetrahydro-4*H*-cyclohepta[*b*]thiophene-3-carboxylic acid methyl ester (3i) Light yellow solid 204 mg; 91% yield; mp 85-86 °C;^{1}H NMR (400 MHz, DMSO-d_6) δ 7.03 (s, 2H), 3.69 (s, 3H), 2.97 – 2.83 (m, 2H), 1.75 (dt, J = 11.2, 6.0 Hz, 2H), 1.52 (qd, J = 11.2, 6.0 Hz, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 165.7, 161.8, 137.3, 119.4, 104.7, 50.8, 32.2, 28.4, 28.3, 28.0, 27.2. ESI-MS *m/z*: 226.3 $[M + H]^+$. Anal. Calcd for $C_{11}H_{15}NO_2S$: C, 58.64; H, 6.71; N, 6.22. Found C, 58.62; H, 6.72; N, 6.25.

2-Amino-5,5-dimethyl-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylic acid methyl ester (3j) Light yellow solid 200 mg; 84% yield; mp 98-99 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.21 (s, 2H), 3.68

(s, 3H), 2.58 (t, *J* = 6.4 Hz, 2H), 2.20 (s, 2H), 1.41 (t, *J* = 6.4 Hz, 2H), 0.93 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 165.9, 163.5, 130.2, 115.2, 102.7, 50.7, 37.9, 35.6, 30.3, 28.0, 24.6. ESI-MS *m/z*: 240.2 [M + H]$^+$. Anal. Calcd for $C_{12}H_{17}NO_2S$: C, 60.22; H, 7.16; N, 5.85. Found C, 60.18; H, 7.18; N, 5.89.

5-Acetylamino-2-amino-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylic acid methyl ester (3k) Light yellow solid 243 mg; 91% yield; mp 205-206 °C; IR ν_{max} 3398, 3380, 3281, 2942, 2484, 1665, 1641, 1593, 1577, 1492, 1442, 1283, 1144, 789, 778, cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.89 (d, *J* = 7.6 Hz, 1H), 7.25 (s, 2H), 4.00 – 3.86 (m, 1H), 3.68 (s, 3H), 2.80 (dt, *J* = 17.2, 4.8 Hz, 1H), 2.67 (dd, *J* = 15.6, 5.2 Hz, 1H), 2.62 – 2.53 (m, 1H), 2.29 (dd, *J* = 15.6, 8.4 Hz, 1H), 1.81 (s, 4H), 1.62 – 1.53 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 169.1, 165.8, 163.8, 131.3, 113.6, 102.6, 50.7, 45.1, 30.6, 28.5, 25.4, 23.2. ESI-MS *m/z*: 269.3 [M + H]$^+$. Anal. Calcd for $C_{12}H_{16}N_2O3S$: C, 53.71; H, 6.01; N, 10.44. Found C, 53.73; H, 5.98; N, 10.46.

2-Amino-5-phenyl-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylic acid methyl ester (3l) Light yellow solid 229 mg; 80% yield; mp 118-119 °C; IR ν_{max} 3449, 3328, 2930, 2911, 2883, 2831, 1732, 1672, 1581, 1491, 1440, 1262, 1008, 788, 776, 739, 699 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.35 – 7.30 (m, 5H), 7.29 – 7.21 (m, 2H), 3.72 (s, 3H), 3.03 – 2.78 (m, 2H), 2.72 – 2.64 (m, 2H), 2.62 – 2.56 (m, 1H), 2.00 – 1.79 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 165.8, 163.7, 146.4, 131.6, 128.8, 127.3, 126.6, 115.5, 102.7, 50.7, 33.8, 32.2, 30.1, 27.3. ESI-MS *m/z*: 288.4 [M + H]$^+$. Anal. Calcd for $C_{16}H_{17}NO_2S$: C, 66.87; H, 5.96; N, 4.87; 11.16. Found C, 66.85; H, 5.98; N, 4.84.

