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PAPER

An efficient synthesis of dihydrothiophene ureidoformamides by domino reactions of 1,3-thiazolidinedione under catalyst-free conditions†

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An efficient synthesis of dihydrothiophene ureidoformamides by the domino reactions of aldehydes, malononitrile, amines and 1,3-thiazolidinedione in PEG 400/H_2O is studied. The reaction is free of catalysts and toxic solvents, of shorter reaction time and with ease of the product isolation, making it more environmentally friendly and suitable for large-scale operations.

Introduction

Green chemistry, which emphasizes the development of environmentally benign chemical processes and technologies has attracted much attention in recent years.[1] Domino reactions defined as processes of two or more bond-forming reactions under identical conditions have emerged as a powerful tool to achieve the goal of green chemistry.[2] Because the subsequent transformation takes place at the functionalities obtained in the former transformation in domino reactions, they allow the efficient synthesis of complex molecules from simple substrates in an ecologically and economically favorable way. In addition, the use of "green" solvents such as water,[3] poly(ethylene glycol)[4] and glycerol[5] is also considered advantageous as a medium for reaction and workup relative to flammable, volatile or toxic organic solvents.

The active methylene derivatives with both electrophilic and nucleophilic sites, have proven to be valuable tools in the synthesis of a wide variety of molecular systems, especially complex heterocyclic scaffolds.[6] A representative example of such compounds is 1,3-thiazolidinedione, which is an important synthetic intermediate in various synthetic transformations, since thiazolidineone structures are widely present in a number of biologically active and medicinal agents.[7] Therefore, it will be interesting and significant to apply 1,3-thiazolidinedione in domino reactions for preparation of new and useful organic compounds.

Recently, Sun *et al.* have reported the synthesis of dihydrothiophene ureidoformamides by domino reactions of 1,3-thiazolidinedione in acetonitrile using organic amines as catalyst,[8] but these protocols fail to meet the requirements of green chemistry due to long reaction time, low yields and the use of toxic solvents and catalysts. Thus, we wish to explore a more "green" and efficient process for the synthesis of these compounds, obtaining more information about the mechanism of the domino reactions and ascertaining its scope and limitation. Along this line, we describe here a facile, eco-friendly method for efficient synthesis of dihydrothiophene ureidoformamides from aldehydes, malononitrile, amines and 1,3-thiazolidinedione in PEG 400/H_2O under catalyst-free conditions.

Results and discussion

Water as a cheap, safe and non-toxic solvent, is considered as the preferential choice of medium for organic reactions in view of economic and environmental problems.[9] As a part of our interest in using water as solvent for organic synthesis, we performed a domino reaction of **1a**, **2**, **3** and **4a** in water at 80 °C in the absence of catalysts. First, a mixture of **1a** and **2** was stirred for 10 min in water at 80 °C, then **3** and **4a** were added and stirred for additional 8 h at the same temperature. After the reaction completed, a low yield (19%) of **5a** was obtained (Table 1, entry 1). Several organic solvents, such as EtOH, CH_3CN, acetone, n-hexane, DMF, PEG 400 were applied to the reaction to further explore the solvent effects on the reaction (Table 1, entries 2–7), however, only EtOH and PEG 400 provided poor yields of the desired product.

Based on these results, it was found that polar protic solvents had a promotion effect on the reaction. Thus, the domino reaction was carried out in PEG 400/H_2O and EtOH/H_2O to improve the unsatisfactory results (Table 1, entries 8, 9), and PEG 400/H_2O gave the better yield (74%).

Further investigations indicated that **9a** was the key intermediate to initiate the reaction. Only in PEG 400/H_2O, **1a** could react with **2** completely to yield **9a** under identical conditions, preventing the reaction of **1a** and **3** to form **10a** which is the

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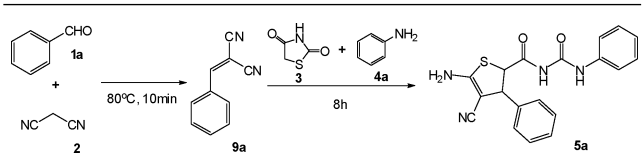
Table 1 Solvent effects on the reaction[a]



Entry	T/°C	Solvent (v/v)	Yield (%)[b]
1	80	H_2O	19
2	Reflux	EtOH	23
3	Reflux	CH_3CN	Trace
4	Reflux	Acetone	Trace
5	Reflux	n-Hexane	Trace
6	80	DMF	Trace
7	80	PEG 400	43
8	80	PEG 400/H_2O(1 : 1)	74
9	80	EtOH/H_2O(1 : 1)	57

