NEW SYNTHESES OF 2,4-DIAMINOTHIOPHENES - USE OF (1,3-OXATHIOL-2-YLIDENE)MALONONITRILE

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Abstract - Preparation of 2,4-diaminothiophenes using (1,3-oxathiol-2-ylidene)-malononitrile as intermediate was achieved.

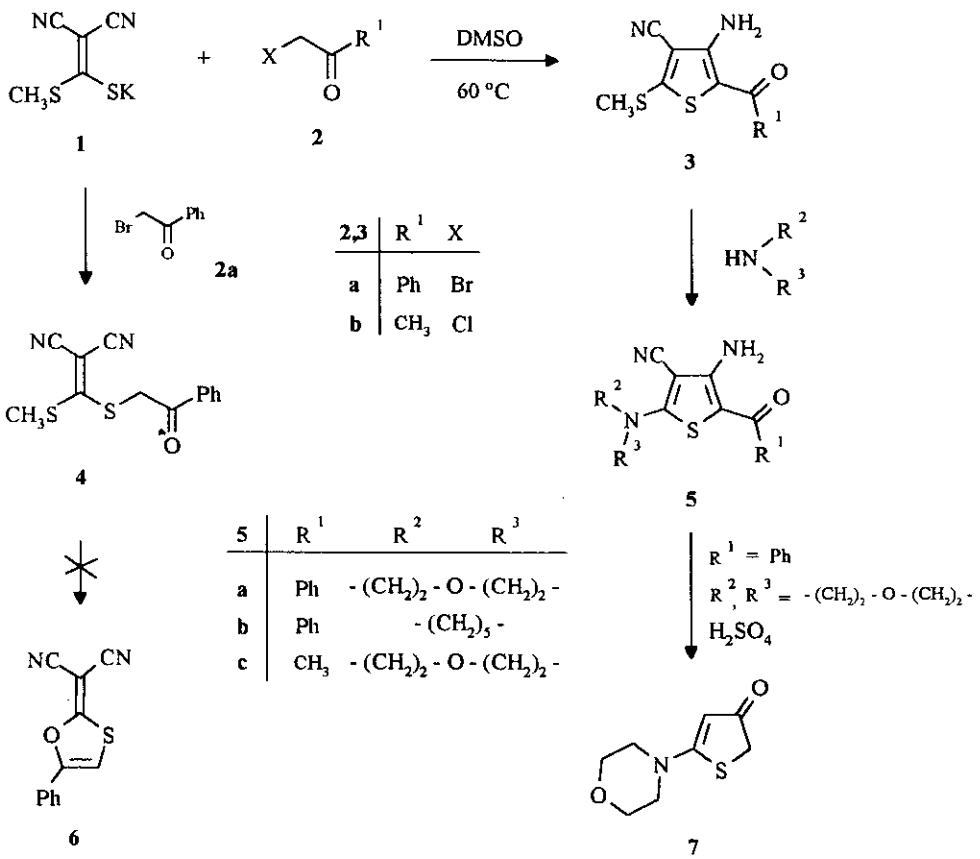
Thiophenes with new patterns of substitution are of interest as potential to pharmaceuticals[1] and dyestuffs.[2] A lot of highly substituted thiophenes can be obtained by the *Gewald* synthesis[3] which has found widespread application. For the synthesis of 2,4-diaminothiophenes we employed a strategy which involves a *Thorpe-Ziegler* cyclization step to form an amino group.

RESULTS AND DISCUSSION

The potassium thiolate (**1**) as starting material was obtained by a three step procedure from malononitrile, sulfur and methyl iodide as recently published.[4]

