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Heterocycle Synthesis

2-Bromo-2-chloro-3-arylpropanenitriles as C-3 Synthons for the Synthesis of Functionalized 3-Aminothiophenes

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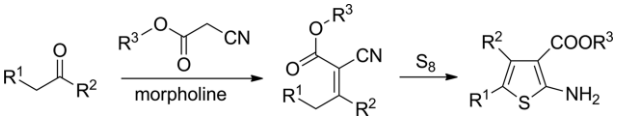
Abstract: 2-Bromo-2-chloro-3-arylpropanenitriles can be prepared by Meerwein reaction from 2-chloroacrylonitrile and various aryldiazonium salts under copper(II) bromide catalysis. They proved to be stable compounds which form 2-chlorocinnnamonitriles upon treatment with bases. Reaction of the title compounds with substituted thioglycolates gave substituted 3-aminothiophenes which have not yet been accessible by other routes. Three-component reactions with the title compound, sodium sulfide and bromonitromethane, chloroacetonitrile, or ethyl 4-chloroacetoacetate gave 2-nitro- and 2-cyano-substituted 3-aminothiophenes, and thienopyridinediones in high yields and in one single step, respectively.

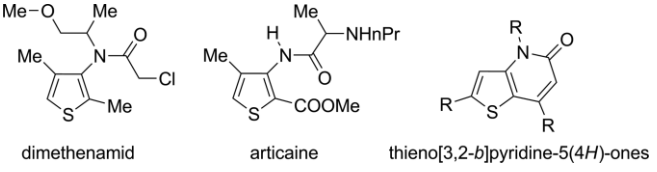
Introduction

Undoubtedly thiophenes[1] belong to the most important heterocyclic ring systems, as thiophene derivatives have found numerous applications[2] as biologically active compounds[3] or as structure increments of new materials. Thus, thiophenes proved to be active as antifungal,[4] channel blocking,[5] antitumor[6] (Raltitrexed, Tomudex®), and anti-parasitic compounds.[7] Among the latter mentioned, antileishmanial activities have been reported.[8] They were also developed as inhibitors of the NorA multidrug transporter of bacteria[9] and 17β-hydroxysteroid dehydrogenase type 1,[10] and as agonists of the sphingosine-1-phosphate 1 receptor.[11] Concerning materials chemistry, liquid crystals,[12] non-linear optical materials,[13] conducting polymers,[14] photoluminescent compounds,[15] semiconductors,[16] and light-emitting materials[17] on the basis of thiophenes have been described. Thiophenes can be prepared by the formation of one, two or three bonds from suitable starting materials by ring closure reactions, concerted cycloadditions, rearrangements, or functionalization of an existing thiophene ring.[1] Among these methods, the Gewald reaction[18] is very convenient to prepare 2-aminothiophenes with a high degree of functionalization (Scheme 1), and nowadays, the chemistry of 2-aminothiophenes is still one of the most extensive and dynamic fields of thiophene research.[19] Gewald's thiophenes possess the stabilizing β-enaminocarbonyl chromophore which also allows for numerous subsequent functionalizations.[20]



Scheme 1. Gewald synthesis of 2-aminothiophenes.

In comparison to the syntheses of 2-aminothiophenes, the preparations of 3-aminothiophenes, which are also underrepresented in nature,[21] are less developed. Nevertheless, 3-aminothiophenes constitute partial structures of numerous bioactive molecules such as the herbicide and fungicide dimethenamid[22] or the local anesthetic articaine,[23] among many others (Scheme 2). Fused systems such as thieno[3,2-*b*]pyridine-5(4*H*)ones were developed very recently as tunable fluorescent dyes.[24]



Scheme 2. 3-Aminothiophenes as biologically active compounds and new materials

First prepared in 1926[25] 3-aminothiophenes can be obtained by Hoffmann or Curtius rearrangements[21] or by Pd-catalyzed amination starting from 3-halothiophenes.[26] Very recently, a 6π-electrocyclization involving a vinyl sulfide linked to an in-situ generated keteniminium salt for the synthesis of 3-

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aminothiophenes was developed by which one bond is formed to close the ring.[21] Concerning two- or three-component reactions, 3-aminothiophenes can be obtained from unsaturated functionalized nitriles **I**–**III** by Thorpe–Ziegler-type cyclizations, where the 3-aminothiophenes are often 5-aryl-substituted (Figure 1). By far the mostly applied starting materials are substituted nitriles **I**,[27] whereas only a few applications of α-substituted nitriles **II**[28] or 1-cyanoalkynes **III**[29] have been described. The syntheses of the precursors **I** and **II**, however, are limited to suitably substituted acetophenones[27] and benzaldehydes[28] as starting materials, respectively. In most cases, the syntheses of the nitriles **I** and **II** are restricted to donor-substituents attached to the aromatic ring, whereas acceptor-substituents result in strongly decreased yields of the nitriles formed. A few examples using β-oxo-substituted nitriles as alternative to **I** have been described.[30] The starting materials are available by Meerwein reaction, i.e. the coupling of arenediazonium salts with substituted alkenes using copper(II) salts as catalyst,[31] or by its variations.[32] Aryl-alkenes as well as aryl-alkanes can thus be prepared from arenediazonium salts which combine several advantages as starting materials in organic synthesis. They can easily be prepared from a broad variety of – often inexpensive – aniline derivatives at ambient reaction conditions. It is not astonishing that the Meerwein arylation has developed to a broadly applicable and versatile synthetic approach for the functionalization of alkenes[33] for the preparation of interesting target molecules such as natural products and drugs.[34]

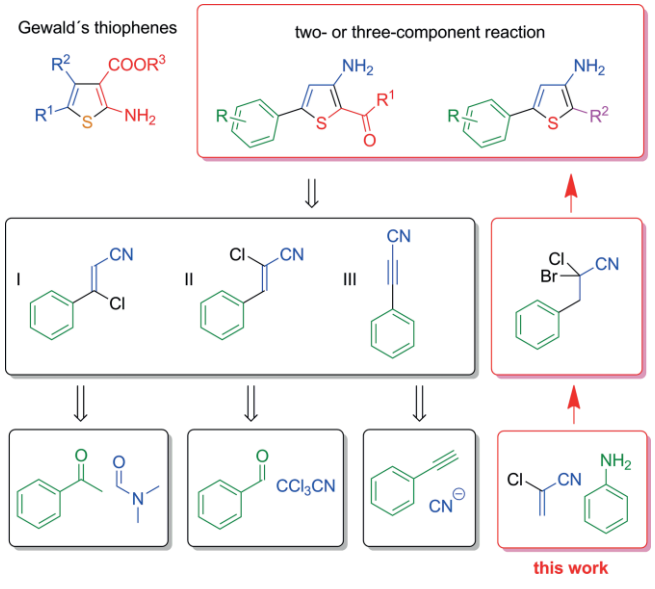
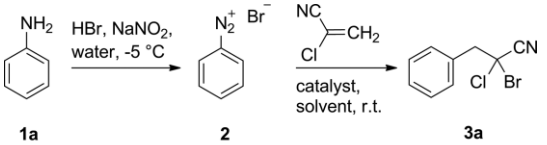


Figure 1. Synthetic approaches to functionalized thiophenes.

In continuation of our interest in heterocycle synthesis[35] including thiophene functionalization,[27c,27d,36] and Meerwein reactions[37] we report here on a useful synthesis of 3-aminothiophene derivatives starting from 2-bromo-2-chloro-3-phenylpropanenitriles. To the best of our knowledge, this substance class has not yet been described. It allows for the introduction of a large number of functional groups in thiophene syntheses which are otherwise difficult or even impossible to prepare.

Results and Discussion

To investigate optimal reaction conditions of the Meerwein reaction for the synthesis of 2-bromo-2-chloro-3-phenylpropanenitriles, aniline **1a** and 2-chloroacrylonitrile were used as model compounds (Scheme 3). 2-Chloroacrylonitrile was obtained in two steps from acrylonitrile by chlorination followed by dehydrochlorination of the formed dichloro compound. First, aniline **1a** was added to an aqueous solution of hydrogen bromide (2.2 equiv.) and then cooled to –5 °C. A saturated solution of sodium nitrite (1.1 equiv.) in water was added to the resulting anilinium bromide within 5 min in the temperature range from –5 to +5 °C to form the phenyl diazonium bromide **2** in situ which was directly used for the arylation of 2-chloroacrylonitrile without prior isolation.



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

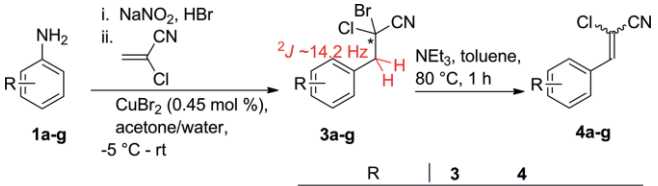
	catalyst (mol%)	solvent[a]	by-product[b]	yield[c] (%)
1	CuBr (15)	acetone	50	15
2	CuBr (10)	acetone	45	17
3	CuBr (5)	acetone	40	26
4	CuBr (1)	acetone	37	30
5	$CuBr_2$ (15)	acetone	16	40
6	$CuBr_2$ (5)	acetone	17	39
7	$CuBr_2$ (1)	acetone	15	40
8	$CuBr_2$ (0.45)	acetone	14	41
9	$CuBr_2$ (0.45)	EtOH	PhOH	0
10	$CuBr_2$ (0.45)	MeOH	PhOH	0
11	$CuBr_2$ (0.45)	AcOH	-	25
12	$CuBr_2$ (0.45)	DMF	-	20
13	$CuBr_2$ (0.45)	1,4-dioxane	-	5

[a] solvent/water = 1:1. [b] Sandmeyer product (bromobenzene). [c] isolated yield.

Scheme 3. Optimization of reaction conditions.

During optimization of the reaction conditions we found that propanenitrile **3a** was formed in 41 % yield, when the reaction was carried out in acetone/water (1:1) in the presence of $CuBr_2$ (0.45 mol-%). The product **3a** was finally separated by distillation under reduced pressure. Using other polar organic solvents such as dioxane, acetic acid, DMF, or DMSO, respectively, diminished the yield of nitrile **3a**. In comparison to copper(II) bromide, the reaction with copper(I) bromide also decreased the yield of the product due to the formation of bromobenzene by Sandmeyer reaction. Applying the optimized conditions, the arylation of 2-chloroacrylonitrile **2** with other electron-poor and electron-rich arenediazonium salts **1b**–**g** was performed (Scheme 4). The resulting propanenitriles **3a**–**g** were extracted with dichloromethane from the reaction mixtures and distilled under reduced pressure (1–3 Torr). Distillations under slightly higher pressures (≈ 10 Torr) have led to a partial loss of HBr and formation of cinnamonitriles **4a**–**g** which are also available on treatment of **3a**–**g** with NEt_3 in toluene in almost quantitative yields. The previously undescribed nitriles **3a**–**g** have a pungent smell and proved to be stable on storage at 4 °C over a period of 5 years without any traces of decomposition. The hydrogen atoms of the methylene groups are diastereotopic

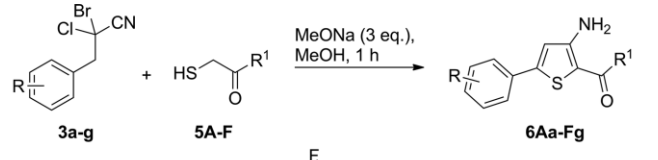
due to the asymmetric environment of the adjacent chiral carbon atom of **3a**–**g** and give two overlapped doublets with coupling constants ^2J of approximately 14.2 Hz in the chemical shift range from 3.77 to 4.17 ppm, depending on the substitution pattern. A comparison of NMR data of the 2-chlorocinnnamonitriles **4** with literature values[38] shows that **4a**,**b**,**e**,**g** are formed exclusively as *Z*-isomers, whereas the other derivatives gave mixtures of *Z*/*E*-isomers. Compound **4a** has been prepared before starting from benzaldehyde and chloroacetonitrile[39] or trichloroacetonitrile,[40] by the reaction of a dioxazaborocane derivative with zinc(II) cyanide in the presence of copper(II) nitrate,[41] and by treatment of cinnamonitrile with HCl/DMF/oxone in low yield.[42] The compounds **4a** and **4c** are also available starting from the corresponding 2-cyano-3-phenylacrylates[43] or the benzaldehydes and 4-azido-3-chloro-5-methoxy-2(5*H*)furanone.[44] They have not been synthesized before as described here. To the best of our knowledge, the cinnamonitriles **4b**, **4f**, and **4g** are new compounds.