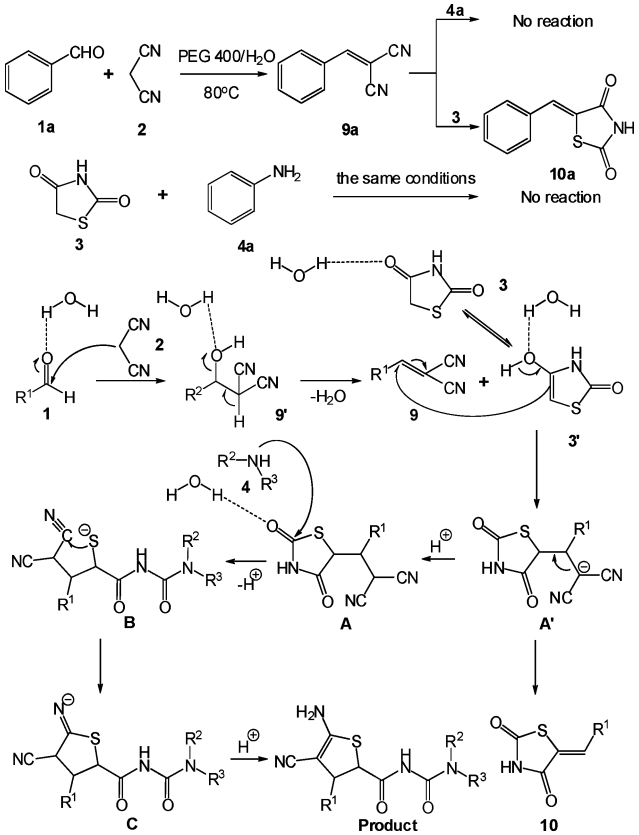
[a] Reaction conditions: after **1a** (2 mmol) and **2** (2.2 mmol) were stirred for 10 min in solvent (4 ml), **3** (2 mmol) and **4a** (2 mmol) were added and stirred for additional 8 h. [b] Isolated yield.

main side prodcut in the reaction. The reasons for this could be explained as follows. (1) The use of PEG 400 increases the solubility of reactants, which leads to larger interfacial area, lower mass transfer resistance.[10] (2) The promoting effects of water to the reaction could be attributed to its hydrophobic, polarity and hydro-bonding effects.[11] *Hydrophobic effect*: The hydrophobic effect leads to high negative volume of activation which means greater stabilization of activated complexes than hydrophobic reactants in the reaction. *Polarity effect*: The high polarity of water results in the more polar translated states than initial states, so the reaction speed can be increased. *Hydrogen-bonding effect*: Water could activate the reactants and intermediate products by forming the hydrogen bonds with the carbonyl oxygen and hydroxyl oxygen respectively (Scheme 1), making them easy to form corresponding products. It was found that only polar protic solvents could give the desired product, and the hydrogen-bonding effect is the main difference between polar protic solvents and other solvents, so the hydrogen-bonding effect may be the key factor to promote the reaction.

Encouraged by the remarkable results, we decided to use various aromatic aldehydes and aromatic amines to ascertain the scope and generality of the protocol, and a serious of dihydrothiophene ureidoformamides **5a–h** were prepared in moderate to good yields (Table 2). The reaction was not affected obviously by the characteristics of the substituent group on aniline or benzaldehyde. In addition, 1-naphthaldehyde, 1-naphthalenamine and aminopyridine were also applied to the protocol successfully.

Efforts were also made to expand the scope of the method to aliphatic amines, and the results were summarized in Table 3. Various primary and secondary amines were employed, and afforded the desired products **6a–h**. However, we failed to use other amines including benzyl amine, formamide, aminoethanol, 5-aminotetrazole in the protocol, due to the low nucleophilicity of their amino groups.

To further broaden the scope of the reaction, we also focused on employing aliphatic aldehydes to the protocol. To our delight,

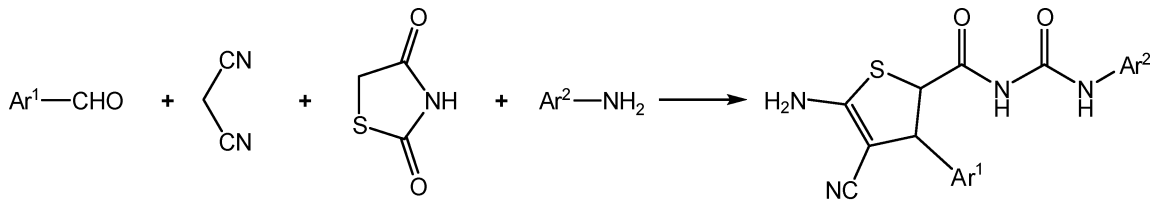


Scheme 1 A plausible mechanism for the formation of dihydrothiophene ureidoformamides from **1**, **2**, **3** and **4**.

cyclohexane aldehyde **1e** in place of aromatic aldehydes could react with **2**, **3** and **4**, and the target products **7a–i** could be obtained (Table 4). Although the protocol could accept a wide variety of aldehydes **1** and amines **4**, we were unable to extend it to other active methylene compounds including ethyl cyanoacetate, 3-cyanoacetylindole instead of malononitrile. Further, it was noteworthy that the reaction of aldehydes **1**, malononitrile **2**, 1,3-thiazolidinedione **3** and diamines **4k–m** could afford the bis-dihydrothiophene ureidoformamido compounds **8a–d** (Table 5).