Alkylation of **1** is known to give *S*-alkylated products, which can be submitted to a *Thorpe-Ziegler* cyclization reaction to give 3-aminothiophenes. The use of phenacyl bromide (**2a**) gave 3-amino-2-benzoyl-5-methylthiothiophene (**3a**). We assumed that the reaction with phenacyl bromide (**2a**) would afford in the first step a 1,4-oxathiafulvalene derivative (**6**), but we only detected an open-chain alkylated product (**4**). The raising of temperature gave the 3-aminothiophene (**3**) as ring closure product. For further structural assignment we were able to substitute the methylthio group in **3** by secondary amines. This reaction doesn't proceed involving the formation of **6** as intermediate product, because from our experience electron-acceptor substituted 2-methylthiothiophenes undergo substitution reactions with nucleophiles. In this way we obtained 2,4-diaminothiophenes (**5**) which were first synthesized by a procedure making use of *N,N*-dialkyl-*N*-(1,3-oxathiol-2-ylidene)iminium salts.[5] Besides the known de-benzoylation of **5a** in a basic medium,[5] we also found, that treatment with sulfuric acid simultaneously cause debenzoylation, decarboxylation and hydrolyis of the 4-amino group to yield **7**. **1** was alkylated with

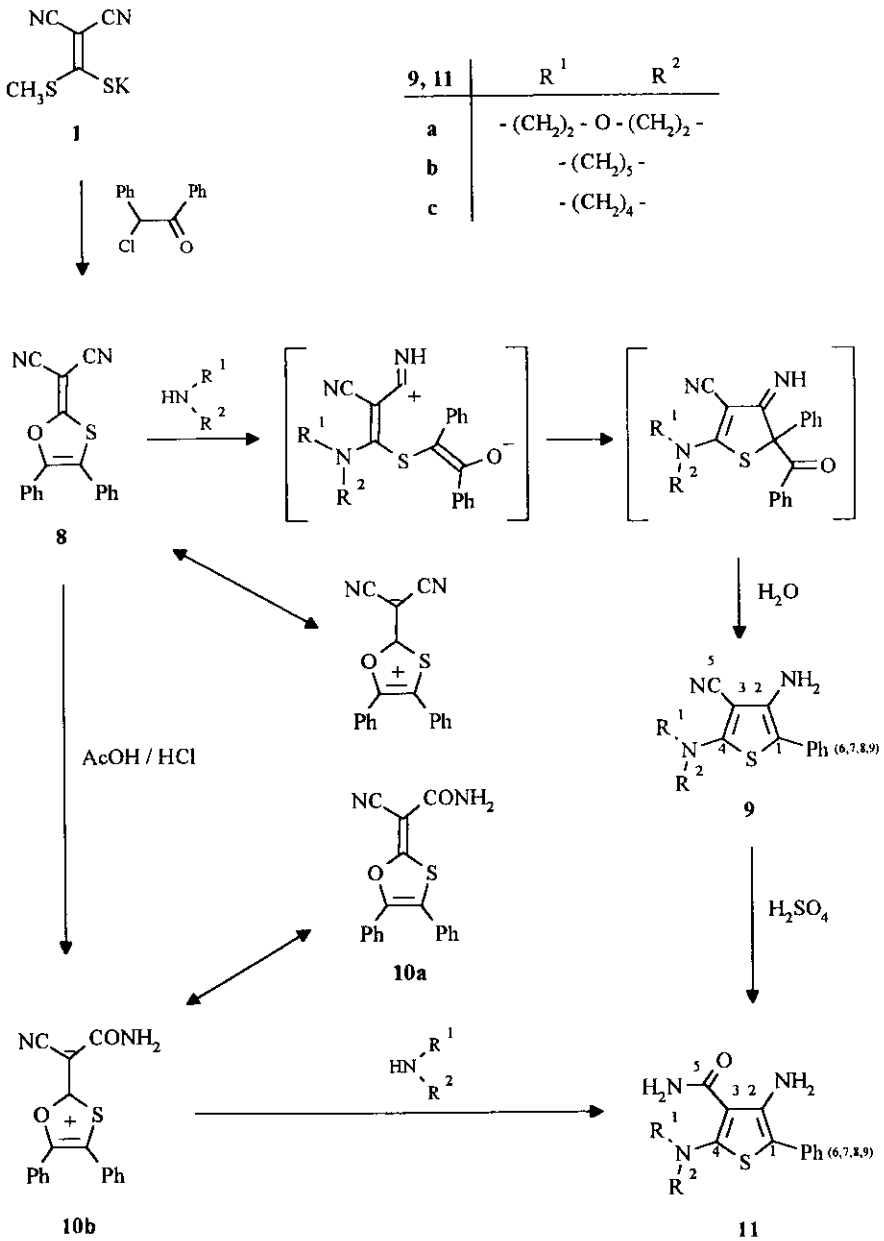
desyl chloride to give with extrusion of methanethiol the 1,4-oxathiafulvalene derivative (**8**). Here the formation of the 1,4-oxathiafulvalene (**8**) is possible because of the stabilizing effect of the phenyl groups.