	R	3	4
a	H	40%	92% (*Z*)
b	3-Me	58%	94% (*Z*)
c	4-Me	46%	94% (*E*/*Z* = 7/3)
d	4-F	71%	95% (*E*/*Z* = 6/4)
e	3-CF_3	78%	95% (*Z*)
f	3-Ac	69%	95% (*E*/*Z* = 7/3)
g	3-COOMe	69%	95% (*Z*)

Scheme 4. Syntheses of propanenitriles **3** and 2-chlorocinnamonitriles **4**.

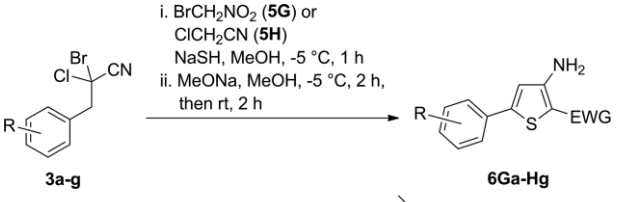
The 2-bromo-2-chloro-3-phenylpropanenitriles **3a**–**g** underwent smooth reactions with a broad variety of thioglycolates **5A-F** in the presence of sodium methoxide in methanol within 1 h. Thus, the 3-aminothiophenes **6Aa-Fg** were prepared in good to excellent yields which differ in their substitution pattern in positions C-2 and C-5 (Scheme 5). The thiophene **6Aa** has *i.a.* been prepared before according to route **I** (Figure 1) in 54 % yield,[45] and a similar yield was given in a patent.[46] An alternative approach starts from acetophenone which is subjected to a Vilsmeier–Haak reaction, followed by condensation with hydroxylamine and subsequent treatment with methyl mercaptoacetate.[47] According to a literature research, the entire series from **6Ba**, **6Ca**, **6Da**, **6Ea** to **6Fa** are new compounds. Their syntheses seem to be very difficult or even impossible to accomplish by established methods.



	R=	A	B	C	D	E	F
a	H	75%	81%	74%	65%	48%	79%
b	3-Me	80%	87%	61%	71%	80%	56%
c	4-Me	71%	78%	67%	86%	80%	85%
d	4-F	84%	87%	83%	76%	84%	81%
e	3-CF_3	82%	87%	80%	89%	77%	90%
f	3-Ac	86%	78%	85%	80%	80%	90%
g	3-COOMe	82%	75%	75%	80%	80%	66%

Scheme 5. Formation of 3-amino-5-arylthiophenes with various substituents at C-2 and C-5 position (**6Aa**-**Fg**).

In continuation of this project, we performed three-component reactions for the preparation of 3-aminothiophenes **6Ga**–**g** and **6Ha**–**g** starting from 2-bromo-2-chloro-3-phenylpropanenitriles **3a**–**g** employing sodium sulfide and bromonitromethane **5G** or chloroacetonitrile **5H** (Scheme 6). Best results were achieved when methanol as solvent and freshly prepared sodium hydrosulfide were used. Exchanging the solvent to DMF and applying harsher reaction conditions such as reflux temperature caused decreased yields. In comparison to literature-known procedures to synthesize 2-nitro-3-amino-5-phenylthiophene **6Ga** according to route **I** (Figure 1) which gave very low yields,[48] the method described here is very useful. Alternative methods to prepare 3-aminothiophene-2-carbonitriles such as **6Ha**, however, gave better yields. They use *S*-(isocyanomethyl) ethanethioate and bromoethene[49] or 3-phenylpropiolonitrile[50] as starting materials, respectively.

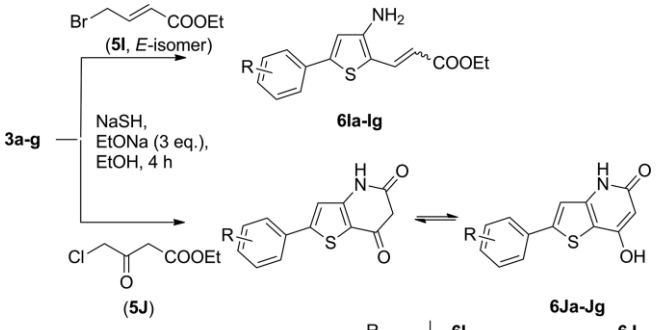


	EWG= / R=	-NO_2 G	-CN H
a	H	72%	63%
b	3-Me	56%	65%
c	4-Me	81%	79%
d	4-F	76%	82%
e	3-CF_3	61%	60%
f	3-Ac	65%	63%
g	3-COOMe	70%	65%

Scheme 6. Three component reaction for the synthesis of 3-aminothiophenes.

Replacing the methanol and sodium methoxide by ethanol and sodium ethoxide gave the opportunity to perform the reaction with ethyl 4-bromocrotonate **5I** or ethyl 4-chloroacetoacetate **5J**, because transesterification reactions during the three-component reaction are not disturbing. Interestingly, the reaction with **5I** stopped on the step of the Thorpe–Ziegler-type cyclization, whereas **5Ja**–**g** induced a cascade reaction which resulted in the formation of thienopyridinediones **6Ja**–**g** (Scheme 7). The latter proved to be poorly soluble in all NMR solvents tested. According to the ^{1}H NMR spectra, the compounds **6J** exist in the enol form and the corresponding proton gives singlets in the range from 5.58 to 5.76 ppm in the ^{1}H NMR spectra.

The structure of compound **6Ja** was also proven by a single-crystal X-ray analysis the molecular drawing of which is shown in Figure 2. Single crystals of 2-phenylthieno[3,2-*b*]pyridine-5,7(4*H*,6*H*)-dione **6Ja** were obtained by diffusion of methanol into a saturated solution of the compound in DMF.



	R	6I	6J
a	H	74% (*E*)	85%
b	3-Me	65% (*E*)	57%
c	4-Me	57% (*E*/*Z*=0.94/0.06)	69%
d	4-F	86% (*E*)	77%
e	3-CF_3	57% (*E*)	57%
f	3-Ac	68% (*E*/*Z*=0.75/0.25)	74%
g	3-COOMe	61% (*E*)	66%

Scheme 7. Formation of thiophenes **6** by three-component reactions.

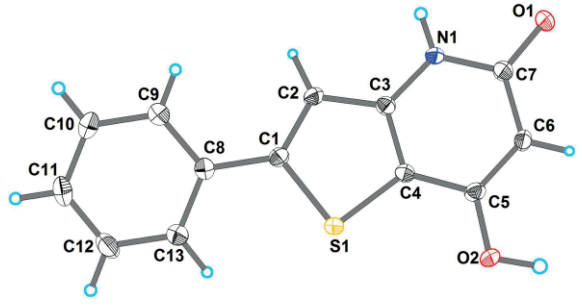


Figure 2. View of the molecular structure derived from the single-crystal X-ray analysis (displacement parameters are drawn at 50 % probability level).

The compound **6Ja** crystallized in the monoclinic space group $P2_1/n$ with one pyridinedione molecule and one DMF molecule in the asymmetric unit. The molecule of **6Ja** is almost planar, the dihedral angle between the phenyl ring and the thiophene core is 10.8(2)°. The distance between two adjacent parallel molecules of **6Ja** is 359.7 pm, which corresponds to the distance of π–π stacking interactions. The hydroxyl hydrogen atom is involved in O–H···O hydrogen bonding with the carbonyl oxygen atom of the neighboring molecule, connecting them into an infinite zigzag H-bonded chain (Fig S2). In contrast, the N-bonded hydrogen atom of the pyridinedione core forms an N–H···O hydrogen bond with the DMF molecule. The distance C5–C6 of 138.1(2) pm indicates a considerable double bond character and proves the enol form in solid-state.

Conclusions

The reported method for the bromoarylation of 2-chloroacrylonitrile by Meerwein reaction for the synthesis of the hitherto undescribed title compounds, 2-bromo-2-chloro-3-arylpropanenitriles, is reliable and affords the desired products in good yields under mild conditions. These propanenitriles are very stable compounds and proved to be useful in two- or three-component syntheses of functionalized thiophenes which are otherwise difficult or even impossible to prepare.

Experimental Section

Melting points are uncorrected and were determined in an apparatus according to Dr. Tottoli (Büchi). The ATR-IR spectra were obtained on a Bruker Alpha in the range of 400 to 4000 cm^{-1}. ^1H and ^{13}C NMR spectra were recorded on a Bruker 170 Avance 500 spectrometer (at 500 MHz for ^1H NMR, 126 MHz for ^{13}C NMR), a Bruker Avance III 600 MHz spectrometer (at 600 MHz for ^1H NMR, 151 MHz for ^{13}C NMR), and a Bruker Avance 400 MHz spectrometer (at 400 MHz for ^1H NMR, 101 MHz for ^{13}C NMR). Multiplicities are described by using the following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, and m = multiplet. Signal orientations in DEPT experiments were described as follows: o = no signal; + = up (CH, CH_3); – = down (CH_2). The mass spectra were measured with a Varian 320 MS Triple Quad GC/MS/MS (EIMS) or with an Agilent LCMSD series HP 1100 with APIES at fragmentor voltages as indicated. Elemental analysis was performed on a Carlo Erba 1106 analyzer.

Crystal structure determination of 6Ja: Single-crystal data for **6Ja** were collected on an Agilent Gemini+ four-circle diffractometer equipped with an Atlas CCD detector, using graphite monochromatized Mo-K_α radiation. Data were treated using the CrysAlis PRO program.[51] The structure was solved using SHELXS and refined by least-squares method on F^2 by SHELXL with the following graphical user interfaces of OLEX2.[52] N-bonded and O-bonded H atoms in **6Ja** were derived from the Fourier difference syntheses and refined in an isotropic mode. The other hydrogen atoms were placed on geometrically calculated positions and refined as riding atoms with relative isotropic displacement parameters.

6Ja: yellow needles, $C_{13}H_9NO_2S{\cdot}C_3H_7NO$, M_r = 316.37, crystal size 0.15 × 0.41 × 0.44 mm, monoclinic, space group $P\ 2_1/n$ (no. 14), temperature 150(2) K, wavelength 0.71073 Å, a = 7.3297(3) Å, b = 8.8005(3) Å, c = 23.6124(11) Å, β = 95.155(4)°, V = 1516.96(11) $Å^3$, Z = 4, ρ = 1.385 g/cm^3, absorption coeff. = 0.227 mm^{-1}, $F(000)$ = 664, θ range for data collection 2.47–28.80°, limiting indices $-9 \le h \le 9$, $-11 \le k \le 11$, $-26 \le l \le 31$, refinement method: full-matrix least-squares on F^2, measured reflections = 13943, used in refinement = 3400, free parameters = 209, goodness-of-fit on F^2 = 1.060, $R\ [F_0^2 > 2\sigma(F_0^2)]$ = 0.0405, $wR\ (F^2)$ = 0.0961, largest diff. peak/hole = 0.28/–0.34 e $Å^{-3}$.

CCDC 1957206 (for **6Ja**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

General Procedure of the Meerwein Arylation: The corresponding aniline **1**, (0.10 mol) was added to 40 % aqueous HBr (34.3 mL, 0.22 mol). The mixture was cooled to –5 °C, and a saturated solution of 7.6 g (0.11 mol) of sodium nitrite was added dropwise at such a rate that the temperature did not exceed 5 °C. A cold solution of freshly-prepared diazonium salt **2** was added dropwise whilst stirring to a mixture of $CuBr_2$ (0.100 g, 0.448 mmol), 2-chloroacrylonitrile (0.8 mL, 0.100 mol), and acetone (50 mL). The rate of the addition was selected so that nitrogen evolved at a rate of 2–3 bubbles per second (addition time 0.5–1 h). The mixture was then stirred until nitrogen no longer evolved, 200 mL of water was added, the organic layer was separated, and the aqueous layer was extracted with DCM (3 × 15 mL). The combined extract were dried with $MgSO_4$, evaporated, and the residue was distilled under reduced pressure.