The interesting and remarkable results obtained by the protocol prompted us to explore more details about the reaction mechanism. The continued research indicated the reaction of **9a** and **3** provided **10a** as the final product in the absence of **4a**, so it could be concluded that amine **4** was a necessary reactant to initiate the ring-opening reaction of thiozolidinedione structure (Scheme 1). According to the above results, a plausible mechanism for the formation of dihydrothiophene ureidoformamides from **1**, **2**, **3** and **4** was illustrated in Scheme 1. First, **9** is formed by the Knoevenagel condensation of **1** with **2**. The second step is the Michael addition of **3′** which has better nucleophilic character than **3**, and **9** to yield the adduct **A**. Then, **4** attacks the carbonyl group of thiazolidinedione in a ring-opening reaction to give a sulfide anion **B**, which intramolecularly nucleophilically attacks one of the cyano groups to form **C**.[8] Finally, the product is formed through an imine-enamine tautomerization process. If there is no amine **4** in the reaction, the ring-opening reaction will be inhibited, and **10** is produced from **9** and **3′** as final product.

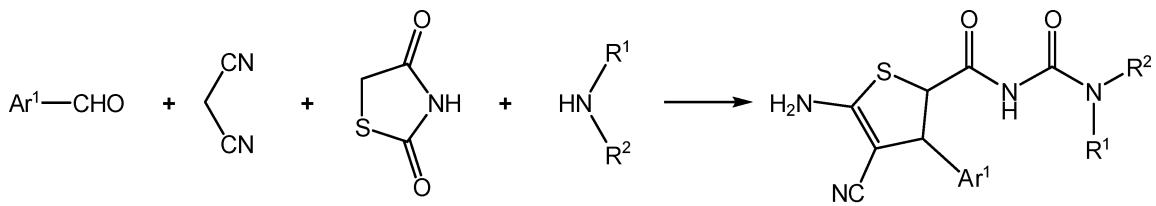
Table 2 The reaction of aromatic aldehydes, malononitrile, 1,3-thiazolidinedione and aromatic amines[a]



Entry	Aldehyde Ar[1]	1	Amine Ar[2]	4	Product	Yield (%)[b]
1	Ph	**1a**	Ph	**4a**	**5a**	74
2	4-ClC_6H_4	**1b**	Ph	**4a**	**5b**	90
3	4-$MeOC_6H_4$	**1c**	Ph	**4a**	**5c**	68
4	1-Naphthyl	**1d**	Ph	**4a**	**5d**	86
5	Ph	**1a**	4-ClC_6H_4	**4b**	**5e**	54
6	Ph	**1a**	4-MeC_6H_4	**4c**	**5f**	76
7	Ph	**1a**	1-Naphthyl	**4d**	**5g**	71
8	Ph	**1a**	2-Pyridyl	**4e**	**5h**	27

[a] Reaction conditions: after **1** (2 mmol) and **2** (2.2 mmol) were stirred for 10 min in PEG 400/H_2O (4 ml v/v = 1 : 1) at 80 °C, **3** (2 mmol) and **4** (2 mmol) were added and stirred for additional 8 h at the same temperature. [b] Isolated yield.

Table 3 The reaction of aromatic aldehydes, malononitrile, 1,3-thiazolidinedione and aliphatic amines[a]



Entry	Aldehyde Ar[1]	1	4		Product	Yield (%)[b]
1	Ph	**1a**	Piperidine	**4f**	**6a**	51
2	Ph	**1a**	Morpholine	**4g**	**6b**	55
3	Ph	**1a**	Diethylamine	**4h**	**6c**	27
4	Ph	**1a**	Cyclohexylamine	**4i**	**6d**	63
5	4-ClC_6H_4	**1b**	Cyclohexylamine	**4i**	**6e**	51
6	4-$MeOC_6H_4$	**1c**	Cyclohexylamine	**4i**	**6f**	44
7	1-Naphthyl	**1d**	Cyclohexylamine	**4i**	**6g**	54
8	Ph	**1a**	Butylamine	**4j**	**6h**	54

[a] Reaction conditions: after **1** (2 mmol) and **2** (2.2 mmol) were stirred for 10 min in PEG 400/H_2O (4 ml v/v = 1 : 1) at 80 °C, **3** (2 mmol) and **4** (2 mmol) were added and stirred for additional 6 h at the same temperature. [b] Isolated yield.

Conclusions

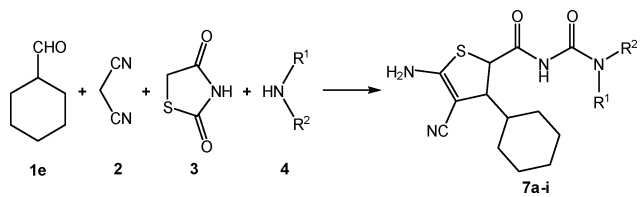
The domino reactions of aldehydes, malononitrile, amines and 1,3-thiazolidinedione for formation of dihydrothiophene ureidoformamides in PEG 400/H_2O under catalyst-free conditions are reported. We have extended the scope of the previously discovered tandem reactions of 1,3-thiazolidinedione, malononitrile, aromatic aldehydes, and amines. The process provides an opportunity to avoid toxic solvents and catalysts, and resource consumption compare to the previous reaction systems. The protocol is available for large-scale operations, owing to its simple work-up procedure, shorter reaction time and higher yields. The potential to apply the reaction in synthetic and medicinal chemistry are also quite significant.