Scheme 1

One nitrile group of **8** can be transformed to the carboxamide (**10**) under strongly acidic conditions. No mixture of cis/trans-isomers of **10** was observed, which can be explained by free rotation resulting from a polar structure (**10b**) as shown in Scheme 2.

Both 1,4-oxathiafulvalene derivative (**8**) and (**10**) were used to prepare 2,4-diaminothiophenes. This ring transformation process starts with the attack of an amine at the C-2 position of the 1,4-oxathiafulvalene. The subsequent ring opening is followed by a ring closure to the 3-iminothiophene, which itself is stabilized by debenzoylation in the presence of water to the 2,4-diaminothiophenes (**9**) and (**11**). For structural elucidation **9a** was converted to **11a** by treatment with sulfuric acid.



Numbering of C-atoms relates to ^{13}C NMR spectra

Scheme 2

Financial support by the BMFT and the Arzneimittelwerk Dresden GmbH is gratefully acknowledged.

EXPERIMENTAL

Melting points were measured on a Kofler hot-stage apparatus. ^{1}H NMR spectra and ^{13}C NMR spectra were obtained in $CDCl_3$ or DMSO-d_6 using an AC-200 MHz Bruker spectrometer. The IR spectra were recorded on a spectrophotometer Specord 75 (Fa. Carl-Zeiss Jena). Elemental analyses were determined on a EA 1108 (Fa. Carlo Erba Hofheim).

Potassium (2,2-dicyano-1-methylsulfanylethen-1-yl)thiolate (1)

This compound was prepared according to a described procedure[4] and recrystallized from *n*-propanol, mp 274-276°C.

4-Amino-5-benzoyl-2-methylsulfanylthiophene-3-carbonitrile (3a)

To a mixture of phenacyl bromide (1.98 g, 10 mmol) and acetic acid (4 mL), a solution of **1** (1.94 g, 10 mmol) in dimethyl sulfoxide (20 mL) was added dropwise at 60 °C. After complete addition, the mixture was stirred for 30 min and then poured into water (200 mL). After 2 h the crude product was collected by filtration and recrystallized from ethanol to yield product (**3a**) (1.8 g, 66 %), mp 149-151 °C; Anal. Calcd for $C_{13}H_{10}N_2OS_2$: C, 56.91; H, 3.67; N, 10.21; S, 23.37. Found: C, 56.79; H, 3.70; N, 10.19; S, 23.44.

5-Acetyl-4-amino-2-methylsulfanylthiophene-3-carbonitrile (3b)

To chloroacetone (14 g, 150 mmol), a solution of **1** (9.7 g, 50 mmol) in dimethyl sulfoxide (20 mL) was added dropwise at 60 °C. Then potassium carbonate (10 g, 72 mmol) was added , the mixture was stirred for 30 min at 60 °C and poured into ice-water (400 mL). After 2 h the crude product was collected by filtration and recrystallized from acetic acid to yield product (**3b**) (3.6 g, 34 %), mp 207-212 °C; ^{1}H NMR (DMSO-d_6) δ 7.50 (s, 2H, NH_2), 2.70 (s, 3H, $COCH_3$), 2.25 (s, 3H, SCH_3); Anal. Calcd for $C_8H_8N_2OS_2$: C, 45.26; H, 3.80; N, 13.20; S, 30.21. Found: C, 45.19; H, 3.84; N, 13.22; S, 30.56.

2-[Methylsulfanyl-(2-oxo-2-phenylethylsulfanyl)methylene]malononitrile (4)

To a solution of phenacyl bromide (1.98 g, 10 mmol) in dimethyl sulfoxide (5 mL), a solution of **1** (1.94 g, 10 mmol) in dimethyl sulfoxide (20 mL) was added dropwise at 0 °C. After complete addition, the mixture was stirred 2 h at room temperature and then poured onto ice (100 g). The crude product was collected by filtration and recrystallized from tetrachloromethane to yield product (**4**) (1.8 g, 66 %), mp 89-91 °C; Anal. Calcd for $C_{13}H_{10}N_2OS_2$: C, 56.91; H, 3.67; N, 10.21; S, 23.37. Found: C, 56.79; H, 3.65; N, 9.95; S, 23.03.