2-Bromo-2-chloro-3-phenylpropanenitrile (3a): Yield 9.780 g, 40 %, light yellow oil, b.p. 116–120 °C/2 Torr. ^1H NMR (500 MHz, [D_6]DMSO): δ = 7.50–7.46 (m, 2H), 7.46–7.41 (m, 3H), 4.06 (d, J = 14.2 Hz, 1H, CH_2), 4.00 (d, J = 14.2 Hz, 1H, CH_2) ppm. ^{13}C NMR

(126 MHz, [D$_6$]DMSO): δ = 133.2, 131.1, 128.7, 128.5, 116.3, 51.7, 51.2 ppm. IR (ATR): $\tilde{\nu}$ = 3033, 2930, 1757, 1741, 1515, 1427, 1258, 1202, 1081, 1023, 1011, 958, 882, 812, 771, 726, 699, 627, 602, 577, 513, 496, 479, 425 cm^{-1}. MS (ESI): *m/z* = 244.0 [M + H]$^+$. Elemental analysis calcd. for C_9H_7BrClN: C 44.21, H 2.89, N 5.73, found: C 44.03, H 2.81, N 5.60.

2-Bromo-2-chloro-3-(3-methylphenyl)propanenitrile (3b): Yield 14.993 g, 58 %, a light yellow oil, b.p. 119–120 °C/2 Torr, m.p. 16 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.35–7.30 (m, 1H, C_6H_4), 7.27–7.23 (m, 3H, C_6H_4), 3.82 (d, *J* = 14.3 Hz, 1H, CH_2), 3.77 (d, *J* = 14.3 Hz, 1H, CH_2), 2.42 (s, 3H, CH_3) ppm. ^{13}C NMR (126 MHz, [D$_6$]DMSO): δ = 138.4, 132.2, 131.6, 129.7, 128.6, 128.0, 115.8, 54.0, 51.4, 21.4 ppm. IR (ATR): $\tilde{\nu}$ = 3028, 2920, 2219, 1608, 1429, 1331, 1169, 1131, 803, 759, 718, 697, 638, 441 cm^{-1}. MS (ESI): *m/z* = 258.0 [M + H]$^+$. Elemental analysis calcd. for $C_{10}H_9BrClN$: C 46.46, H 3.51, N 5.42, found: C 46.32; H 3.48; N 5.50.

2-Bromo-2-chloro-3-(4-methylphenyl)propanenitrile (3c): Yield 11.891 g, 46 %, white crystals, b.p. 123–125 °C/2 Torr, m.p. 49 °C. ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 7.34 (d, *J* = 7.8, 2H, C_6H_4), 7.21 (d, *J* = 7.8, 2H, C_6H_4), 3.97 (d, *J* = 14.3, 1H, CH_2), 3.92 (d, *J* = 14.3, 1H, CH_2), 2.31 (s, 3H, CH_3) ppm. ^{13}C NMR (126 MHz, [D$_6$]DMSO): δ = 138.0, 131.0, 130.2, 129.1, 116.4, 51.5, 51.3, 20.9 ppm. IR (ATR): $\tilde{\nu}$ = 3029, 2932, 2923, 1915, 1708, 1612, 1515, 1427, 1318, 1223, 1113, 1070, 1023, 958, 884, 812, 770, 726, 706, 627, 602, 513, 496, 478, 425 cm^{-1}. MS (ESI): *m/z* = 258.0 [M + H]$^+$. Elemental analysis calcd. for $C_{10}H_9BrClN$: C 46.46, H 3.51, N 5.42, found: C 46.35, H 3.44, N 5.39.

2-Bromo-2-chloro-3-(4-fluorophenyl)propanenitrile (3d): Yield 18.637 g, 71 %, white crystals, b.p. 105–107 °C/3 Torr, m.p. 29 °C. ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 7.51 (dd, J_{HH} = 8.3, J_{HF} = 5.7 Hz, 2H C_6H_4), 7.24 (t, *J* = 8.8 Hz, 2H, C_6H_4), 4.04 (d, *J* = 14.3 Hz, 1H, CH_2), 3.99 (d, *J* = 14.3 Hz, 1H, CH_2) ppm. ^{13}C NMR (126 MHz, [D$_6$]DMSO): δ = 162.4 (d, *J* = 245.4 Hz), 133.3 (d, *J* = 8.4 Hz), 129.5 (d, *J* = 3.0 Hz), 116.2, 115.4 (d, *J* = 21.5 Hz), 51.2 (d, *J* = 2.1 Hz), 50.6 ppm. IR (ATR): $\tilde{\nu}$ = 2219, 1600, 1508, 1430, 1419, 1225, 1161, 1101, 1014, 967, 885, 833, 786, 706, 624, 602, 583, 538, 519, 498, 486, 433 cm^{-1}. MS (ESI): *m/z* = 261.9 [M + H]$^+$. Elemental analysis calcd. for $C_9H_6BrClFN$: C 41.18, H 2.30, N 5.34, found: C, 41.09, H 2.22, N 5.29.

2-Bromo-2-chloro-3-[3-(trifluoromethyl)phenyl]propanenitrile (3e): Yield 24.375 g, 78 %, light yellow oil, b.p. 106–107 °C/2 Torr. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.76–7.68 (m, 2H, C_6H_4), 7.66 (d, *J* = 7.5 Hz, 1H, C_6H_4), 7.60–7.54 (m, 1H, C_6H_4), 3.91 (d, *J* = 14.4 Hz, 1H, CH_2), 3.87 (d, *J* = 14.4 Hz, 1H, CH_2) ppm. ^{13}C NMR (126 MHz, [D$_6$]DMSO): δ = 135.2, 134.4, 129.4, 129.1 (d, *J* = 31.8 Hz), 127.7 (q, *J* = 3.8 Hz), 125.3 (q, *J* = 3.7 Hz), 124.0 (q, *J* = 272.3 Hz), 116.1, 50.4 ppm. IR (ATR): $\tilde{\nu}$ = 2219, 1725, 1600, 1510, 1452, 1432, 1333, 1312, 1201, 1165, 1122, 1101, 1075, 1039, 970, 912, 810, 768, 701, 660, 585, 421 cm^{-1}. MS (ESI): *m/z* = 311.9 [M + H]$^+$. Elemental analysis calcd. for $C_{10}H_6BrClF_3N$: C 38.43, H 1.94, N 4.48, found: C 38.40, H 1.87, N 4.39.

3-(3-Acetylphenyl)-2-bromo-2-chloropropanenitrile (3f): Yield 19.768 g, 69 %, white crystals, b.p. 170–172 °C/2 Torr, m.p. 48 °C. ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 8.08 (s, 1H, C_6H_4), 8.01 (d, 1H, *J* = 7.5 Hz, C_6H_4), 7.73 (d, *J* = 7.4 Hz, 1H, C_6H_4), 7.61–7.56 (m, 1H, C_6H_4), 4.16 (d, *J* = 14.3 Hz, 1H, CH_2), 4.10 (d, *J* = 14.3 Hz, 1H, CH_2), 2.59 (s, 3H, CH_3) ppm. ^{13}C NMR (126 MHz, [D$_6$]DMSO): δ = 197.6, 136.9, 135.8, 133.8, 130.7, 128.9, 128.7, 116.3, 50.9, 50.8, 26.8 ppm. IR (ATR): $\tilde{\nu}$ = 3343, 3041, 2973, 2935, 1680, 1600, 1429, 1358, 1268, 1190, 1098, 1070, 1021, 954, 881, 806, 755, 695, 653, 587, 495, 465, 420 cm^{-1}. MS (ESI): *m/z* = 286.0 [M + H]$^+$. Elemental analysis calcd. for $C_{11}H_9BrClNO$: C 46.11, H 3.17, N 4.89, found: C 45.98, H 3.08, N 4.75.

Methyl 3-(2-Bromo-2-chloro-2-cyanoethyl)benzoate (3g): Yield 17.847 g, 69 %, white crystals, b.p. 167–169 °C/2 Torr, m.p. 76 °C. ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 8.10 (s, 1H, C_6H_4), 8.00 (d, *J* = 7.8 Hz, 1H, C_6H_4), 7.75 (d, *J* = 7.6 Hz, 1H, C_6H_4), 7.58 (dd, *J* = 4.6, 10.8 Hz, 1H, C_6H_4), 4.17 (d, *J* = 14.1 Hz, 1H, CH_2), 4.12 (d, *J* = 14.1 Hz, 1H, CH_2), 3.87 (s, 3H, CH_3) ppm. ^{13}C NMR (126 MHz, [D$_6$]DMSO): δ = 165.9*, 136.1, 136.0*, 135.9, 134.9, 133.9*, 133.0, 132.0, 131.9*, 131.7, 129.89, 129.83*, 129.77, 129.5, 129.4*, 129.3, 129.01, 128.96*, 128.90, 116.9, 116.2*, 115.4, 52.34*, 51.25, 50.77*, 50.74*, 50.1 ppm. IR (ATR): $\tilde{\nu}$ = 3029, 2219, 1722, 1608, 1437, 1425, 1203, 1114, 800, 625, 495, 220 cm^{-1}. MS (ESI): *m/z* = 302.0 [M + H]$^+$. Elemental analysis calcd. for $C_{11}H_9BrClNO_2$: C 43.67, H 3.00, N 4.63, found: C 43.56, H 2.97, N 4.50. *: most stable rotamer. Signals of three rotamers are present in ^{13}C NMR spectra of this compound.

General Procedure for the Preparation ot the 2-chloro-3-aryl-prop-2-enenitriles 4: To a solution of propanenitrile **3** (50 mmol, 1 equiv.) in toluene (30 mL) NEt_3 (7.63 mL, 55 mmol, 1.1 equiv.) was added dropwise whilst stirring. The resulting mixture was stirred for 1 h under reflux. The mixture was then cooled to r.t. and water (30 mL) was added, the organic layer was separated, dried with $MgSO_4$, and the solvents evaporated. The residue was distilled under reduced pressure.

2-Chloro-3-phenylprop-2-enenitrile (4a): Yield 7.525 g, 92 %, light yellow oil, b.p. 106–110 °C/2 Torr. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.78–7.71 (m, 2H), 7.47–7.45 (m, 3H), 7.34 (s, 1H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 142.4, 131.9, 131.4, 130.5, 129.0, 116.5, 101.6 ppm. IR (ATR): $\tilde{\nu}$ = 2933, 2219, 1452, 1333, 1201, 1165, 1124, 1075, 810, 768, 701, 660 cm^{-1}. Spectroscopic data are in agreement with those reported in the literature.[41]

2-Chloro-3-(3-methylphenyl)prop-2-enenitrile (4b): Yield 8.347 g, 94 %, a light yellow oil, b.p. 96–99 °C/2 Torr. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.64–7.47 (m, 2H), 7.39–7.25 (m, 3H), 2.42 (s, 3H, CH_3) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 145.6, 142.6, 139.1, 132.2, 129.4, 129.1, 125.9, 112.4, 100.0, 21.4 ppm. IR (ATR): $\tilde{\nu}$ = 3029, 2922, 2861, 2219, 1608, 1484, 1451, 1429, 1380, 1331, 1285, 1245, 1168, 1130, 1074, 967, 921, 888, 785, 761, 690, 601, 548, 441 cm^{-1}. MS (ESI): *m/z* = 178.0 [M + H]$^+$. Elemental analysis calcd. for $C_{10}H_8ClN$: C 67.62, H 4.54, N 7.89, found: C 67.49, H 4.45, N 7.78.

2-Chloro-3-(4-methylphenyl)prop-2-enenitrile (4c): Yield 8.347 g, 94 %, a light yellow oil, b.p. 96–99 °C/2 Torr. ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 7.93 (s, 0.3H, CH), 7.87 (s, 0.7H, CH), 7.74 (d, *J* = 8.1 Hz, 0.6H, C_6H_4), 7.64 (d, *J* = 8.1 Hz, 1.4H, C_6H_4), 7.32 (d, *J* = 7.9 Hz, 2H, C_6H_4), 2.35 (s, 3H, CH_3) ppm. ^{13}C NMR (126 MHz, [D$_6$]DMSO): δ = 146.4, 144.3, 143.3, 142.0, 141.8, 130.6, 129.9, 129.6, 128.7, 116.8, 115.5, 98.3, 97.4, 21.3, 21.2 ppm. Spectroscopic data are in agreement with those reported in the literature.[53]

2-Chloro-3-(4-fluorophenyl)prop-2-enenitrile (4d): Yield 8.621 g, 95 %, white crystals, b.p. 84–87 °C/2 Torr, m.p. 28 °C. ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 8.00 (s, 0.4H, CH), 7.94 (s, 0.6H, CH), 7.90 (dd, J_{HF} = 5.6 Hz, J_{HF} = 8.6 Hz, 0,8H, C_6H_4), 7.81 (dd, J_{HF} = 5.5 Hz, J_{HF} = 8.5 Hz, 1.2H, C_6H_4), 7.39–7.34 (m, 2H, C_6H_4) ppm. ^{13}C NMR (126 MHz, [D$_6$]DMSO): δ = 163.5 (d, *J* = 251.0 Hz), 163.4 (d, *J* = 251.8 Hz), 145.2, 142.2, 133.1 (d, *J* = 9.1 Hz), 131.2 (d, *J* = 9.0 Hz), 128.3 (d, *J* = 3.3 Hz), 128.0 (d, *J* = 3.3 Hz), 116.4 (d, *J* = 22.1 Hz), 116.2 (d, *J* = 22.0 Hz), 115.4, 115.2, 99.0 (d, *J* = 2.3 Hz), 98.4 (d, *J* = 2.4 Hz) ppm. IR (ATR): $\tilde{\nu}$ = 3077, 3031, 2220, 1599, 1507, 1415, 1287, 1237, 1162, 1111, 1012, 968, 830, 788, 686, 623, 583, 566, 538, 515, 414 cm^{-1}. MS (ESI): *m/z* = 182.0 [M + H]$^+$. Elemental analysis calcd. for C_9H_5ClFN: C 59.53, H 2.78, N 7.71, found: C 59.42, H 2.71, N 7.63. To the best of our knowledge, no spectroscopic data have been reported.