2-Amino-5-ethyl-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylic acid methyl ester (3m) Light yellow solid 184 mg; 77% yield; mp 72-73 °C; IR ν_{max} 3423, 3314, 2941, 2906, 2850, 1658, 1593, 1487, 1396, 1264, 1050 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.20 (s, 2H), 3.67 (s, 3H), 2.76 (d, *J* = 17.6 Hz, 1H), 2.61 – 2.40 (m, 2H), 2.17 – 1.98 (m, 1H), 1.88 – 1.75 (m, 1H), 1.61 – 1.49 (m, 1H), 1.33 (dt, *J* = 21.2, 6.8 Hz, 2H), 1.24 (dd, *J* = 10.8, 5.6 Hz, 1H), 0.91 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 165.8, 163.5, 131.7, 115.5, 102.8, 50.7, 36.2, 30.4, 28.9, 28.7, 26.7, 11.8. ESI-MS *m/z*: 240.2 [M + H]$^+$. Anal. Calcd for $C_{12}H_{17}NO_2S$: C, 60.22; H, 7.16; N, 5.85. Found C, 60.24; H, 7.13; N, 5.86.

2-Amino-5-isopropylthiophene-3-carboxylic acid ethyl ester (4a) Light yellow oil 183 mg; 86% yield; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.12 (s, 2H), 6.50 (s, 1H), 4.16 (q, *J* = 7.1 Hz, 2H), 2.91 – 2.81 (m, 1H), 1.24 (t, *J* = 7.2 Hz, 3H), 1.17 (d, *J* = 6.8 Hz, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.9, 162.9, 132.2, 119.0, 103.2, 59.2, 29.2, 24.3, 14.9. ESI-MS *m/z*: 214.3 [M + H]$^+$. Anal. Calcd for $C_{10}H_{15}NO_2S$: C, 56.31; H, 7.09; N, 6.57. Found C, 56.33; H, 7.12; N, 6.54.

2-Amino-*N*-methyl-5-(1-methylethyl)-3-thiophenecarboxamide (4b) Light brown solid 150 mg; 76% yield; mp 119-120 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.54 (d, *J* = 4.4 Hz, 1H), 7.00 (s, 2H), 6.74 (s, 1H), 3.03 – 2.72 (m, 1H), 2.67 (d, *J* = 4.4 Hz, 3H), 1.18 (d, *J* = 6.8 Hz, 6H); ^{13}C NMR (100 MHz,

DMSO-d_6) δ 166.5, 159.4, 131.8, 118.5, 106.8, 29.3, 25.8, 24.5. ESI-MS *m/z*: 199.1 $[M + H]^+$. Anal. Calcd for $C_9H_{14}N_2OS$: C, 54.52; H, 7.12; N, 14.13. Found C, 54.49; H, 7.13; N, 14.11.

2-Amino-5-isopropylthiophene-3-carboxylic acid amide (4c) Light yellow solid 174 mg; 95% yield; mp 164-165 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.06 (s, 2H), 6.75 (s, 1H), 6.63 (br, 1H), 2.94 – 2.75 (m, 1H), 1.18 (d, *J* = 6.8 Hz, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 163.2, 155.4, 130.0, 112.2, 102.1, 24.8, 19.4. ESI-MS *m/z*: 185.3 $[M + H]^+$. Anal. Calcd for $C_8H_{12}N_2OS$: C, 52.15; H, 6.56; N, 15.20. Found C, 52.17 H, 6.55 N, 15.23.

[2-Amino-5-(1-methylethyl)-3-thienyl]phenylmethanone (4d) Light yellow oil 176 mg; 72% yield; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.33 (s, 2H), 7.57 (d, *J* = 7.6 Hz, 2H), 7.52 – 7.43 (m, 3H), 6.41 (s, 1H), 2.92 – 2.82 (m, 1H), 1.15 (d, *J* = 6.8 Hz, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 189.2, 166.6, 141.6, 131.8, 130.7, 128.7, 128.0, 120.4, 112.5, 29.3, 24.3. ESI-MS *m/z*: 246.1 $[M + H]^+$. Anal. Calcd for $C_{14}H_{15}NOS$: C, 68.54; H, 6.16; N, 5.71. Found C, 68.55; H, 6.18; N, 5.68.