Experimental

General procedure for the preparation of dihydrothiophene ureidoformamides from aldehyde, malononitrile, 1,3-thiazolidinedione and amine

A mixture of aldehyde (2.0 mmol) and malononitrile (2.2 mmol) in PEG 400/H_2O (4.0 ml, v/v = 1 : 1) was stirred at 80 °C for 10 min. Then amine (2.0 mmol) and 1,3-thiazolidinedione

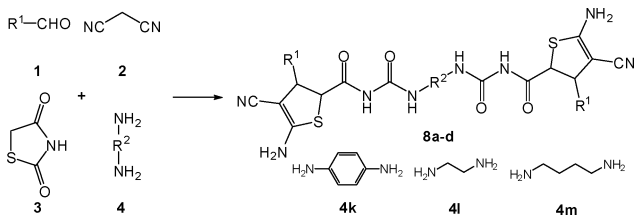
Table 4 The reaction of cyclohexanaldehyde, malononitrile, 1,3-thiazolidinedione and amines[a]



Entry	4		Product	Yield (%)[b]
1	Aniline	**4a**	**7a**	73
2	*p*-Chloroaniline	**4b**	**7b**	46
3	*p*-Toluidine	**4c**	**7c**	68
4	1-Naphthalenamine	**4d**	**7d**	65
5	Piperidine	**4f**	**7e**	70
6	Morpholine	**4g**	**7f**	34
7	Diethylamine	**4h**	**7g**	25
8	Cyclohexylamine	**4i**	**7h**	60
9	Butylamine	**4j**	**7i**	65

[a] Reaction conditions: after **1e** (2 mmol) and **2** (2.2 mmol) were stirred for 10 min in PEG 400/H_2O (4 ml v/v = 1 : 1) at 80 °C, **3** (2 mmol) and **4** (2 mmol) were added and stirred for additional 4 h at the same temperature. [b] Isolated yield.

Table 5 The reaction of aldehydes, malononitrile, 1,3-thiazolidinedione and diamines[a]



Entry	Aldehyde	Diamine	Time/h	Product	Yield (%)[b]
1	**1a**	**4k**	10	**8a**	87
2	**1a**	**4l**	8	**8b**	84
3	**1a**	**4m**	8	**8c**	76
4	**1e**	**4m**	6	**8d**	65

[a] Reaction conditions: after **1** (2 mmol) and **2** (2.2 mmol) were stirred for 10 min in PEG 400/H_2O (4 ml v/v = 1 : 1) at 80 °C, **3** (2 mmol) and **4** (1 mmol) were added and stirred for the period of time listed in Table 5 at the same temperature. [b] Isolated yield.

(2.0 mmol) were added and the reaction was stirred at the same temperature for several hours monitored by TLC. After the reaction completed, water (10 ml) was added to the mixture, and the precipitate was separated by filtration and washed with water. The crude product was recrystallized or washed with a mixture of ethanol and n-hexane to give the pure product.

Data for unknown compounds

5-Amino-4-cyano-3-(naphthalen-1-yl)-*N*-(phenylcarbamoyl)-2,3-dihydrothiophene-2-carboxamide 5d. Mp: 236–238 °C; white solid, ^{1}H NMR (500 MHz, DMSO-d_6): δ = 4.15 (s, 1H), 5.46 (s, 1H), 7.10–7.13 (m, 1H), 7.34–7.40 (m, 4H), 7.47 (d, 1H, *J* = 7.0 Hz), 7.57–7.66 (m, 5H), 7.91–7.95 (m, 2H), 8.03 (d, 1H, *J* = 8.0 Hz). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 55.10, 69.25, 118.64, 120.31, 122.87, 124.35, 124.94, 126.08, 126.44, 127.48, 128.72, 129.42, 129.60, 130.84, 134.38, 136.40, 137.91, 150.97, 162.80, 172.88. MS (ESI) *m*/*z*: 413 (M-H)$^-$. Anal. calcd for $C_{23}H_{18}N_4O_2S$: C, 66.65; H, 4.38; N, 13.52%, Found: C, 66.68; H, 4.29; N, 13.74%.

5-Amino-4-cyano-*N*-(1-naphthylcarbamoyl)-3-phenyl-2,3-dihydrothiophene-2-carboxamide 5g. Mp: 230–232 °C; white solid; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 4.28 (s, 1H), 4.71 (s, 1H), 7.30–7.34 (m, 3H), 7.40–7.43 (m, 4H), 7.51–7.54 (m, 1H), 7.59–7.62 (m, 1H), 7.70–7.73 (m, 1H), 7.76 (d, 1H, *J* = 8.0 Hz), 7.99–8.01 (m, 2H), 8.09 (d, 1H, *J* = 6.5 Hz), 11.01 (br, 2H). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 52.03, 55.81, 70.93, 118.63, 118.76, 120.87, 125.03, 126.04, 126.28, 126.74, 127.21, 127.61, 128.03, 129.15, 129.25, 132.87, 134.09, 142.10, 151.51, 162.24, 173.60. MS (ESI) *m*/*z*: 413 (M-H)$^-$. Anal. calcd for $C_{23}H_{18}N_4O_2S$: C, 66.65; H, 4.38; N, 13.52%, Found: C, 66.71; H, 4.48; N, 13.77%.