2-Chloro-3-[3-(trifluoromethyl)phenyl]prop-2-enenitrile (4e): Yield 8.621 g, 95 %, a light yellow oil, b.p. 106–108 °C/5 Torr. ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 8.17–8.02 (m, 3H, CH, C$_6$H$_4$), 7.89 (d, J = 7.7 Hz, 1H, C$_6$H$_4$), 7.79–7.75 (m, 1H, C$_6$H$_4$) ppm. ^{13}C NMR (126 MHz, [D$_6$]DMSO): δ = 146.5, 143.5, 137.1, 131.5, 131.0 (q, J = 32.6 Hz), 126.0 (q, J = 3.6 Hz), 125.0 (q, J = 272.8 Hz), 122.6 (q, J = 4.2 Hz), 115.3, 98.6 ppm. IR (ATR): $\tilde{\nu}$ = 3032, 2924, 2219, 1609, 1430, 1331, 1202, 1168, 1128, 1074, 909, 802, 761, 692, 659, 601, 442 cm^{-1}. MS (ESI): m/z = 232.0 [M + H]$^+$. Elemental analysis calcd. for C$_{10}$H$_5$ClF$_3$N: C 51.86, H 2.18, N 6.05, found: C 51.64, H 2.11, N 5.97. To the best of our knowledge, no spectroscopic data have been reported.

3-(3-Acetylphenyl)-2-chloroprop-2-enenitrile (4f) Yield 8.621 g, 95 %, white crystals, b.p. 141–146 °C/2 Torr, m.p. 43–44 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO), (two isomers 3:7): δ = 8.37 (s, 0.3H, CH), 8.33 (s, 0.7H, CH), 8.13 (s, 0.3H, C$_6$H$_4$), 8.11–8.05 (m, 2H, C$_6$H$_4$), 7.99 (d, J = 7.7 Hz, 0.7H, C$_6$H$_4$), 7.72–7.67 (m, 1H, C$_6$H$_4$), 2.62 (s, 1.2H, CH$_3$), 2.61 (s, 1.8H, CH$_3$) ppm. ^{13}C NMR (126 MHz, [D$_6$]DMSO): δ = 197.3, 197.2, 149.1, 145.7, 142.8, 137.3, 137.1, 134.3, 132.5, 131.8, 130.8, 130.7, 129.8, 129.7, 129.4, 128.3, 116.2, 115.0, 100.5, 99.8, 26.7 ppm. IR (ATR): $\tilde{\nu}$ = 3034, 2217, 1677, 1594, 1577, 1493, 1425, 1357, 1274, 1199, 1069, 1013, 958, 939, 917, 891, 794, 712, 677, 589, 551, 521, 489 cm^{-1}. MS (ESI): m/z = 206.0 [M + H]$^+$. Elemental analysis calcd. for C$_{11}$H$_8$ClNO: C 64.25, H 3.92, N 6.81, found: C 64.08, H 3.84, N 6.77.

Methyl 3-(2-chloro-2-cyanoethenyl)benzoate (4g): Yield 8.621 g, 95 %, white crystals, b.p. 146–150 °C/2 Torr, m.p 74 °C. ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 8.18 (s, 1H), 8.02 (d, J = 7.5 Hz, 1H), 7.97 (d, J = 7.1 Hz, 1H), 7.68 (t, J = 7.5 Hz, 1H), 3.88 (s, 3H) ppm. ^{13}C NMR (126 MHz, [D$_6$]DMSO): δ = 165.7, 147.9, 142.6, 136.8, 133.4, 130.5, 129.8, 129.0, 116.3, 101.0, 26.7 ppm. IR (ATR): $\tilde{\nu}$ = 3075, 3061, 3043, 2960, 2214, 1722, 1607, 1579, 1437, 1424, 1305, 1280, 1205, 1115, 1087, 1067, 1042, 1012, 799, 747, 676, 604, 589, 550, 495 cm^{-1}. MS (ESI): m/z = 222.0 [M + H]$^+$. Elemental analysis calcd. for C$_{11}$H$_8$ClNO$_2$: C 59.61, H 3.64, N 6.32, found: C 59.44, H 3.54, N 6.20.

General Method for Preparation of Methyl 3-Amino-5-arylthiophene-2-carboxylates (6Aa–Ag), 3-Amino-*N*-R-5-arylthiophene-2-carboxamides (6Ba–Eg), and 1-(3-Amino-5-arylthiophen-2-yl)ethanones (6Fa–Fg): A solution of propanenitrile **3** (3 mmol) in methanol (5 mL) was added dropwise whilst stirring to a mixture of appropriate thiol (**5A**–**F**) (3.02 mmol) with a solution of MeONa (9 mL, 1 M) in methanol at ambient temperature. The resulting mixture was stirred under reflux over a 1 h. The solvent was evaporated under reduced pressure. Acetic acid (20 mL, ω = 2 %) was added to residue. The product was filtered off and recrystallized from (methanol or methanol/DMF). In the case of **6B**–**F** the reaction was performed at r.t.

Methyl 3-Amino-5-phenylthiophene-2-carboxylate (6Aa): Yield 0.524 g, 75 %, white crystals, m.p. 99–100 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 7.62–7.65 (m, 2H, C$_6$H$_5$), 7.38–7.48 (m, 3H, C$_6$H$_5$), 7.00 (s, 1H, thiophene), 4.29 (br.s, 2H, NH$_2$), 3.74 (s, 3H, CH$_3$) ppm. Spectroscopic data are in agreement with those reported in the literature.[54]

Methyl 3-Amino-5-(3-methylphenyl)thiophene-2-carboxylate (6Ab): Yield 0.592 g, 80 %, white crystals, m.p. 83–84 °C. ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 7.48–7.37 (m, 2H, C$_6$H$_4$), 7.31 (t, J = 7.5 Hz, 1H, C$_6$H$_4$), 7.20 (d, J = 7.2 Hz, 1H, C$_6$H$_4$), 6.97 (s, 1H, thiophene), 6.60 (s, 2H, NH$_2$), 3.72 (s, 3H, OCH$_3$), 2.33 (s, 3H, CH$_3$) ppm. ^{13}C NMR (126 MHz, [D$_6$]DMSO): δ = 164.0, 155.4, 147.8, 138.6, 132.7, 129.9, 129.2, 126.1, 122.8, 116.2, 96.8, 51.0, 21.0 ppm. Spectroscopic data are in agreement with those reported in the literature.[55]

Methyl 3-Amino-5-(4-methylphenyl)thiophene-2-carboxylate (6Ac): Yield 0.526 g, 71 %, white crystals, m.p. 141–142 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 7.51 (d, J = 8.2 Hz, 2H, C$_6$H$_4$), 7.24 (d, J = 7.9 Hz, 2H, C$_6$H$_4$), 6.93 (s, 1H, thiophene), 6.58 (s, 2H, NH$_2$), 3.73 (s, 3H, OCH$_3$), 2.32 (s, 3H, CH$_3$) ppm. ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 163.9, 155.6, 147.7, 138.8, 130.0, 129.7, 125.4, 115.6, 96.1, 50.9, 20.8 ppm. IR (ATR): $\tilde{\nu}$ = 3491, 3372, 2951, 1660, 1589, 1549, 1514, 1461, 1291, 1276, 1188, 1115, 1083, 1012, 961, 841, 804, 782, 764, 714, 655, 587, 471, 437 cm^{-1}. Spectroscopic data are in agreement with those reported in the literature.[56]

Methyl 3-Amino-5-(4-fluorophenyl)thiophene-2-carboxylate (6Ad): Yield 0.633 g, 84 %, white crystals, m.p. 159–160 °C. ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 7.67 (dd, J_{HH} = 6.5 Hz, J_{HF} = 5.5 Hz, 2H, C$_6$H$_4$), 7.27 (dd, J_{HH} = 8.4 Hz, J_{HF} = 7.4 Hz, 2H, C$_6$H$_4$), 6.94 (s, 1H, thiophene), 6.61 (s, 2H, NH$_2$), 3.73 (s, 3H, CH$_3$) ppm. ^{13}C NMR (126 MHz, [D$_6$]DMSO): δ = 164.0, 162.6 (d, J = 247.0 Hz), 155.6, 146.5, 129.5 (d, J = 3.1 Hz), 127.9 (d, J = 8.4 Hz), 116.4, 116.2 (d, J = 22.0 Hz), 96.7, 51.0 ppm. Spectroscopic data are in agreement with those reported in the literature.[27i]

Methyl 3-Amino-5-[3-(trifluoromethyl)phenyl]thiophene-2-carboxylate (6Ae): Yield 0.740 g, 82 %, white crystals, m.p. 95–96 °C. ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 7.92 (d, J = 7.7 Hz, 1H, C$_6$H$_4$), 7.89 (s, 1H, C$_6$H$_4$), 7.74 (d, J = 7.7 Hz, 1H, C$_6$H$_4$), 7.67 (t, J = 7.7 Hz, 1H, C$_6$H$_4$), 7.13 (s, 1H, thiophene), 6.62 (s, 2H, NH$_2$), 3.74 (s, 3H, CH$_3$) ppm. ^{13}C NMR (126 MHz, [D$_6$]DMSO): δ = 163.9, 155.4, 145.4, 133.9, 130.5, 130.0 (q, J = 31.8 Hz), 129.7, 125.6 (q, J = 3.3 Hz), 123.9 (q, J = 272.6 Hz), 121.9 (q, J = 3.7 Hz), 117.7, 97.6, 51.1 ppm. Spectroscopic data are in agreement with those reported in the literature.[56]

Methyl 5-(3-Acetylphenyl)-3-aminothiophene-2-carboxylate (6Af): Yield 0.709 g, 86 %, white crystals, m.p. 96–97 °C. ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 8.08 (s, 1H, C$_6$H$_4$), 7.94 (d, J = 7.4 Hz, 1H, C$_6$H$_4$), 7.85 (d, J = 7.0 Hz, 1H, C$_6$H$_4$), 7.60–7.54 (m, 1H, C$_6$H$_4$), 7.11 (s, 1H, thiophene), 6.63 (s, 2H, NH$_2$), 3.72 (s, 3H, OCH$_3$), 2.61 [s, 3H, C(O)CH$_3$] ppm. ^{13}C NMR (126 MHz, [D$_6$]DMSO): δ = 197.6, 163.9, 155.2, 146.4, 137.5, 133.2, 130.0, 129.8, 128.8, 124.8, 117.2, 97.5, 51.1, 26.9 ppm. IR (ATR): $\tilde{\nu}$ = 3418, 3344, 1710, 1642, 1582, 1518, 1449, 1324, 1301, 1274, 1184, 1104, 1080, 1034, 834, 814, 753, 731, 681, 644, 510 cm^{-1}. MS (ESI): m/z = 276.1 [M + H]$^+$. Elemental analysis calcd. for C$_{14}$H$_{13}$NO$_3$S: C 61.07, H 4.76, N 5.09, found: C 60.99, H 4.65, N 4.94.