1-(2-Amino-5-isopropylthiophen-3-yl)-ethanone (4e) Light yellow solid 166 mg; 91% yield; mp 126-127 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.92 (s, 2H), 6.63 (s, 1H), 2.91 – 2.84 (m, 1H), 2.24 (s, 3H), 1.19 (d, *J* = 6.8 Hz, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 192.3, 163.8, 131.6, 119.9, 113.7, 29.4, 28.4, 24.4. ESI-MS *m/z*: 184.3 $[M + H]^+$. Anal. Calcd for $C_9H_{13}NOS$: C, 58.98; H, 7.15; N, 7.64. Found C, 59.01; H, 7.13; N, 7.65.

2-Amino-5-isopropylthiophene-3-carboxylic acid *tert*-butyl ester (4f) Light yellow oil 229 mg; 95% yield; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.01 (s, 2H), 6.43 (s, 1H), 2.90 – 2.80 (m, 1H), 1.48 (s, 9H), 1.16 (d, *J* = 6.8 Hz, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.7, 162.2, 131.7, 119.5, 104.6, 79.2, 29.2, 28.6, 24.4. ESI-MS *m/z*: 242.4 $[M + H]^+$. Anal. Calcd for $C_{12}H_{19}NO_2S$: C, 59.72; H, 7.93; N, 5.80. Found C, 59.74; H, 7.96; N, 5.78.

2-Amino-5-isopropylthiophene-3-carboxylic acid phenylamide (4g) Light brown solid 163 mg; 63% yield; mp 44-45 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.22 (s, 1H), 7.68 (dd, *J* = 8.4, 1.2 Hz, 2H), 7.34 – 7.24 (m, 4H), 7.10 – 6.99 (m, 2H), 2.94 – 2.87 (m, 1H), 1.23 (d, *J* = 6.8 Hz, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.6, 161.6, 140.0, 131.6, 128.8, 123.2, 120.7, 118.6, 106.2, 29.4, 24.5. ESI-MS *m/z*: 261.2 $H]^+$. Anal. Calcd for $C_{14}H_{16}N_2OS$: C, 64.58; H, 6.19; N, 10.76. Found C, 64.56; H, 6.21; N, 10.75.

[2-Amino-5-(1-methylethy1)-3-thienyl]-2-thienylmethanone (4h) Light yellow solid 215 mg; 86% yield; mp 100-101 °C; IR ν_{max} 3355, 3251, 2956, 2924, 2865, 1747, 1567, 1434, 1264 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.30 (s, 2H), 7.85 (dd, *J* = 5.2, 1.2 Hz, 1H), 7.72 (dd, *J* = 3.6, 1.2 Hz, 1H), 7.20 (dd, *J* = 5.2, 3.6 Hz, 1H), 6.90 (d, *J* = 1.2 Hz, 1H), 3.05 – 2.81 (m, 1H), 1.21 (d, *J* = 6.8 Hz, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 179.4, 166.9, 145.9, 132.5, 131.9, 130.6, 128.5, 119.4, 111.7, 29.4, 24.3.ESI-MS *m/z*: 252.3 $[M + H]^+$. Anal. Calcd for $C_{12}H_{13}NOS_2$: C, 57.34; H, 5.21; N, 5.57. Found C, 57.36; H, 5.19; N, 5.59.