5-Amino-4-cyano-3-phenyl-*N*-(pyridin-2-ylcarbamoyl)-2,3-dihydrothiophene-2-carboxamide 5h. Mp: 202–204 °C; white solid; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 4.26 (s, 1H), 4.63 (s, 1H), 7.13–7.16 (m, 1H), 7.25 (s, 2H), 7.30–7.41 (m, 5H), 7.80–7.83 (m, 1H), 7.91 (s, 1H), 8.33 (d, 1H, *J* = 4.0 Hz), 10.62 (br, 1H), 10.98 (br, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 51.84, 56.03, 70.82, 113.53, 118.68, 120.20, 127.60, 128.01, 129.22, 139.07, 142.00, 148.69, 150.89, 151.26, 162.08, 172.92. MS (ESI) *m*/*z*: 364 (M-H)$^-$. Anal. calcd for $C_{18}H_{15}N_5O_2S$: C, 59.16; H, 4.14; N, 19.17%, Found: C, 59.29; H, 4.43; N, 18.88%.

***N*-[(5-Amino-4-cyano-3-phenyl-2,3-dihydrothiophen-2-yl)carbonyl]morpholine-4-carboxamide 6b.** Mp: 216–218 °C; white solid; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 3.35 (d, 4H, *J* = 5.5 Hz), 3.54–3.56 (m, 4H), 4.42 (s, 1H), 4.60 (d, 1H, *J* = 2.5 Hz), 7.12 (s, 2H), 7.28–7.31 (m, 3H), 7.36–7.39 (m, 2H), 10.09 (s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 45.13 51.48, 56.13, 66.30, 71.24, 118.88, 127.49, 127.88, 129.23, 142.75, 152.85, 162.20, 171.40. MS (ESI) *m*/*z*: 357 (M-H)$^-$. Anal. calcd for $C_{17}H_{18}N_4O_3S$: C, 56.97; H, 5.06; N, 15.63%, Found: C, 57.06; H, 5.28; N, 15.44%.

5-Amino-4-cyano-*N*-(cyclohexylcarbamoyl)-3-phenyl-2,3-dihydrothiophene-2-carboxamide 6d. Mp: 228–230 °C; white solid; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.25–1.35 (m, 5H), 1.54 (d, 1H, *J* = 12 Hz), 1.64 (d, 2H, *J* = 8.0 Hz), 1.81 (d, 2H, *J* = 5.0 Hz), 3.56 (s, 1H), 4.08 (s, 1H), 4.55 (d, 1H, *J* = 2.0 Hz), 7.20 (s, 2H), 7.29–7.39 (m, 5H), 8.17 (s, 1H), 10.43 (s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 24.62, 25.51, 32.70, 48.33, 51.99, 55.66, 70.89, 118. 64, 127.57, 127.96, 129.20, 141.99, 152.46, 162.19, 172.40. MS (ESI) *m*/*z*: 369 (M-H)$^-$. Anal. calcd for $C_{19}H_{22}N_4O_2S$: C, 61.60; H, 5.99; N, 15.12%, Found: C, 61.37; H, 5.83; N, 15.40%.

5-Amino-3-(4-chlorophenyl)-4-cyano-*N*-(cyclohexylcarbamoyl)-2,3-dihydrothiophene-2-carboxamide 6e. Mp: 240–242 °C; white solid; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.19–1.32 (m, 5H), 1.52 (s, 1H), 1.63 (s, 2H), 1.80 (s, 2H), 3.55 (s, 1H), 4.03 (s, 1H), 4.55 (s, 1H), 7.26 (s, 2H), 7.34 (d, 2H, *J* = 7.5 Hz), 7.44 (d, 2H, *J* = 8.0 Hz), 8.16 (s, 1H), 10.44 (s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 24.62, 25.49, 32.70, 48.49, 51.20, 55.51, 70.51, 118.52, 129.15, 129.52, 132.54, 140.95, 152.47, 162.47, 172.27.

MS (ESI) *m/z*: 403 $(M-H)^-$. Anal. calcd for $C_{19}H_{21}ClN_4O_2S$: C, 56.36; H, 5.23; N, 13.84%, Found: C, 56.44; H, 5.09; N, 13.68%.

5-Amino-4-cyano-*N*-(cyclohexylcarbamoyl)-3-(4-methoxyphenyl)-2,3-dihydrothiophene-2-carboxamide 6f. Mp: 224–226 °C; white solid; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.19–1.35 (m, 5H), 1.53 (d, 1H, *J* = 12.5 Hz), 1.63 (s, 2H), 1.80 (d, 2H, *J* = 5 Hz), 3.55 (s, 1H), 3.75 (s, 3H), 4.01 (s, 1H), 4.50 (d, 1H, *J* = 2.0 Hz), 6.93 (d, 2H, *J* = 8.5 Hz), 7.17–7.22 (m, 4H), 8.17 (s, 1H), 10.44 (s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 24.63, 25.49, 48.31, 51.40, 55.57, 55.88, 71.19, 114.56, 118.70, 128.69, 133.77, 152.45, 159.13, 161.85, 172.44. MS (ESI) *m/z*: 399 $(M-H)^-$. Anal. calcd for $C_{20}H_{24}N_4O_3S$: C, 59.98; H, 6.04; N, 13.99%, Found: C, 60.02; H, 5.99; N, 13.87%.