Methyl 3-Amino-5-[3-(methoxycarbonyl)phenyl]thiophene-2-carboxylate (6Ag): Yield 0.715 g, 82 %, off-white crystals, m.p. 124–126 °C. ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 8.11 (d, J = 1.3 Hz, 1H, 2H-C$_6$H$_4$), 7.95 (dd, J = 7.7, 1.1 Hz, 1H, 6H-C$_6$H$_4$), 7.93–7.87 (m, 1H, C$_6$H$_4$), 7.61 (t, J = 7.8 Hz, 1H, C$_6$H$_4$), 7.09 (s, 1H, thiophene), 5.82–5.34 (br.s, 2H, NH$_2$), 3.88 (s, 3H, CH$_3$), 3.74 (s, 3H, CH$_3$) ppm. ^{13}C NMR (126 MHz, [D$_6$]DMSO): δ = 165.7, 163.9, 155.8, 146.0, 133.3, 130.6, 130.2, 130.0, 129.6, 125.8, 117.1, 98.5, 52.5, 51.1 ppm. IR (ATR): $\tilde{\nu}$ = 3433, 1670, 1634, 1590, 1550, 1515, 1463, 1428, 1365, 1313, 1268, 1235, 1075, 948, 900, 832, 782, 748, 690, 677, 590, 492, 434 cm^{-1}. MS (ESI): m/z = 292.1 [M + H]$^+$. Elemental analysis calcd. for C$_{14}$H$_{13}$NO$_4$S: C 57.72, H 4.50, N 4.81, found: C 57.59, H 4.43, N 4.74.

3-Amino-*N*,5-diphenylthiophene-2-carboxamide (6Ba): Yield 0.714 g, 81 %, white crystals, m.p. 203–204 °C. ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 9.33 (s, 1H, NH), 7.68 (d, J = 8.4 Hz, 2H, Ph), 7.65 (d, J = 8.1 Hz, 2H, Ph), 7.47 (t, J = 7.2 Hz, 2H, Ph), 7.42–7.37 (m, 1H, Ph), 7.29 (t, J = 7.3 Hz, 2H, Ph), 7.06–7.01 (m, 2H, Ph, thiophene), 6.82–6.54 (br.s, 2H, NH$_2$) ppm. ^{13}C NMR (126 MHz, [D$_6$]DMSO): δ = 163.2, 155.1, 144.5, 139.4, 133.0, 129.4, 129.0, 128.4, 125.4, 123.0, 120.7,

116.9, 100.2 ppm. IR (ATR): $\tilde{\nu}$ = 3473, 3364, 3250, 3054, 1616, 1585, 1514, 1489, 1464, 1432, 1320, 1307, 1274, 1233, 1097, 1072, 907, 824, 747, 684, 636, 510 cm^{-1}. MS (ESI): *m/z* = 295.1 $[M + H]^+$. Elemental analysis calcd. for $C_{17}H_{14}N_2OS$: C 69.36, H 4.79, N 9.52, found: C 69.28, H 4.70, N 9.40.

3-Amino-5-(3-methylphenyl)-*N*-phenylthiophene-2-carboxamide (6Bb): Yield 0.803 g, 87 %, light yellow crystals, m.p. 171–172 °C. ^1H NMR (500 MHz, [D_6]DMSO): δ = 9.30 (s, 1H, NH), 7.68 (d, *J* = 7.7 Hz, 2H, Ar), 7.48–7.42 (m, 2H, Ar), 7.35 (t, *J* = 7.5 Hz, 1H, Ar), 7.29 (t, *J* = 7.8 Hz, 2H, Ar), 7.21 (d, *J* = 7.6 Hz, 1H, Ar), 7.03 (t, *J* = 7.3 Hz, 1H, Ar), 7.00 (s, 1H, thiophene), 6.68 (s, 2H, NH_2), 2.36 (s, 3H, CH_3) ppm. ^{13}C NMR (126 MHz, [D_6]DMSO): δ = 163.2, 155.1, 144.7, 139.4, 138.6, 133.0, 129.6, 129.2, 128.4, 126.0, 123.0, 122.6, 120.7, 116.8, 100.0, 21.0 ppm. IR (ATR): $\tilde{\nu}$ = 3471, 3362, 3264, 1622, 1581, 1533, 1499, 1456, 1434, 1316, 1267, 1234, 1176, 1093, 1072, 903, 872, 826, 781, 748, 722, 686, 636, 616, 543, 513, 489, 432 cm^{-1}. MS (ESI): *m/z* = 309.1 $[M + H]^+$. Elemental analysis calcd. for $C_{18}H_{16}N_2OS$: C 70.10, H 5.23, N 9.08, found: C 70.00, H 5.14, N 8.97.

3-Amino-5-(4-methylphenyl)-*N*-phenylthiophene-2-carboxamide (6Bc): Yield 0.720 g, 78 %, light yellow crystals, m.p. 205–206 °C. ^1H NMR (500 MHz, [D_6]DMSO): δ = 9.29 (s, 1H, NH), 7.68 (d, *J* = 7.6 Hz, 2H, Ar), 7.54 (d, *J* = 8.1 Hz, 2H, Ar), 7.32–7.27 (m, 4H, Ar), 7.03 (t, *J* = 7.4 Hz, 1H, Ar), 6.97 (s, 1H, thiophene), 6.68 (s, 2H, NH_2), 2.33 (s, 3H, CH_3). ppm. ^{13}C NMR (126 MHz, [D_6]DMSO): δ = 163.2, 155.2, 144.7, 139.4, 138.6, 130.3, 129.9, 128.4, 125.4, 123.0, 120.7, 116.3, 99.7, 20.9 ppm. IR (ATR): $\tilde{\nu}$ = 3470, 3358, 1616, 1582, 1520, 1499, 1460, 1433, 1319, 1270, 1232, 1177, 1100, 1074, 1018, 811, 750, 692, 567, 541, 511 cm^{-1}. MS (ESI): *m/z* = 309.1 $[M + H]^+$. Elemental analysis calcd. for $C_{18}H_{16}N_2OS$: C 70.10, H 5.23, N 9.08, found: C 69.96, H 5.15, N 8.94.

3-Amino-5-(4-fluorophenyl)-*N*-phenylthiophene-2-carboxamide (6Bd): Yield 0.814 g, 87 %, white crystals, m.p. 226–227 °C. ^1H NMR (500 MHz, [D_6]DMSO): δ = 9.32 (s, 1H, NH), 7.75–7.63 (m, 4H, Ar), 7.35–7.26 (m, 4H, Ar), 7.03 (t, *J* = 7.3 Hz, 1H, Ar), 6.98 (s, 1H, thiophene), 6.69 (s, 2H, NH_2) ppm. ^{13}C NMR (126 MHz, [D_6]DMSO): δ = 163.2, 162.4 (d, *J* = 246.7 Hz), 155.1, 143.4, 139.3, 129.7 (d, *J* = 2.9 Hz), 128.4, 127.6 (d, *J* = 8.2 Hz), 123.0, 120.7, 117.1, 116.3 (d, *J* = 21.9 Hz), 100.2 ppm. IR (ATR): $\tilde{\nu}$ = 3473, 3363, 3252, 3202, 1615, 1581, 1524, 1462, 1435, 1320, 1270, 1229, 1158, 1096, 1074, 1012, 911, 837, 821, 754, 694, 611, 576, 563, 541, 511, 495, 440 cm^{-1}. MS (ESI): *m/z* = 313.1 $[M + H]^+$. Elemental analysis calcd. for $C_{17}H_{13}FN_2OS$: C, 65.37, H 4.19, N, 8.97, found: C 65.40, H 4.07, N 8.90.

3-Amino-*N*-phenyl-5-[3-(trifluoromethyl)phenyl]thiophene-2-carboxamide (6Be): Yield 0.944 g, 87 %, cream-colored crystals, m.p. 167–168 °C. ^1H NMR (500 MHz, [D_6]DMSO): δ = 9.38 (s, 1H, NH), 7.96 (d, *J* = 7.6 Hz, 1H, Ar), 7.91 (s, 1H, Ar), 7.76 (d, *J* = 7.6 Hz, 1H, Ar), 7.72 (d, *J* = 7.7 Hz, 1H, Ar), 7.71–7.66 (m, 2H, Ar), 7.30 (t, *J* = 7.9 Hz, 2H, Ar), 7.18 (s, 1H, thiophene), 7.04 (t, *J* = 7.3 Hz, 1H, Ar), 6.71 (s, 2H, NH_2) ppm. ^{13}C NMR (126 MHz, [D_6]DMSO): δ = 163.1, 155.1, 142.3, 139.3, 134.1, 130.7, 130.1 (q, *J* = 32.5 Hz), 129.4, 128.5, 125.3 (q, *J* = 3.4 Hz), 123.1, 121.8 (q, *J* = 278.5 Hz), 121.7 (q, *J* = 3.6 Hz), 120.7, 118.3, 101.0 ppm. IR (ATR): $\tilde{\nu}$ = 3473, 1616, 1575, 1464, 1436, 1319, 1124, 803, 749, 725, 693, 676, 510, 428, 415 cm^{-1}. MS (ESI): *m/z* = 363.1 $[M + H]^+$. Elemental analysis calcd. for $C_{18}H_{13}F_3N_2OS$: C 59.66, H 3.62, N 7.73, found: C 59.49, H 3.54, N 7.68.

5-(3-Acetylphenyl)-3-amino-*N*-phenylthiophene-2-carboxamide (6Bf): Yield 0.786 g, 78 %, light yellow crystals, m.p. 187–188 °C. ^1H NMR (500 MHz, [D_6]DMSO): δ = 9.37 (s, 1H, NH), 8.16 (s, 1H, 2H-C_6H_4), 7.98 (d, *J* = 7.7 Hz, 1H, Ar), 7.92 (d, *J* = 8.4 Hz, 1H, Ar), 7.69 (d, *J* = 7.7 Hz, 2H, Ar), 7.63 (t, *J* = 7.7 Hz, 1H, Ar), 7.30 (t, *J* = 7.9 Hz, 2H, Ar), 7.14 (s, 1H, thiophene), 7.04 (t, *J* = 7.3 Hz, 1H, Ar), 6.72 (s, 2H, NH_2), 2.64 (s, 3H, CH_3) ppm. ^{13}C NMR (126 MHz, [D_6]DMSO): δ = 197.6, 163.1, 155.2, 143.3, 139.3, 137.6, 133.4, 129.9, 129.7, 128.7, 128.5, 124.6, 123.1, 120.7, 117.6, 100.5, 26.9 ppm. IR (ATR): $\tilde{\nu}$ = 3433, 3400, 3311, 1671, 1634, 1590, 1551, 1515, 1463, 1428, 1365, 1313, 1269, 1235, 1071, 948, 900, 830, 786, 748, 717, 690, 677, 592, 492, 437 cm^{-1}. MS (ESI): *m/z* = 337.1 $[M + H]^+$. Elemental analysis calcd. for $C_{19}H_{16}N_2O_2S$: C 67.84, H 4.79, N 8.33, found: C 67.73, H 4.70, N 8.25.

Methyl 3-[4-amino-5-(phenylcarbamoyl)thiophen-2-yl]benzoate (6Bg): Yield 0.792 g, 75 %, light yellow crystals, m.p. 152–153 °C. ^1H NMR (500 MHz, [D_6]DMSO): δ = 9.37 (s, 1H, NH), 8.17 (s, 1H, 2H-C_6H_4), 8.00–7.91 (m, 2H, Ar), 7.69 (d, *J* = 7.2 Hz, 2H, Ar), 7.65–7.56 (m, 1H, Ar), 7.37–7.24 (m, 2H, Ar), 7.13 (s, 1H, thiophene), 7.07–6.99 (m, 1H, Ar), 6.72 (s, 2H, NH_2), 3.90 (s, 3H, CH_3) ppm. ^{13}C NMR (126 MHz, [D_6]DMSO): δ = 165.8, 163.1, 155.2, 142.9, 139.3, 133.5, 130.6, 130.0, 129.9, 129.3, 128.5, 125.7, 123.1, 120.7, 117.6, 100.5, 52.5 ppm. IR (ATR): $\tilde{\nu}$ = 3413, 3351, 3314, 1718, 1634, 1576, 1520, 1436, 1321, 1301, 1277, 1229, 1108, 1082, 1003, 959, 904, 819, 752, 688, 642, 548, 508, 469, 409 cm^{-1}. MS (ESI): *m/z* = 353.1 $[M + H]^+$. Elemental analysis calcd. for $C_{19}H_{16}N_2O_3S$: C 64.76, H 4.58, N 7.95, found: C 64.61, H 4.49, N 7.90.