2-Amino-5-*tert*-butylthiophene-3-carboxylic acid methylamide (4i) Light yellow solid 197 mg; 93% yield; mp 109-110 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.55 (d, J = 4.4 Hz, 1H), 6.98 (s, 2H), 6.76 (s, 1H), 2.67 (d, J = 4.4 Hz, 3H), 1.24 (s, 9H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.5, 159.3, 135.9, 118.0, 106.7, 33.9, 32.2, 25.8. ESI-MS *m/z*: 213.2 $[M + H]^+$. Anal. Calcd for $C_{10}H_{16}N_2OS$: C, 56.57; H, 7.60; N, 13.19. Found C, 56.61; H, 7.58; N, 13.21.

(2-Amino-5-*tert*-butylthiophen-3-yl)phenylmethanone (4j) Light yellow oil 199 mg; 77% yield; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.31 (s, 2H), 7.57 (dd, J = 7.6, 1.6 Hz, 2H), 7.51 – 7.47 (m, 3H), 6.39 (s, 1H), 1.22 (s, 9H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 189.3, 166.6, 141.6, 135.8, 130.9, 128.7, 128.0, 119.6, 112.5, 33.8, 31.8. ESI-MS *m/z*: 260.3 $[M + H]^+$. Anal. Calcd for $C_{15}H_{17}NOS$: C, 69.46; H, 6.61; N, 5.40. Found C, 69.49; H, 6.63; N, 5.38.

[(2-Amino-5-*tert*-butylthiophen-3-yl)thiophen-2-yl]methanone (4k) Yellow solid 222 mg; 84% yield; mp 77-78 °C; IR ν_{max} 3373, 3283, 2950, 2861, 1580, 1566, 1293 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.27 (s, 2H), 7.84 (d, J = 4.8 Hz, 1H), 7.71 (d, J = 4.8 Hz, 1H), 7.28 – 7.18 (m, 1H), 6.86 (s, 1H), 1.28 (s, 9H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 179.5, 166.8, 145.8, 136.5, 131.9, 130.7, 128.5, 118.7, 111.8, 33.9, 31.9. ESI-MS *m/z*: 266.1 $[M + H]^+$. Anal. Calcd for $C_{13}H_{15}NOS_2$: C, 58.83; H, 5.70; N, 5.28. Found C, 58.79; H, 5.72; N, 5.27.

2-Amino-5-phenylthiophene-3-carboxylic acid ethyl ester (4l) Light yellow solid 158 mg; 64% yield; mp 117-118 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.52 – 7.43 (m, 4H), 7.34 (t, J = 7.6 Hz, 2H), 7.24 (s, 1H), 7.19 (t, J = 7.2 Hz, 1H), 4.22 (q, J = 7.2 Hz, 2H), 1.29 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.8, 163.9, 134.2, 129.4, 126.7, 124.4, 122.7, 121.5, 105.4, 59.6, 15.0. ESI-MS *m/z*: 248.2 $[M + H]^+$. Anal. Calcd for $C_{13}H_{13}NO_2S$: C, 63.13; H, 5.30; N, 5.66. Found C, 63.09; H, 5.32; N, 5.68.

[(2-Amino-5-phenylthiophen-3-yl)thiophen-2-yl]methanone (4m) Light yellow solid 256 mg; 90% yield; mp 172-173 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.56 (s, 2H), 7.98 – 7.86 (m, 2H), 7.62 (s, 1H), 7.55 (d, J = 7.6 Hz, 2H), 7.37 (t, J = 7.6 Hz, 2H), 7.30 – 7.18 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 179.9, 167.6, 145.6, 134.1, 132.5, 131.4, 129.4, 128.8, 127.0, 124.9, 122.9, 121.7, 113.7. ESI-MS *m/z*: 286.2 $[M + H]^+$. Anal. Calcd for $C_{15}H_{11}NOS_2$: C, 63.13; H, 3.89; N, 4.91. Found C, 63.11; H, 3.92; N, 4.89.