5-Amino-4-cyano-*N*-(cyclohexylcarbamoyl)-3-(naphthalen-1-yl)-2,3-dihydrothiophene-2-carboxamide 6g. Mp: 238–240 °C; white solid; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.22–1.31 (m, 5H), 1.54 (s, 1H), 1.67 (s, 2H), 1.85 (s, 2H), 3.57 (s, 1H), 4.04 (s, 1H), 5.39 (s, 1H), 7.36 (s, 2H), 7.44 (d, 1H, *J* = 7.0 Hz), 7.58–7.63 (m, 3H), 7.84 (d, 1H, *J* = 7.0 Hz), 7.93 (d, 1H, *J* = 7.5 Hz), 8.02 (d, 1H, *J* = 7.5 Hz), 8.19 (s, 1H), 10.47 (s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 24.69, 25.51, 32.69, 48.52, 55.05, 69.26, 118.61, 122.73, 124.93, 126.06, 126.41, 127.41, 128.67, 129.60, 130.84, 134.37, 136.41, 152.37, 162.81, 172.54. MS (ESI) *m/z*: 419 $(M-H)^-$. Anal. calcd for $C_{23}H_{24}N_4O_2S$: C, 65.69; H, 5.75; N, 13.32%, Found: C, 65.44; H, 5.68; N, 13.53%.

5-Amino-*N*-(butylcarbamoyl)-4-cyano-3-(naphthalen-1-yl)-2,3-dihydrothiophene-2-carboxamide 6h. Mp: 228–230 °C; white solid; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 0.88–0.91 (s, 3H), 1.26–1.34 (m, 2H), 1.43–1.48 (m, 2H), 3.16 (d, 2H, *J* = 6.5 Hz), 4.10 (s, 1H), 4.56 (d, 1H, *J* = 2.5 Hz), 7.20 (s, 2H), 7.29–7.32 (m, 3H), 7.37–7.40 (m, 2H), 8.20 (br, 1H), 10.40 (s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 14.06, 19.97, 31.67, 39.15, 52.10, 55.66, 70.82, 118.65, 127.57, 127.97, 129.21, 141.99, 153.30, 162.19, 172.08. MS (ESI) *m/z*: 343 $(M-H)^-$. Anal. calcd for $C_{17}H_{20}N_4O_2S$: C, 59.28; H, 5.85; N, 16.27%, Found: C, 59.22; H, 5.69; N, 16.34%.

5-Amino-4-cyano-3-cyclohexyl-*N*-(phenylcarbamoyl)-2,3-dihydrothiophene-2-carboxamide 7a. Mp: 226–228 °C; white solid; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.08–1.24 (m, 5H), 1.52 (s, 1H), 1.64–1.75 (m, 5H), 3.30 (d, 1H, *J* = 13.5 Hz), 4.20 (s, 1H), 6.99 (s, 2H), 7.08–7.11 (m, 1H), 7.32–7.35 (m, 2H), 7.54 (d, 2H, *J* = 8.0 Hz), 10.23 (s, 1H), 10.72 (s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 26.25, 26.36, 26.47, 29.30, 29.57, 42.31, 50.41, 52.81, 68.73, 119.36, 120.25, 124.28, 129.39, 137.88, 151.05, 161.83, 173.61. MS (ESI) *m/z*: 369 $(M-H)^-$. Anal. calcd for $C_{19}H_{22}N_4O_2S$: C, 61.60; H, 5.99; N, 15.12%, Found: C, 61.42; H, 5.88; N, 15.31%.

5-Amino-*N*-(4-chlorophenylcarbamoyl)-4-cyano-3-cyclohexyl-2,3-dihydrothiophene-2-carboxamide 7b. Mp: 220–222 °C; white solid; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.16–1.24 (m, 5H), 1.52 (s, 1H), 1.63–1.74 (m, 5H), 3.28 (d, 1H, *J* = 2.5 Hz), 4.19 (s, 1H), 6.99 (s, 2H), 7.38 (d, 2H, *J* = 8.5 Hz), 7.59 (s, 2H, *J* = 8.5 Hz), 10.28 (s, 1H), 10.78 (s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 26.24, 26.35, 26.47, 29.32, 29.52, 42.30, 50.41, 52.77, 68.67, 119.37, 121.96, 127.95, 129.22, 136.91, 151.10, 161.84, 173.52. MS (ESI) *m/z*: 403 $(M-H)^-$. Anal. calcd for $C_{19}H_{21}ClN_4O_2S$: C, 56.36; H, 5.23; N, 13.84%, Found: C, 56.40; H, 5.37; N, 13.81%.

5-Amino-4-cyano-3-cyclohexyl-*N*-(p-tolylcarbamoyl)-2,3-dihydrothiophene-2-carboxamide 7c. Mp: 216–218 °C; white solid; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.14–1.23 (m, 5H), 1.52 (s, 1H), 1.67–1.74 (m, 5H), 2.26 (s, 3H), 3.29 (s, 1H), 4.20 (s, 1H), 6.98 (s, 2H), 7.13 (d, 2H, *J* = 7.0 Hz), 7.41 (d, 2H, *J* = 7.0 Hz), 10.17 (s, 1H), 10.70 (s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 20.85, 26.25, 26.36, 26.47, 29.27, 29.57, 42.29, 50.80, 52.37, 52.80, 68.70, 119.37, 120.23, 133.30, 135.32, 151.00, 161.84, 173.57. MS (ESI) *m/z*: 383 $(M-H)^-$. Anal. calcd for $C_{20}H_{24}N_4O_2S$: C, 62.48; H, 6.29; N, 14.57%, Found: C, 62.37; H, 6.36; N, 14.82%.