4-Amino-5-benzoyl-2-(morpholin-4-yl)thiophene-3-carbonitrile (5a)

A solution of **3a** (10.96 g, 40 mmol) in morpholine (20 mL) was refluxed for 30 min at an oil-bath temperature of 170 °C. The solvent was evaporated under reduced pressure and the residue was triturated and washed with water. The crude product was recrystallized with a mixture of acetonitrile/*N*,*N*-dimethylformamide (DMF) (1:1) to yield product (**5a**) (9.5 g, 76 %), mp 240-241 °C; ^{1}H NMR (DMSO-

d_6) δ 7.90 (s, 2H, NH_2) 7.70-7.40 (m, 5H, ArH), 3.65 (t, J = 4.6 Hz, 4H, $O(CH_2)_2$), 3.55 (t, J = 4.6 Hz, 4H, $N(CH_2)_2$) ppm; ^{13}C NMR ($CDCl_3$) δ 95.81 (C1), 157.79 (C2), 79.02 (C3), 167.66 (C4), 115.13 (C5), 50.02 ($N(CH_2)_2$), 65.74 ($O(CH_2)_2$), 185.92 (C8), 140.75 (C9), 128.40 (C10), 127.23 (C11), 130.80 (C12) ppm; Anal. Calcd for $C_{16}H_{15}N_3O_2S$: C, 61.32; H, 4.82; N, 13.41; S, 10.23. Found: C, 61.55; H, 4.93; N, 13.61; S, 10.38.

4-Amino-5-benzoyl-2-(piperidin-1-yl)thiophene-3-carbonitrile (5b)

A solution of **3a** (5.48 g, 20 mmol) in piperidine (10 mL) was refluxed for 30 min at an oil-bath temperature of 170 °C. The solvent was evaporated under reduced pressure and the residue triturated and washed with water. The crude product was recrystallized with acetonitrile to yield product (**5b**) (4.5 g, 72 %), mp 161-163 °C (lit.,[5a]: mp 155-156 °C, ethyl acetate).

5-Acetyl-4-amino-2-(morpholin-4-yl)thiophene-3-carbonitrile (5c)

A solution of **3b** (4.25 g, 20 mmol) in morpholine (5 mL) was refluxed for 30 min at an oil-bath temperature of 170 °C. The solvent was evaporated under reduced pressure and the residue was triturated and washed with water. The crude product was recrystallized with a mixture of acetonitrile/DMF (1:1) to yield product (**5c**) (2.5 g, 50 %), mp 280-282 °C; ^1H NMR (*DMSO-d_6*) δ 7.50 (s, 2H, NH_2), 3.70-3.80 (m, 4H, $O(CH_2)_2$), 3.55-3.65 (m, 4H, $N(CH_2)_2$) ppm; Anal. Calcd for $C_{11}H_{13}N_3O_2S$: C, 52.57; H, 5.21; N, 16.72; S, 12.76. Found: C, 52.26; H, 5.20; N, 16.57; S, 13.03.

***5-Morpholin-4-yl-2H-thiophene-3-one* (7)**

A solution of **5a** (3.13 g, 10 mmol) in sulfuric acid (10 ml, 80 %) was stirred for 1 h at 110 °C. The mixture was poured onto ice (100 g) and a precipitate consisting of benzoic acid was removed by filtration. After neutralization with diluted sodium hydroxide solution (10 %), the resulting solution was evaporated under reduced pressure to dryness and the residue was extracted twice with ethanol. The concentrated ethanolic solution was allowed to stand for crystallization to yield product (**7**) (0.95 g, 51 %), mp 186-188 °C (ethanol); ^1H NMR ($CDCl_3$): δ 5.35 (s, 1H, CH), 3.75 (t, J = 4.8 Hz, 4H, $O(CH_2)_2$), 3.6 (s, 2H, CH_2), 3.4 (t, J = 4.8 Hz, 4H, $N(CH_2)_2$) ppm; ^{13}C NMR (DMSO-d_6): δ 38.33 (C1), 195.18 (C2), 93.90 (C3), 177.83 (C4), 48.56 ($N(CH_2)_2$), 65.45 ($O(CH_2)_2$) ppm; Anal. Calcd for $C_8H_{11}NO_2S$: C, 51.87; H, 5.99; N, 7.56; S, 17.31. Found: C, 52.06; H, 6.07; N, 7.54; S, 17.35.