2-Amino-5-butylthiophene-3-carboxylic acid amide (4n) Light yellow solid 114 mg; 58% yield; mp 92-93 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.05 (s, 2H), 6.73 (s, 1H), 2.51 (t, J = 7.2 Hz, 2H), 1.59 – 1.44 (m, 2H), 1.37 – 1.25 (m, 2H), 0.89 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 168.0, 160.6, 124.1, 121.4, 106.7, 33.2, 29.3, 21.9, 14.1. ESI-MS *m/z*: 199.3 $[M + H]^+$. Anal. Calcd for $C_9H_{14}N_2OS$: C, 54.52; H, 7.12; N, 14.13. Found C, 54.54; H, 7.09; N, 14.15.

[(2-Amino-5-butylthiophen-3-yl)thiophen-2-yl]methanone (4o) Yellow solid 230 mg; 87% yield; mp 63-64 °C; IR ν_{max} 3379, 3274, 2955, 2927, 2869, 1566, 1447, 1350, 1272, 770, 759 cm^{-1}; ^{1}H NMR (400

MHz, DMSO-d_6) δ 8.30 (s, 2H), 7.84 (dd, *J* = 5.2, 1.2 Hz, 1H), 7.72 (dd, *J* = 3.6, 1.2 Hz, 1H), 7.19 (dd, *J* = 5.2, 3.6 Hz, 1H), 6.94 (s, 1H), 2.59 (t, *J* = 7.2 Hz, 2H), 1.52 (dt, *J* = 20.8, 7.6 Hz, 2H), 1.33 (dq, *J* = 14.4, 7.2 Hz, 2H), 0.89 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 179.3, 167.3, 145.9, 131.9, 130.6, 128.5, 125.4, 121.7, 111.9, 33.1, 29.3, 22.0, 14.1. ESI-MS *m/z*: 266.0 $[M + H]^+$. Anal. Calcd for $C_{13}H_{15}NOS_2$: C, 58.83; H, 5.70; N, 5.28. Found C, 58.86; H, 5.68; N, 5.30.

(2-Amino-5,6-dihydro-4*H*-cyclopenta[*b*]thiophen-3-yl)-(4-chlorophenyl)methanone(4p) Light yellow solid 202 mg; 73% yield; mp 197-198 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.42 (s, 2H), 7.54 – 7.45 (m, 2H), 7.43 – 7.34 (m, 2H), 2.59 (t, *J* = 7.2 Hz, 2H), 2.14 – 2.01 (m, 2H), 1.93 (t, *J* = 6.8 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 189.2, 172.5, 141.1, 140.3, 134.7, 129.3, 128.4, 121.0, 109.8, 31.4, 28.8, 27.4. ESI-MS *m/z*: 278.2 $[M + H]^+$. Anal. Calcd for $C_{14}H_{12}ClNOS$: C, 60.54; H, 4.35; N, 5.04. Found C, 60.57; H, 4.33; N, 5.02.

[(2-Amino-5,6-dihydro-4*H*-cyclopenta[*b*]thiophen-3-yl)thiophen-2-yl]methanone(4q)Light brown solid 223 mg; 85% yield; mp 91-92 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.81 (dd, *J* = 4.8, 1.2 Hz, 1H), 7.51 (s, 2H), 7.37 (dd, *J* = 3.6, 1.2 Hz, 1H), 7.12 (dd, *J* = 4.8, 3.6 Hz, 1H), 2.47 (d, *J* = 6.0 Hz, 2H), 2.09 (t, *J* = 6.0 Hz, 2H), 1.71 (dd, *J* = 10.4, 4.4 Hz, 2H), 1.54 – 1.43 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 182.8, 163.9, 145.4, 131.6, 131.4, 130.8, 127.8, 117.6, 114.7, 27.7, 24.6, 23.2, 23.0. ESI-MS *m/z*: 264.1 $[M + H]^+$. Anal. Calcd for $C_{13}H_{13}NOS_2$: C, 59.28; H, 4.98; N, 5.32. Found C, 59.28; H, 4.98; N, 5.32.