3-Amino-*N*-(2-fluorophenyl)-5-phenylthiophene-2-carboxamide (6Ca): Yield 0.692 g, 74 %, light yellow crystals, m.p. 148–149 °C. ^1H NMR (500 MHz, [D_6]DMSO): δ = 9.17 (s, 1H, NH), 7.65 (d, *J* = 7.3 Hz, 2H, Ar), 7.54 (t, *J* = 7.5 Hz, 1H, Ar), 7.47 (t, *J* = 7.5 Hz, 2H, Ar), 7.40 (t, *J* = 7.2 Hz, 1H, Ar), 7.28–7.13 (m, 3H, Ar), 7.02 (s, 1H, thiophene), 6.64 (s, 2H, NH_2) ppm. ^{13}C NMR (126 MHz, [D_6]DMSO): δ = 163.0, 156.0 (d, *J* = 246.6 Hz), 154.9, 144.9, 133.0, 129.4, 129.0, 127.1, 126.4 (d, *J* = 7.8 Hz), 126.1 (d, *J* = 12.0 Hz), 125.5, 124.2 (d, *J* = 3.5 Hz), 117.0, 115.7 (d, *J* = 20.2 Hz), 100.2 ppm. IR (ATR): $\tilde{\nu}$ = 3424, 3313, 1646, 1617, 1595, 1520, 1459, 1446, 1327, 1255, 1186, 1117, 1074, 1032, 936, 826, 766, 745, 726, 691, 534, 499, 457 cm^{-1}. MS (ESI): *m/z* = 313.1 $[M + H]^+$. Elemental analysis calcd. for $C_{17}H_{13}FN_2OS$: C 65.37, H 4.19, N 8.97, found: C 65.39, H 4.11, N, 8.88,

3-Amino-*N*-(2-fluorophenyl)-5-(3-methylphenyl)thiophene-2-carboxamide (6Cb): Yield 0.596 g, 61 %, yellow crystals, m.p. 131–132 °C. ^1H NMR (400 MHz, [D_6]DMSO): δ = 9.14 (s, 1H, NH), 7.60–7.53 (m, 1H, Ar), 7.49–7.42 (m, 2H, Ar), 7.35 (t, *J* = 7.6 Hz, 1H, Ar), 7.29–7.15 (m, 4H, Ar), 7.02 (s, 1H, thiophene), 6.64 (s, 2H, NH_2), 2.37 (s, 3H, CH_3) ppm. ^{13}C NMR (101 MHz, [D_6]DMSO): δ = 162.9 (o), 155.8 (d, *J* = 246.2 Hz, o), 154.9 (o), 145.0 (o), 138.5 (o), 132.9 (o), 129.6 (+), 129.1 (+), 126.9 (d, *J* = 1.6 Hz, +), 126.2 (d, *J* = 7.8 Hz, +), 126.0 (d, *J* = 14.3 Hz, o), 125.9 (+), 124.1 (d, *J* = 3.4 Hz, +), 122.6 (+), 116.7 (+), 115.6 (d, *J* = 20.0 Hz, +), 100.0 (o), 20.9 (+) ppm. IR (ATR): $\tilde{\nu}$ = 3383, 3030, 1646, 1521, 1496, 1454, 1426, 1388, 1364, 1333, 1116, 996, 762, 725, 692, 623, 553, 506, 486, 449 cm^{-1}. MS (ESI): *m/z* = 327.1 $[M + H]^+$. Elemental analysis calcd. for $C_{18}H_{15}FN_2OS$: C 66.24, H 4.63, N 8.58, found: C 66.17, H 4.57, N 8.44.

3-Amino-*N*-(2-fluorophenyl)-5-(4-methylphenyl)thiophene-2-carboxamide (6Cc): Yield 0.655 g, 67 %, light yellow crystals, m.p. 191–192 °C. ^1H NMR (500 MHz, [D_6]DMSO): δ = 9.11 (s, 1H, NH), 7.53 (d, *J* = 8.1 Hz, 3H, Ar), 7.27 (d, *J* = 7.9 Hz, 2H, Ar), 7.25–7.12 (m, 3H, Ar), 6.97 (s, 1H, thiophene), 6.62 (s, 2H, NH_2), 2.33 (s, 3H, CH_3) ppm. ^{13}C NMR (126 MHz, [D_6]DMSO): δ = 163.0, 155.9 (d, *J* = 246.3 Hz), 155.0, 145.1, 138.7, 130.3, 129.9, 127.0, 126.3 (d, *J* = 7.5 Hz), 126.2 (d, *J* = 12.2 Hz), 125.4, 124.2 (d, *J* = 3.1 Hz), 116.4, 115.7 (d, *J* = 19.9 Hz), 99.7, 20.9 ppm. IR (ATR): $\tilde{\nu}$ = 3419, 3312, 3024, 1646, 1616, 1592, 1515, 1445, 1321, 1267, 1185, 1108, 1032, 932, 840, 809, 775, 745, 718, 637, 531, 501, 449 cm^{-1}. MS (ESI): *m/z* =

327.1 [M + H]$^+$. Elemental analysis calcd. for $C_{18}H_{15}FN_2OS$: C 66.24, H 4.63, N 8.58, found: C 66.11, H 4.56, N 8.48.

3-Amino-*N*-(2-fluorophenyl)-5-(4-fluorophenyl)thiophene-2-carboxamide (6Cd): Yield 0.821 g, 83 %, light yellow crystals, m.p. 174–175 °C. ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 9.16 (s, 1H, NH), 7.69 (dd, J_{HH} = 8.6, J_{HF} = 5.3 Hz, 2H, 4-FC$_6$H$_4$), 7.59–7.49 (m, 1H, 2-FC$_6$H$_4$), 7.31 (t, J = 8.8 Hz, 2H, 4-FC$_6$H$_4$), 7.26–7.14 (m, 3H, 2-FC$_6$H$_4$), 6.98 (s, 1H, thiophene), 6.64 (s, 2H, NH$_2$) ppm. ^{13}C NMR (126 MHz, [D$_6$]DMSO): δ = 163.0, 162.4 (d, J = 246.7 Hz), 156.0 (d, J = 245.1 Hz), 155.0, 143.7, 129.7 (d, J = 3.1 Hz), 127.7 (d, J = 8.4 Hz), 127.1, 126.4 (d, J = 7.8 Hz), 126.1 (d, J = 11.8 Hz), 117.1, 116.3 (d, J = 21.9 Hz), 115.7 (d, J = 20.0 Hz), 100.1 ppm. IR (ATR): $\tilde{\nu}$ = 3487, 3370, 3236, 3212, 1626, 1583, 1511, 1450, 1315, 1274, 1257, 1193, 1156, 1097, 1032, 1011, 934, 836, 818, 749, 714, 630, 563, 533, 488, 461, 449, 434 cm^{-1}. MS (ESI): m/z = 331.1 [M + H]$^+$. Elemental analysis calcd. for $C_{17}H_{12}F_2N_2OS$: C 61.81, H 3.66, N 8.48, found: C 61.70, H 3.60, N 8.39.

3-Amino-*N*-(2-fluorophenyl)-5-[3-(trifluoromethyl)phenyl]thiophene-2-carboxamide (6Ce): Yield 0.912 g, 80 %, yellow crystals, m.p. 167–168 °C. ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 9.25 (s, 1H, NH), 7.95 (d, J = 7.6 Hz, 1H, Ar), 7.92 (s, 1H, Ar), 7.80–7.69 (m, 2H, Ar), 7.57–7.51 (m, 1H, Ar), 7.29–7.15 (m, 4H, Ar, thiophene), 6.66 (s, 2H, NH$_2$) ppm. ^{13}C NMR (126 MHz, [D$_6$]DMSO): δ = 162.9, 156.0 (d, J = 246.2 Hz), 154.9, 142.6, 134.1, 130.7, 130.1 (q, J = 31.7 Hz), 129.5, 127.2, 126.5 (d, J = 8.0 Hz), 126.0 (d, J = 12.1 Hz), 125.4 (q, J = 3.5 Hz), 124.2 (d, J = 3.5 Hz), 124.0 (q, J = 272.7 Hz), 121.7 (q, J = 3.5 Hz), 118.3, 115.7 (d, J = 20.0 Hz), 100.9 ppm. IR (ATR): $\tilde{\nu}$ = 3477, 3421, 3403, 3351, 1647, 1580, 1513, 1449, 1316, 1268, 1250, 1163, 1118, 1070, 1000, 971, 934, 886, 822, 803, 773, 751, 723, 692, 676, 640, 533, 490, 438 cm^{-1}. MS (ESI): m/z = 381.1 [M + H]$^+$. Elemental analysis calcd. for $C_{18}H_{12}F_4N_2OS$: C 56.84, H 3.18, N 7.36, found: C 56.77, H 3.10, N 7.39.

5-(3-Acetylphenyl)-3-amino-*N*-(2-fluorophenyl)thiophene-2-carboxamide (6Cf): Yield 0.902 g, 85 %, yellow crystals, m.p. 174–175 °C. ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 9.23 (s, 1H, NH), 8.15 (s, 1H, Ar), 7.98 (d, J = 7.7 Hz, 1H, Ar), 7.91 (d, J = 7.6 Hz, 1H, Ar), 7.63 (t, J = 7.7 Hz, 1H, Ar), 7.58–7.50 (m, 1H, Ar), 7.31–7.16 (m, 3H, Ar), 7.14 (s, 1H, thiophene), 6.66 (s, 2H, NH$_2$), 2.64 (s, 3H, CH$_3$) ppm. ^{13}C NMR (126 MHz, [D$_6$]DMSO): δ = 197.6, 162.9, 156.0 (d, J = 246.6 Hz), 155.0, 143.7, 137.6, 133.4, 129.9 (d, J = 7.5 Hz), 128.7, 127.2, 126.4 (d, J = 7.1 Hz), 126.0 (d, J = 12.1 Hz), 124.7, 124.2, 124.2, 117.7, 115.7 (d, J = 20.0 Hz), 100.5, 26.9 ppm. IR (ATR): $\tilde{\nu}$ = 3441, 3418, 3407, 3306, 1674, 1640, 1593, 1547, 1512, 1447, 1320, 1268, 1255, 1217, 1189, 1105, 1077, 1023, 904, 828, 786, 745, 716, 679, 645, 591, 488, 448 cm^{-1}. MS (ESI): m/z = 355.1 [M + H]$^+$. Elemental analysis calcd. for $C_{19}H_{15}FN_2O_2S$: C 64.39, H 4.27, N 7.90, found: C 64.41, H 4.19, N 7.82.

Methyl 3-{4-amino-5-[(2-fluorophenyl)carbamoyl]thiophen-2-yl}benzoate (6Cg): Yield 0.832 g, 75 %, light yellow crystals, m.p. 153–154 °C. ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 9.08 (s, 1H, NH), 8.22–8.09 (m, 1H, Ar), 8.01–7.87 (m, 2H, Ar), 7.69–7.54 (m, 2H, Ar), 7.29–7.15 (m, 3H, Ar), 7.13 (s, 1H, thiophene), 6.58 (s, 2H, NH$_2$), 3.91 (s, 3H, CH$_3$) ppm. ^{13}C NMR (126 MHz, [D$_6$]DMSO): δ = 165.8, 162.9, 156.0 (d, J = 246.7 Hz), 155.0, 143.3, 133.4, 130.6, 130.03, 129.97, 129.3, 127.2, 126.5 (d, J = 7.8 Hz), 126.0 (d, J = 11.3 Hz), 125.7, 124.2 (d, J = 3.1 Hz), 117.7, 115.7 (d, J = 20.2 Hz), 100.5, 52.5 ppm. IR (ATR): $\tilde{\nu}$ = 3456, 3419, 3344, 2948, 1709, 1641, 1584, 1518, 1449, 1324, 1301, 1273, 1184, 1104, 1081, 1034, 834, 812, 753, 731, 681, 644, 512, 448 cm^{-1}. MS (ESI): m/z = 371.1 [M + H]$^+$. Elemental analysis calcd. for $C_{19}H_{15}FN_2O_3S$: C 61.61, H 4.08, N 7.56, found: C 61.52, H 4.01, N 7.44.