2-(4,5-Diphenyl-[1,3]oxathiol-2-ylidene)malonodinitrile (8)

A mixture of **1** (1.94 g, 10 mmol) and desyl chloride (2.31 g, 10 mmol) (purchased from Fluka) in dimethyl sulfoxide (10 mL) was stirred 1.5 h at 60 °C. The reaction mixture was poured into water (200 mL), the oily precipitate was triturated with methanol and the solidified crude product was collected by filtration and washed with methanol. After recrystallization from ethanol the product (**8**) (1.0 g, 33 %), mp 140-142 °C, was obtained. IR (KBr): 2219, 2208 (CN) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.60-7.20 (m, 10 H, Ar-H) ppm; ^{13}C NMR ($CDCl_3$): δ 113.01, 110.85 (C1,C1′, 2CN), 55.40 (C2), 183.71 (C3), 147.32 (C4), 117.13

(C5), 126.23 (C6), 129.30, 127.83 (C7, C8), 130.55 (C9) ppm; Anal. Calcd for $C_{18}H_{10}N_2OS$: C, 71.50; H, 3.33; N, 9.26; S, 10.60. Found: C, 71.56; H, 3.38; N, 9.26; S, 10.57.

4-Amino-2-(morpholin-4-yl)-5-phenylthiophene-3-carbonitrile (9a)

A solution of **8** (3.02 g, 10 mmol) in morpholine (10 mL) was refluxed for 3 h at an oil-bath temperature of 180 °C. Morpholine was evaporated under reduced pressure and the residue was triturated with ethyl acetate. The crude product was recrystallized from ethanol to yield the product **(9a)** (2.3 g, 81 %), mp 163-165 °C; IR (KBr): 2193 (CN), 3326, 3410 (NH) cm^{-1}; ^1H NMR (DMSO-d_6): δ 7.45-7.35, 7.25-7.10 (m, 5H, phenyl-H), 5.05 (s, 2H, NH_2), 3.80-3.70 (m, 4H, $O(CH_2)_2$), 3.45-3.35 (m, 4H, $N(CH_2)_2$) ppm; ^{13}C NMR (DMSO-d_6): δ 97.51 (C1), 163.61 (C2), 83.52 (C3), 140,16 (C4), 115.89 (C5), 133.42 (C6), 126.04 (C7), 129.04 (C8), 125.29 (C9), 50.23 ($N(CH_2)_2$), 65.24 ($O(CH_2)_2$) ppm; Anal. Calcd for $C_{15}H_{15}N_3OS$: C, 63.13; H, 5.30; N, 14.72; S, 11.24. Found: C, 63.20; H, 5.39; N, 14.67; S, 11.21.

4-Amino-5-phenyl-2-(piperidin-1-yl)thiophene-3-carbonitril (9b)

A solution of **8** (3.02 g, 10 mmol) in piperidine (10 mL) was refluxed for 3 h at an oil-bath temperature of 180 °C. Piperidine was evaporated under reduced pressure and the residue was triturated with ethyl acetate. The crude product was recrystallized from ethanol to yield the product **(9b)** (1.9 g, 67 %), mp 122-124 °C; IR (KBr): 2194 (CN), 3330, 3445 (NH) cm^{-1}; ^1H NMR (DMSO-d_6): δ 7.4-7.3, 7.2-7.1 (m, 5H, phenyl-H), 5.0 (s, 2H, NH_2), 3.5-3.4 (m, 4H, $N(CH_2)_2$), 1.8-1.6 (m, 6H, CH_2) ppm; ^{13}C NMR (DMSO-d_6): δ 96.14 (C1), 163.51 (C2), 82.09 (C3), 140.06 (C4), 116.31 (C5), 133.68 (C6), 125.83 (C7), 128.99 (C8), 124.95 (C9), 51.52 ($N(CH_2)_2$), 24.74 ($2CH_2$), 23.10 (CH_2) ppm; Anal. Calcd. for $C_{16}H_{17}N_3S$: C, 67.81; H, 6.05; N, 14.83; S, 11.31. Found: C, 67.94; H, 6.39; N, 14.70; S, 11.19.