[(2-Amino-4,5,6,7-tetrahydro-benzo[*b*]thiophen-3-yl)-(4-chloro-phenyl)]methanone(4r) Light yellow solid 253 mg; 87% yield; mp 124-125 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.16 (s, 2H), 7.55 – 7.44 (m, 2H), 7.43 – 7.34 (m, 2H), 2.44 (t, *J* = 6.4 Hz, 2H), 1.79 – 1.59 (m, 3H), 1.50 – 1.29 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 189.7, 166.4, 141.6, 134.9, 130.2, 129.4, 128.6, 117.2, 113.7, 27.9, 24.6, 23.0, 22.9. ESI-MS *m/z*: 292.3 $[M + H]^+$. Anal. Calcd for $C_{15}H_{14}ClNOS$: C, 61.74; H, 4.84; N, 4.80. Found C, 61.77; H, 4.82; N, 4.81.

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REFERENCES

1. S. Touil and K. Khalladi, *Heterocycles*, 2014, **89**, 753.
2. Y. N. Mabkhot, N. A. Kaal, S. Alterary, M. S. Mubarak, A. Alsayari, and A. Bin Muhsinah, *J. Heterocycl. Chem.*, 2019, **56**, 2945.
3. I. C. F. R. Ferreira, R. C. Calhelha, L. M. Estevinho, and M.-J. R. P. Queiroz, *Bioorg. Med. Chem.*

Lett., 2004, **14**, 5831.

4. I. Jarak, M. Kralj, L. Šuman, G. Pavlović, J. Dogan, I. Piantanida, M. Žinić, K. Pavelić, and G. Karminski-Zamola, *J. Med. Chem.*, 2005, **48**, 2346.
5. I. C. F. R. Ferreira, M. -J. R. P. Queiroz, M. Vilas-Boas, L. M. Estevinho, A. Begouin, and G. Kirsch, *Bioorg. Med. Chem Lett.*, 2006, **16**, 1384.
6. A. J. Davis, J. Shi, H. A. Pritchard, P. S. Chadha, N. Leblanc, G. Vasilikostas, Z. Yao, A. S. Verkman, A. P. Albert, and I. A. Greenwood, *Br. J. Pharmacol.*, 2013, **168**, 773.
7. C. Ballatore, A. B. Smith, 3rd, V. M. Lee, J. Q. Trojanowski, and K. R. Brunden, *Expert Opin. Ther. Pat.*, 2014, **24**, 355.
8. S. H. Choi, S. Ryu, K. Sim, C. Song, I. Shin, S. S. Kim, Y. S. Lee, J. Y. Park, and T. Sim, *Eur. J. Med. Chem.*, 2020, **208**, 112688.
9. M. S. Abaee, A. Hadizadeh, M. M. Mojtahedi, and M. R. Halvagar, *Tetrahedron Lett.*, 2017, **58**, 1408.
10. K. Bozorov, L. F. Nie, J. Zhao, and H. A. Aisa, *Eur. J. Med. Chem.*, 2017, **140**, 465.
11. Y. Han, W.-Q. Tang, and C.-G. Yan, *Tetrahedron Lett.*, 2014, **55**, 1441.
12. F. Javadi and R. Tayebee, *Microporous Mesoporous Mater.*, 2016, **231**, 100.
13. Y. Le, Y. Zhang, Q. Wang, N. Rao, D. Li, L. Liu, G. Ouyang, and L. Yan, *Tetrahedron Lett.*, 2021, **68**, 152903.
14. P. Liu and W. Chen, *J. Mater. Chem. C*, 2020, **8**, 9391.
15. G. Revelant, S. Dunand, S. Hesse, and G. Kirsch, *Synthesis*, 2011, 2935.
16. M. Sridhar, R. M. Rao, N. H. K. Baba, and R. M. Kumbhare, *Tetrahedron Lett.*, 2007, **48**, 3171.