3-Amino-*N*-benzyl-5-phenylthiophene-2-carboxamide (6Da): Yield 0.600 g, 65 %, white crystals, m.p. 135–136 °C. ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 8.11 (s, 1H, NH), 7.59 (d, J = 6.9 Hz, 2H, Ar), 7.44 (t, J = 7.0 Hz, 2H, Ar), 7.40–7.17 (m, 6H, Ar), 6.97 (s, 1H, thiophene), 6.50 (s, 2H, NH$_2$), 4.37 (d, J = 5.2 Hz, 2H, CH$_2$) ppm. ^{13}C NMR (126 MHz, [D$_6$]DMSO): δ = 164.4, 153.9, 143.5, 140.4, 133.2, 129.3, 128.7, 128.2, 127.2, 126.6, 125.4, 117.0, 100.5, 42.1 ppm. IR (ATR): $\tilde{\nu}$ = 3405, 3282, 2923, 1619, 1585, 1528, 1436, 1364, 1318, 1296, 1242, 1171, 1092, 970, 837, 822, 787, 756, 743, 701, 685, 613, 560, 515, 473, 446 cm^{-1}. MS (ESI): m/z = 309.1 [M + H]$^+$. Elemental analysis calcd. for $C_{18}H_{16}N_2OS$: C 70.10, H 5.23, N 9.08, found: C 69.7, H 5.15, N 8.98.

3-Amino-*N*-benzyl-5-(3-methylphenyl)thiophene-2-carboxamide (6Db): Yield 0.685 g, 71 %, light yellow crystals, m.p. 150–151 °C. ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 8.11 (s, 1H, NH), 7.55 (t, J = 6.9 Hz, 1H, Ar), 7.49–7.40 (m, 2H, Ar), 7.34 (t, J = 7.6 Hz, 1H, Ar), 7.26–7.16 (m, 5H, Ar), 7.00 (s, 1H, thiophene), 6.62 (s, 2H, NH$_2$), 4.37 (d, J = 5.6 Hz, 2H, CH$_2$), 2.36 (s, 3H, CH$_3$) ppm. ^{13}C NMR (126 MHz, [D$_6$]DMSO): δ = 163.0, 154.9, 145.5, 138.6, 133.0, 129.7, 129.2, 127.0, 126.3, 126.1, 124.2, 122.7, 116.8, 115.7, 100.1, 42.1, 21.0 ppm. IR (ATR): $\tilde{\nu}$ = 3533, 3419, 3309, 1639, 1615, 1592, 1516, 1445, 1323, 1251, 1183, 1110, 1080, 1031, 930, 826, 786, 745, 708, 689, 648, 602, 525, 478, 448, 427 cm^{-1}. MS (ESI): m/z = 323.1 [M + H]$^+$. Elemental analysis calcd. for $C_{19}H_{18}N_2OS$: C 70.78, H 5.63, N 8.69, found: C 70.80, H 5.55, N 8.73.

3-Amino-*N*-benzyl-5-(4-methylphenyl)thiophene-2-carboxamide (6Dc): Yield 0.830 g, 86 %, light yellow crystals, m.p. 154–155 °C. ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 8.06[†] (t, J = 5.2 Hz, 1H, NH), 7.48 (d, J = 7.5 Hz, 2H, Ar), 7.34–7.28 (br.s, 4H, Ar), 7.27–7.16 (m, 3H, Ar), 6.91 (s, 1H, thiophene), 6.48 (s, 2H, NH$_2$), 4.37 (d, J = 5.6 Hz, 2H, CH$_2$), 2.32 (s, 3H, CH$_3$) ppm. ^{13}C NMR (126 MHz, [D$_6$]DMSO): δ = 164.4, 153.9, 143.7, 140.4, 138.3, 130.5, 129.8, 128.2, 127.2, 126.6, 125.3, 116.5, 100.1, 42.1, 20.9 ppm. IR (ATR): $\tilde{\nu}$ = 3473, 3295, 3028, 2913, 1606, 1589, 1520, 1450, 1310, 1240, 1155, 1097, 1028, 974, 872, 809, 715, 693, 512, 445 cm^{-1}. MS (ESI): m/z = 323.1 [M + H]$^+$. Elemental analysis calcd. for $C_{19}H_{18}N_2OS$: C 70.78, H 5.63, N 8.69, found: C 70.66, H 5.56, N 8.58.

[†] Mutual splitting of signals of NH and CH$_2$ groups is present in the ^{1}H NMR spectra of **6Dc**–**6Dg**.

3-Amino-*N*-benzyl-5-(4-fluorophenyl)thiophene-2-carboxamide (6Dd): Yield 0.743 g, 76 %, cream-colored crystals, m.p. 171–172 °C. ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 8.10[†] (t, J = 5.7 Hz, 1H, NH), 7.63 (dd, J = 8.2, 5.2 Hz, 2H, C$_6$H$_4$), 7.37–7.08 (m, 7H, Ar), 6.92 (s, 1H, thiophene), 6.50 (s, 2H, NH$_2$), 4.37 (d, J = 5.7 Hz, 2H, CH$_2$) ppm. ^{13}C NMR (126 MHz, [D$_6$]DMSO): δ = 164.3, 162.2 (d, J = 243.5 Hz), 153.9, 142.3, 140.4, 129.9 (d, J = 3.6 Hz), 128.2, 127.5 (d, J = 8.4 Hz), 127.2, 126.6, 117.2, 116.2 (d, J = 22.1 Hz), 95.5, 42.1 ppm. IR (ATR): $\tilde{\nu}$ = 3454, 3340, 3281, 1611, 1588, 1525, 1450, 1363, 1317, 1230, 1160, 1095, 1029, 1013, 977, 872, 841, 825, 716, 695, 563, 495, 448 cm^{-1}. MS (ESI): m/z = 327.1 [M + H]$^+$. Elemental analysis calcd. for $C_{18}H_{15}FN_2OS$: C 66.24, H 4.63, N 8.58, found: C 66.17, H 4.55, N 8.43.

3-Amino-*N*-benzyl-5-[3-(trifluoromethyl)phenyl]thiophene-2-carboxamide (6De): Yield 1.003 g, 89 %, light yellow crystals, m.p. 148–149 °C. ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 8.19[†] (t, J = 5.9 Hz, 1H, NH), 7.90 (d, J = 7.7 Hz, 1H, Ar), 7.85 (s, 1H, Ar), 7.75–7.65 (m, 2H, Ar), 7.33–7.29 (br.s, 4H, Ar), 7.26–7.19 (m, 1H, Ar), 7.13 (s, 1H, thiophene), 6.52 (s, 2H, NH$_2$), 4.38 (d, J = 5.9 Hz, 2H, CH$_2$) ppm. ^{13}C NMR (126 MHz, [D$_6$]DMSO): δ = 164.2, 153.8, 141.3, 140.3, 134.2, 130.6, 130.0 (q, J = 31.2 Hz), 129.3, 128.2, 127.3, 126.6, 125.1 (q, J = 3.8 Hz), 121.9 (q, J = 276.7 Hz), 121.6 (q, J = 3.8 Hz), 118.4, 101.4, 42.2 ppm. IR (ATR): $\tilde{\nu}$ = 3410, 3298, 2981, 1634, 1583, 1549, 1524,

1443, 1422, 1327, 1315, 1277, 1232, 1163, 1117, 1072, 1027, 980, 963, 894, 829, 800, 738, 725, 692, 675, 607, 518, 447 cm^{-1}. MS (ESI): m/z = 377.1 $[M + H]^+$. Elemental analysis calcd. for $C_{19}H_{15}F_3N_2OS$: C 60.63, H 4.02, N 7.44, found: C 60.50, H 3.94, N 7.32.

5-(3-Acetylphenyl)-3-amino-*N*-benzylthiophene-2-carboxamide (6Df): Yield 0.840 g, 80 %, light yellow crystals, m.p. 186–187 °C. ^1H NMR (500 MHz, [D$_6$]DMSO): δ = 8.18^t (t, J = 5.9 Hz, 1H, NH), 8.10 (s, 1H, C_6H_4), 7.95 (d, J = 7.7 Hz, 1H, Ar), 7.86 (d, J = 7.8 Hz, 1H, Ar), 7.60 (t, J = 7.8 Hz, 1H, Ar), 7.36–7.26 (m, 4H, Ar), 7.25–7.19 (m, 1H, Ar), 7.09 (s, 1H, thiophene), 6.52 (s, 2H, NH_2), 4.38 (d, J = 5.9 Hz, 2H, CH_2), 2.63 (s, 3H, CH_3) ppm. ^{13}C NMR (126 MHz, [D$_6$]DMSO): δ = 197.6, 164.2, 153.9, 142.3, 140.3, 137.6, 133.6, 129.8, 129.7, 128.4, 128.2, 127.3, 126.6, 124.5, 117.8, 101.0, 42.17, 26.9 ppm. IR (ATR): $\tilde{\nu}$ = 3450, 3329, 3266, 1681, 1593, 1531, 1428, 1359, 1315, 1271, 1220, 1175, 1105, 1081, 1029, 981, 948, 912, 872, 838, 792, 762, 725, 695, 684, 639, 589, 514, 461, 432 cm^{-1}. MS (ESI): m/z = 351.1 $[M + H]^+$. Elemental analysis calcd. for $C_{20}H_{18}N_2O_2S$: C 68.55, H 5.18, N 7.99, found: C 68.48, H 5.10, N 7.82.

Methyl 3-[4-amino-5-(benzylcarbamoyl)thiophen-2-yl]benzoate (6Dg): Yield 0.878 g, 80 %, light yellow crystals, m.p. 141–142 °C. ^1H NMR (500 MHz, [D$_6$]DMSO): δ = 8.20^t (t, J = 6.0 Hz, 1H, NH), 8.12 (t, J = 1.6 Hz, 1H, Ar), 7.98–7.87 (m, 2H, Ar), 7.60 (t, J = 7.8 Hz, 1H, Ar), 7.35–7.28 (m, 4H, Ar), 7.27–7.18 (m, 1H, Ar), 7.08 (s, 1H, thiophene), 6.53 (s, 2H, NH_2), 4.38 (d, J = 6.0 Hz, 2H, CH_2), 3.88 (s, 3H, CH_3) ppm. ^{13}C NMR (126 MHz, [D$_6$]DMSO): δ = 166.1, 164.5, 154.2, 142.2, 140.6, 133.9, 130.9, 130.3, 130.1, 129.4, 128.5, 127.6, 126.9, 125.9, 118.1, 101.3, 52.8, 42.5 ppm. IR (ATR): $\tilde{\nu}$ = 3452, 3340, 3262, 3025, 1719, 1596, 1580, 1527, 1427, 1312, 1291, 1277, 1229, 1174, 1114, 1106, 1021, 1010, 983, 911, 873, 834, 752, 722, 695, 682, 638, 611, 516, 461, 436 cm^{-1}. MS (ESI): m/z = 367.1 $[M + H]^+$. Elemental analysis calcd. for $C_{20}H_{18}N_2O_3S$: C 65.56, H 4.95, N 7.64, found: C 65.42, H 4.88, N 7.50.

2-(Morpholin-4-ylcarbonyl)-5-phenylthiophen-3-amine (6Ea): Yield 0.414 g, 48 %, cream-colored crystals, m.p. 106–107 °C. ^1H NMR (500 MHz, [D$_6$]DMSO): δ = 7.59 (d, J = 7.1 Hz, 2H, C_6H_5), 7.42 (t, J = 7.2 Hz, 2H, C_6H_5), 7.38–7.27 (m, 1H, C_6H_5), 6.95 (s, 1H, thiophene), 6.12 (s, 2H, NH_2), 3.65–3.61 (m, 4H, CH_2), 3.61–3.56 (m, 4H, CH_2) ppm. ^{13}C NMR (126 MHz, [D$_6$]DMSO): δ = 165.3, 152.4, 144.2, 133.0, 129.2, 128.7, 125.4, 116.9, 101.2, 66.3, 45.6 ppm. IR (ATR): $\tilde{\nu}$ = 3419, 3308, 2959, 2892, 2843, 1575, 1533, 1456, 1444, 1392, 1303, 1255, 1214, 1149, 1112, 1073, 1014, 934, 911, 879, 849, 824, 756, 724, 687, 584, 515, 451 cm^{-1}. MS (ESI): m/z = 289.1 $[M + H]^+$. Elemental analysis calcd. for $C_{15}H_{16}N_2O_2S$: C 62.48, H 5.59, N 9.71, found: C 62.37, H 5.47, N 9.66.