4-Amino-5-phenyl-2-(pyrrolidin-1-y)thiophene-3-carbonitrile (9c)

A solution of **8** (3.02 g, 10 mmol) in pyrrolidine (10 mL) was refluxed for 3 h at an oil-bath temperature of 180 °C. Pyrrolidine was evaporated under reduced pressure and the residue was triturated with ethylacetate. The crude product was recrystallized from ethanol/acetonitrile (1:1) to yield the product **(9c)** (2.4 g, 89 %), mp 158-161 °C; IR (KBr): 2187 (CN), 3319, 3432 (NH) cm^{-1}; ^1H NMR (DMSO-d_6): δ 7.40-7.30, 7.15-7.05 (m, 5H, phenyl-H), 5.00 (s, 2H, NH_2), 3.60-3.45 (m, 4H, $N(CH_2)_2$), 2.10-1.90 (m, 4H, CH_2CH_2) ppm; ^{13}C NMR (DMSO-d_6): δ 94.09 (C1), 159.22 (C2), 77.90 (C3), 140.15 (C4), 117.24 (C5), 134.11 (C6), 125.34 (C7), 128.95 (C8), 124.38 (C9), 50.98 ($N(CH_2)_2$), 25.28 (CH_2CH_2); Anal. Calcd for $C_{15}H_{15}N_3S$: C, 66.88; H, 5.61; N, 15.60; S, 11.90. Found: C, 66.98; H, 5.75; N, 15.47; S, 11.80.

2-(4,5-Diphenyl-[1,3]oxathiol-2-ylidene)-2-cyanoacetamide (10)

A solution of **8** (3.02 g, 10 mmol) in acetic acid (40 ml) and hydrochloric acid (20 mL, 36 %) was refluxed for 4 h. The mixture was cooled and the precipitate was collected by filtration and washed with ethanol/water (1:1) to yield the product (10) (2.4 g, 75 %), mp 245-246 °C; IR (KBr): 2205 (CN), 1680 (CONH), 3474 (NH) cm^{-1}; ^1H NMR (DMSO-d_6): δ 7.4-7.6 (m, ArH, $CONH_2$); ^{13}C NMR (DMSO-d_6): δ

75.21 (C1), 178.83 (C2), 144.03 (C3), 118.48 (C4), 114.58 (C5), 164.60 (C6), Phenyl-C: 127.89, 127.06, 130.11, 129.70, 129.49, 129.02, 128.96, 127.18; Anal. Calcd for $C_{18}H_{12}N_2O_2S$: C, 67.48; H, 3.78; N, 8.74; S, 10.01. Found: C, 67.63; H, 3.86; N, 8.88; S, 9.88.

4-Amino-2-(morpholin-4-yl)-5-phenylthiophene-3-carboxamide (11a)

Procedure a:

A solution of **9a** (2.85 g, 10 mmol) in concentrated sulfuric acid (20 mL, 80 %) was stirred 1 h at an oil-bath temperature of 110 °C. The mixture was cooled and poured onto ice (200 g). After neutralization with sodium hydroxide, the solution was extracted with chloroform (50 mL). The organic layer was dried over $MgSO_4$ and evaporated under reduced pressure. The residue was triturated with ethanol and the precipitate filtered to yield the product (**11a**) (1.4 g, 46 %), mp 219-223 °C (ethanol); Anal. Calcd for $C_{15}H_{17}N_3O_2S$: C, 59.38; H, 5.65; N, 13.85; S, 10.57. Found: C, 59.62; H, 5.73; N, 13.89; S, 10.48.