5-Amino-4-cyano-3-cyclohexyl-*N*-(naphthalen-1-ylcarbamoyl)-2,3-dihydrothiophene-2-carboxamide 7d. Mp: 208–210 °C; white solid; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.14–1.25 (m, 5H), 1.56 (s, 1H), 1.65 (d, 1H, *J* = 11.0 Hz), 1.74 (s, 4H), 3.38 (d, 1H, *J* = 2.5 Hz), 4.28 (s, 1H), 7.05 (s, 2H), 7.50–7.54 (m, 1H), 7.57–7.60 (m, 1H), 7.66–7.70 (m, 1H), 7.74 (d, 1H, *J* = 8.5 Hz), 7.95–7.99 (m, 2H), 8.10 (d, 1H, *J* = 7.5 Hz), 11.00 (br, 2H). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 26.28, 26.40, 26.50, 29.30, 29.50, 42.50, 50.51, 52.92, 68.68, 118.51, 119.46, 120.80, 124.97, 125.95, 126.26, 126.71, 127.19, 129.13, 132.85, 134.06, 151.50, 161.94, 174.39. MS (ESI) *m/z*: 419 $(M-H)^-$. Anal. calcd for $C_{23}H_{24}N_4O_2S$: C, 65.69; H, 5.75; N, 13.32%, Found: C, 65.77; H, 6.03; N, 13.62%.

***N*-(5-Amino-4-cyano-3-cyclohexyl-2,3-dihydrothiophene-2-carbonyl)piperidine-1-carboxamide 7e.** Mp: 200–202 °C; white solid; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.07–1.18 (m, 6H), 1.47–1.72 (m, 13H), 3.34 (s, 3H), 4.40 (s, 1H), 6.86 (s, 2H), 9.92 (s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 24.24, 25.92, 26.27, 26.38, 26.49, 29.28, 29.71, 42.38, 45.58, 50.59, 51.92, 68.89, 119.56, 152.57, 161.99, 172.01. MS (ESI) *m/z*: 361 $(M-H)^-$. Anal. calcd for $C_{18}H_{26}N_4O_2S$: C, 59.64; H, 7.23; N, 15.46%, Found: C, 59.74; H, 7.01; N, 15.65%.

***N*-(5-Amino-4-cyano-3-cyclohexyl-2,3-dihydrothiophene-2-carbonyl)morpholine-4-carboxamide 7f.** Mp: 194–196 °C; white solid; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.13–1.23 (m, 5H), 1.47 (s, 1H), 1.65–1.73 (m, 5H), 3.32 (d, 1H, *J* = 2.5 Hz), 3.37 (s, 4H), 3.57 (s, 4H), 4.39 (s, 1H), 6.87 (s, 2H), 10.01 (s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 26.26, 26.38, 26.48, 29.35, 29.64, 42.45, 45.10, 50.70, 51.86, 66.34, 68.89, 119.57, 152.88, 161.96, 172.03. MS (ESI) *m/z*: 363 $(M-H)^-$. Anal. calcd for $C_{17}H_{24}N_4O_3S$: C, 56.02; H, 6.64; N, 15.37%, Found: C, 56.14; H, 7.02; N, 15.18%.

5-Amino-4-cyano-3-cyclohexyl-*N*-(diethylcarbamoyl)-2,3-dihydrothiophene-2-carboxamide 7g. Mp: 192–194 °C; white solid; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.00–1.23 (m, 11H), 1.47 (br, 1H), 1.65–1.73 (m, 5H), 3.27–3.34 (m, 5H), 4.48 (s, 1H), 6.861 (s, 2H), 9.74 (s, 1H).^{13}C NMR (125 MHz, DMSO-d_6): δ = 13.98, 26.26, 26.36, 26.49, 29.31, 29.77, 41.62, 42.34, 50.79, 51.80, 68.89, 119.59, 152.81, 162.00, 172.40. MS (ESI) *m/z*: 349 $(M-H)^-$. Anal. calcd for $C_{17}H_{26}N_4O_2S$: C, 58.26; H, 7.48; N, 15.99%, Found: C, 58.14; H, 7.20; N, 15.92%.

***N*-(5-Amino-4-cyano-3-cyclohexyl-2,3-dihydrothiophene-2-carbonyl)piperidine-1-carboxamide 7h.** Mp: 224–226 °C; white

solid; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.01–1.34 (m, 10H), 1.48–1.54 (m, 2H), 1.64–1.80 (m, 9H), 3.21 (s, 1H), 3.54 (s, 1H), 4.09 (s, 1H), 6.94 (s, 2H), 8.13 (s, 1H), 10.39 (s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 19.01, 24.60, 25.59, 26.25, 26.34, 26.47, 29.20, 29.59, 32.66, 42.22, 48.28, 50.18, 52.82, 56.49, 68.76, 119.32, 152.49, 161.82, 173.25. MS (ESI) *m/z*: 375 (M-H)$^-$. Anal. calcd for $C_{19}H_{28}N_4O_2S$: C, 60.61; H, 7.50; N, 14.88%, Found: C, 60.59; H, 7.26; N, 14.94%.

5-Amino-*N*-(butylcarbamoyl)-4-cyano-3-cyclohexyl-2,3-dihydrothiophene-2-carboxamide 7i. Mp: 198–200 °C; white solid; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 0.86–0.89 (t, 3H), 1.03–1.31 (m, 10H), 1.41–1.48 (m, 3H), 1.63–1.73 (m, 5H), 3.15 (d, 2H, *J* = 6.5 Hz) 3.23 (s, 1H), 4.10 (s, 1H), 6.93 (s, 2H), 8.16 (s, 1H), 10.36 (s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 14.03, 19.96, 26.27, 26.35, 26.47, 29.11, 29.63, 31.66, 39.11, 42.14, 50.10, 52.86, 68.74, 119.31, 153.35, 161.79, 172.96. MS (ESI) *m/z*: 349 (M-H)$^-$. Anal. calcd for $C_{17}H_{26}N_4O_2S$: C, 58.26; H, 7.48; N, 15.99%, Found: C, 58.19; H, 7.64; N, 16.12%.

***N*,*N*′-(1,4-Phenylenebis(azanediyl))bis(oxomethylene)bis(5-amino-4-cyano-3-phenyl-2,3-dihydrothiophene-2-carboxamide) 8a.** Mp: 230–232 °C; light brown solid, ^{1}H NMR (500 MHz, DMSO-d_6): δ = 4.18 (s, 2H), 4.61 (s, 2H), 7.25 (br, 4H), 7.34–7.40 (m, 10H), 7.52 (br, 4H), 10.26 (br, 2H), 10.77 (br, 2H). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 51.96, 55.77, 70.82, 118.69, 120.90, 127.59, 128.01, 129.23, 133.83, 141.98, 151.04, 162.21, 172.75. MS (ESI) *m/z*: 649 (M-H)$^-$. Anal. calcd for $C_{32}H_{26}N_8O_4S_2$: C, 59.06; H, 4.03; N, 17.22%, Found: C, 59.09; H, 4.27; N, 16.97%.

***N*,*N*′-(Ethane-1,2-diylbis(azanediyl))bis(oxomethylene)bis(5-amino-4-cyano-3-phenyl-2,3-dihydrothiophene-2-carboxamide) 8b.** Mp: 206–208 °C; light brown solid, ^{1}H NMR (500 MHz, DMSO-d_6): δ = 3.32 (s, 4H), 4.09 (s, 2H), 4.56 (s, 2H), 7.22 (s, 4H), 7.30–7.37 (m, 6H), 7.39 (d, 4H, *J* = 7.5 Hz), 8.33 (s, 2H), 10.47 (br, 2H). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 39.62, 52.08, 55.67, 70.75, 118.71, 127.58, 127.99, 129.23, 141.95, 153.67, 162.24, 171.83. MS (ESI) *m/z*: 601 (M-H)$^-$. MS (ESI) *m/z*: 649 (M-H)$^-$. Anal. calcd for $C_{28}H_{26}N_8O_4S_2$: C, 55.80; H, 4.35; N, 18.59%, Found: C, 55.59; H, 4.19; N, 18.47%.

***N*,*N*′-(Butane-1,4-diylbis(azanediyl))bis(oxomethylene)bis(5-amino-4-cyano-3-phenyl-2,3-dihydrothiophene-2-carboxamide) 8c.** Mp: 238–240 °C; brown solid, ^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.47 (s, 4H), 3.18 (s, 4H), 4.09 (s, 2H), 4.57 (s, 2H), 7.22 (s, 4H), 7.31 (d, 6H, *J* = 7.0 Hz), 7.37–7.40 (m, 4H), 8.25 (s, 2H), 9.82 (br, 2H). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 27.13, 39.20, 52.06, 55.68, 70.25, 70.79, 118.70, 127.59, 127.98, 129.22, 141.97, 153.36, 162.25, 172.03. MS (ESI) *m/z*: 629 (M-H)$^-$. Anal. calcd for $C_{30}H_{30}N_8O_4S_2$: C, 57.13; H, 4.79; N, 17.77%, Found: C, 56.89; H, 4.77; N, 17.65%.

***N*,*N*′-(Butane-1,4-diylbis(azanediyl))bis(oxomethylene)bis(5-amino-4-cyano-3-cyclohexyl-2,3-dihydrothiophene-2-carboxamide) 8d.** Mp: 210–212 °C; brown solid, ^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.06–1.21 (m, 10H), 1.44 (s, 6H), 1.63–1.71 (m, 10H), 3.15 (s, 4H), 3.23 (s, 2H), 4.10 (s, 2H), 6.94 (s, 4H), 8.19 (s, 2H), 10.35 (br, 2H). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 26.26, 26.35, 26.47, 27.09, 27.90, 29.13, 29.62, 39.16, 42.14, 50.14, 52.83, 68.77, 119.34, 153.40, 161.83, 172.87. MS (ESI) *m/z*: 641 (M-H)$^-$. Anal. calcd for $C_{30}H_{42}N_8O_4S_2$: C, 56.05; H, 6.59; N, 17.43%, Found: C, 56.13; H, 6.72; N, 17.66%.

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