Procedure b:

A solution of **10** (3.2 g, 10 mmol) in morpholine (20 mL) was refluxed for 1 h at an oil-bath temperature of 180 °C. Morpholine was evaporated under reduced pressure, the residue was triturated with ethanol and collected by filtration to yield the product (**11a**) (2.4 g, 79 %), mp 219-224 °C (DMF/ethanol); IR (KBr): 1654 (CONH), 3342, 3422 (NH) cm^{-1}; ^1H NMR (DMSO-d_6): δ 8.15 (s, 1H, CONH), 7.30-7.60 (m, 5H, phenyl-H, CONH), 7.10-7.20 (m, 5H, phenyl-H), 5.90 (s, 2H, NH_2), 3.70-3.80 (t, J = 4.5 Hz, 4H, $O(CH_2)_2$), 2.90-3.00 (t, J = 4.5 Hz, 4H, $N(CH_2)_2$) ppm; ^{13}C NMR (DMSO-d_6): δ 114.51 (C1), 142.09 (C2), 103.45 (C3), 159.25 (C4), 165.84 (C5), 134.31 (C6), 126.44 (C7), 128.96 (C8), 125.39 (C9), 65.86 ($O(CH_2)_2$), 54.67 ($N(CH_2)_2$) ppm; Anal. Calcd for $C_{15}H_{17}N_3O_2S$: C, 59.38; H, 5.65; N, 13.85; S, 10.57. Found: C, 59.67; H, 5.74; N, 13.99; S, 10.46.

4-Amino-2-(piperidin-1-yl)-5-phenylthiophene-3-carboxamide (11b)

A solution of **10** (3.2 g, 10 mmol) in piperidine (20 mL) was refluxed for 1 h at an oil-bath temperature of 180 °C. Piperidine was evaporated under reduced pressure, the residue was triturated with ethanol and filtered off to yield the product (**11b**) (2.0 g, 66 %), mp 201-206 °C (DMF/ethanol); IR (KBr): 1657 (CONH), 3350 (br), 3455 (NH) cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.25 (s, 1H, CONH), 7.30-7.60 (m, 5H, phenyl-H, CONH), 7.15 (m, 5H, phenyl-H), 5.90 (s, 2H, NH_2), 2.85-2.95 (t, J = 4.8 Hz, 4H, $N(CH_2)_2$), 1.55-1.75 (m, 4H, $2CH_2$), 1.40-1.60 (m, 2H, CH_2) ppm; ^{13}C NMR (DMSO-d_6): δ 114.16 (C1), 160.83 (C2), 103.25 (C3), 142.07 (C4), 166.04 (C5), 134.46 (C6), 126.39 (C7), 128.92 (C8), 125.25 (C9), 56.03 ($N(CH_2)_2$), 25.57 ($2CH_2$), 22.95 (CH_2) ppm; Anal. Calcd for $C_{16}H_{19}N_3OS$: C, 63.76; H, 6.35; N, 13.94; S, 10.64. Found: C, 64.03; H, 6.63; N, 14.00; S, 10.85.

4-Amino-2-(pyrrolidin-1-yl)-5-phenylthiophene-3-carboxamide (11c)

A solution of **10** (3.2 g, 10 mmol) in pyrrolidine (20 mL) was refluxed for 1 h at an oil-bath temperature of 180 °C. Pyrrolidine was evaporated under reduced pressure, the residue was triturated with ethanol and

collected by filtration to yield the product (**11c**) (2.0 g, 70 %), mp 173-177 °C (DMF/ethanol); IR (KBr): 1635 (CONH), 3353 (br), 3400 (NH) cm^{-1}; ^1H NMR (DMSO-d_6): δ 7.25-7.45 (m, 5H, phenyl-H, $CONH_2$), 5.40 (s, 2H, NH_2), 3.20 (t, J = 4.5 Hz, 4H, $N(CH_2)_2$), 1.80-2.00 (m, 4H, CH_2CH_2) ppm; ^{13}C NMR (DMSO-d_6): δ 109.29 (C1), 155.83 (C2), 97.66 (C3), 141.60 (C4), 166.86 (C5), 135.11 (C6), 125.59 (C7), 128.85 (C8), 124.13 (C9), 53.42 ($N(CH_2)_2$), 25.08 (CH_2CH_2) ppm; Anal. Calcd for $C_{15}H_{17}N_3OS$: C, 62.69; H, 5.96; N, 14.62; S, 11.16. Found: C, 62.84; H, 5.94; N, 14.73; S, 11.32.

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