5-(3-Methylphenyl)-2-(morpholin-4-ylcarbonyl)thiophen-3-amine (6Eb): Yield 0.724 g, 80 %, light yellow crystals, m.p. 180–181 °C. ^1H NMR (500 MHz, [D$_6$]DMSO): δ = 7.45–7.34 (m, 2H, C_6H_4), 7.30 (t, J = 7.4 Hz, 1H, C_6H_4), 7.17 (d, J = 7.0 Hz, 1H, C_6H_4), 6.93 (s, 1H, thiophene), 6.14 (s, 2H, NH_2), 3.62 (s, 4H, CH_2), 3.59 (s, 4H, CH_2), 2.33 (s, 3H, CH_3) ppm. ^{13}C NMR (126 MHz, [D$_6$]DMSO): δ = 165.4, 152.7, 144.4, 138.5, 132.9, 129.4, 129.1, 125.9, 122.6, 116.8, 100.9, 66.3, 45.6, 21.0 ppm. IR (ATR): $\tilde{\nu}$ = 3441, 3299, 2966, 2913, 2891, 2853, 1579, 1537, 1493, 1466, 1456, 1426, 1378, 1299, 1258, 1157, 1112, 1016, 938, 885, 839, 780, 764, 719, 692, 579, 531, 483, 455, 428 cm^{-1}. MS (ESI): m/z = 303.1 $[M + H]^+$. Elemental analysis calcd. for $C_{16}H_{18}N_2O_2S$: C 63.55, H 6.00, N 9.26, found: C 63.43, H 5.90, N 9.18.

5-(4-Methylphenyl)-2-(morpholin-4-ylcarbonyl)thiophen-3-amine (6Ec): Yield 0.724 g, 80 %, white crystals, m.p. 174–175 °C. ^1H NMR (500 MHz, [D$_6$]DMSO): δ = 7.47 (d, J = 7.4 Hz, 2H, C_6H_4), 7.22 (d, J = 7.2 Hz, 2H, C_6H_4), 6.90 (s, 1H, thiophene), 6.13 (s, 2H, NH_2), 3.62 (s, 4H, CH_2), 3.59 (s, 4H, CH_2), 2.31 (s, 3H, CH_3) ppm. ^{13}C NMR (126 MHz, [D$_6$]DMSO): δ = 165.4, 152.7, 144.4, 138.3, 130.2, 129.8, 125.3, 116.3, 100.5, 66.3, 45.6, 20.8 ppm. IR (ATR): $\tilde{\nu}$ = 3476, 3366, 2980, 2913, 2886, 2849, 1583, 1539, 1509, 1462, 1449, 1428, 1386, 1360, 1304, 1269, 1253, 1215, 1147, 1108, 1007, 932, 877, 836, 805, 757, 717, 661, 578, 514, 473, 447 cm^{-1}. MS (ESI): m/z = 303.1 $[M + H]^+$. Elemental analysis calcd. for $C_{16}H_{18}N_2O_2S$: C 63.55, H 6.00, N 9.26, found: C 63.46, H 5.92, N 9.16.

5-(4-Fluorophenyl)-2-(morpholin-4-ylcarbonyl)thiophen-3-amine (6Ed): Yield 0.771 g, 84 %, white crystals, m.p. 159–160 °C. ^1H NMR (500 MHz, [D$_6$]DMSO): δ = 7.63 (s, 2H, C_6H_4), 7.25 (t, J = 7.2 Hz, 2H, C_6H_4), 6.90 (s, 1H, thiophene), 6.12 (s, 2H, NH_2), 3.62 (s, 4H, CH_2), 3.58 (s, 4H, CH_2) ppm. ^{13}C NMR (126 MHz, [D$_6$]DMSO): δ = 165.2, 162.2 (d, J = 246.2 Hz), 152.4, 143.1, 129.6, 127.6 (d, J = 8.5 Hz), 117.0, 116.2 (d, J = 21.8 Hz), 101.2, 66.3, 45.6 ppm. IR (ATR): $\tilde{\nu}$ = 3439, 3377, 3324, 2985, 2851, 1575, 1533, 1505, 1451, 1392, 1305, 1256, 1232, 1162, 1110, 1071, 1009, 933, 876, 828, 805, 754, 719, 579, 513, 488, 478, 454 cm^{-1}. MS (ESI): m/z = 307.1 $[M + H]^+$. Elemental analysis calcd. for $C_{15}H_{15}FN_2O_2S$: C 58.81, H 4.94, N 9.14, found: C 58.74, H 4.87, N 9.06.

2-(Morpholin-4-ylcarbonyl)-5-[3-(trifluoromethyl)phenyl]thiophen-3-amine (6Ee): Yield 0.822 g, 77 %, light yellow crystals, m.p. 115–116 °C. ^1H NMR (500 MHz, [D$_6$]DMSO): δ = 7.89 (d, J = 7.2 Hz, 1H, C_6H_4), 7.85 (s, 1H, C_6H_4), 7.75–7.60 (m, 2H, C_6H_4), 7.10 (s, 1H, thiophene), 6.11 (s, 2H, NH_2), 3.63 (s, 4H, CH_2), 3.59 (s, 4H, CH_2) ppm. ^{13}C NMR (126 MHz, [D$_6$]DMSO): δ = 165.0, 152.1, 142.0, 134.0, 130.5, 130.0 (q, J = 33.6 Hz), 129.4, 125.0 (q, J = 3.4 Hz), 124.0 (q, J = 272.2 Hz), 121.5 (q, J = 4.2 Hz), 118.3, 102.3, 66.3, 45.6 ppm. IR (ATR): $\tilde{\nu}$ = 3422, 3327, 2961, 2844, 1578, 1537, 1457, 1436, 1418, 1399, 1330, 1305, 1257, 1229, 1163, 1114, 1073, 1015, 964, 880, 828, 801, 749, 725, 692, 665, 586, 516, 467, 436 cm^{-1}. MS (ESI): m/z = 357.1 $[M + H]^+$. Elemental analysis calcd. for $C_{16}H_{15}F_3N_2O_2S$: C 53.93, H 4.24, N 7.86, found: C 53.85, H 4.18, N 7.75.

1-{3-[4-Amino-5-(morpholin-4-ylcarbonyl)thiophen-2-yl]phenyl}ethanone (6Ef): Yield 0.792 g, 80 %, light yellow crystals, m.p. 132–133 °C. ^1H NMR (500 MHz, [D$_6$]DMSO): δ = 8.06 (s, 1H, 2H-C_6H_4), 7.94 (d, J = 7.3 Hz, 1H, C_6H_4), 7.84 (d, J = 7.0 Hz, 1H, C_6H_4), 7.60–7.55 (m, 1H, 5H-C_6H_4), 7.06 (s, 1H, thiophene), 6.13 (s, 2H, NH_2), 3.63 (s, 4H, CH_2), 3.60 (s, 4H, CH_2), 2.62 (s, 3H, CH_3) ppm. ^{13}C NMR (126 MHz, [D$_6$]DMSO): δ = 197.7, 165.1, 152.3, 143.0, 137.6, 133.4, 129.8, 129.8, 128.4, 124.5, 117.7, 101.8, 66.3, 45.6, 26.9 ppm. IR (ATR): $\tilde{\nu}$ = 3449, 3320, 2993, 2970, 2946, 2856, 1674, 1590, 1542, 1491, 1464, 1428, 1394, 1348, 1302, 1275, 1259, 1220, 1180, 1163, 1105, 1062, 1006, 946, 899, 879, 828, 788, 748, 717, 677, 606, 593, 519, 455 cm^{-1}. MS (ESI): m/z = 331.1 $[M + H]^+$. Elemental analysis calcd. for $C_{17}H_{18}N_2O_3S$: C 61.80, H 5.49, N 8.48, found: C 61.69, H 5.40, N 8.45.

Methyl 3-[4-amino-5-(morpholin-4-ylcarbonyl)thiophen-2-yl]-benzoate (6Eg): Yield 0.830 g, 80 %, white crystals, m.p. 140–141 °C. ^1H NMR (500 MHz, [D$_6$]DMSO): δ = 8.08 (s, 1H, 2H-C_6H_4), 7.92 (d, J = 7.5 Hz, 1H, C_6H_4), 7.87 (d, J = 7.1 Hz, 1H, C_6H_4), 7.61–7.56 (m, 1H, C_6H_4), 7.05 (s, 1H, thiophene), 6.14 (s, 2H, NH_2), 3.88 (s, 3H, CH_3), 3.63 (s, 4H, CH_2), 3.60 (s, 4H, CH_2) ppm. ^{13}C NMR (126 MHz, [D$_6$]DMSO): δ = 165.8, 165.1, 152.3, 142.6, 133.4, 130.6, 129.9 (overlapped), 129.1, 125.5, 117.7, 101.8, 66.3, 52.5, 45.6 ppm. IR (ATR): $\tilde{\nu}$ = 3423, 3334, 2956, 2910, 2891, 2852, 1716, 1598, 1547, 1489, 1454, 1429, 1398, 1356, 1295, 1266, 1254, 1220, 1157, 1110, 1080, 1010, 985, 948, 906, 878, 838, 812, 753, 741, 688, 583, 474 cm^{-1}. MS (ESI): m/z = 347.1 $[M + H]^+$. Elemental analysis calcd. for $C_{17}H_{18}N_2O_4S$: C 58.94, H 5.24, N 8.09, found: C 58.80, H 5.16, N 7.96.

1-(3-Amino-5-phenylthiophen-2-yl)ethanone (6Fa): Yield 0.514 g, 79 %, yellow crystals, m.p. 133–134 °C. ^1H NMR (400 MHz,

[D_6]DMSO): δ = 7.66 (d, J = 6.8 Hz, 2H, C_6H_5), 7.49–7.39 (m, 3H, C_6H_5), 7.22 (s, 2H, NH_2), 7.01 (s, 1H, thiophene), 2.28 (s, 3H, CH_3) ppm. ^{13}C NMR (101 MHz, [D_6]DMSO): δ = 189.2, 155.5, 147.7, 132.6, 129.4, 129.2, 125.6, 116.2, 108.5, 28.2 ppm. IR (ATR): $\tilde{\nu}$ = 3413, 3305, 1589, 1525, 1489, 1462, 1362, 1306, 1222, 1181, 1164, 1128, 1016, 958, 927, 824, 759, 724, 683, 638, 617, 588, 549, 466, 449, 436 cm^{-1}. MS (ESI): m/z = 218.1 [M + H]$^+$. Elemental analysis calcd. for $C_{12}H_{11}NOS$: C 66.33, H 5.10, N 6.45, found: C 63.22, H 5.01, N 6.39.

1-[3-Amino-5-(3-methylphenyl)thiophen-2-yl]ethanone (6Fb): Yield 0.388 g, 56 %, yellow crystals, m.p. 125–126 °C. ^{1}H NMR (400 MHz, [D_6]DMSO): δ = 7.47–7.42 (m, 2H, C_6H_4), 7.32 (t, J = 7.5 Hz, 1H, C_6H_4), 7.27–7.11 (m, 3H, C_6H_4, NH_2), 7.00 (s, 1H, thiophene), 2.34 (s, 3H, CH_3), 2.27 (s, 3H, CH_3) ppm. ^{13}C NMR (126 MHz, [D_6]DMSO): δ = 189.6, 156.0, 148.4, 139.0, 133.1, 130.5, 129.6, 126.6, 123.3, 116.6, 108.9, 28.6, 21.4 ppm. IR (ATR): $\tilde{\nu}$ = 3420, 3276, 3161, 2917, 1594, 1521, 1464, 1361, 1310, 1286, 1217, 1168, 1119, 1090, 1017, 971, 943, 891, 866, 836, 774, 706, 685, 673, 642, 572, 549, 440, 425 cm^{-1}. MS (ESI): m/z = 232.1 [M + H]$^+$. Elemental analysis calcd. for $C_{13}H_{13}NOS$: C 67.50, H 5.66, N 6.06, found: C 67.37, H 5.55, N 5.99.

1-[3-Amino-5-(4-methylphenyl)thiophen-2-yl]ethanone (6Fc): Yield 0.589 g, 85 %, dark yellow crystals, m.p. 129–130 °C. ^{1}H NMR (400 MHz, [D_6]DMSO): δ = 7.53 (d, J = 7.9 Hz, 2H, C_6H_4), 7.26–7.20 (m, 4H, C_6H_4, NH_2), 6.96 (s, 1H, thiophene), 2.31 (s, 3H, CH_3), 2.26 (s, 3H, CH_3) ppm. ^{13}C NMR (126 MHz, [D_6]DMSO): δ = 189.5, 156.1, 148.5, 139.6, 130.4, 130.2, 126.0, 116.1, 108.6, 28.6, 21.3 ppm. IR (ATR): $\tilde{\nu}$ = 3405, 3278, 3172, 2919, 1592, 1538, 1501, 1463, 1359, 1309, 1240, 1215, 1184, 1106, 1019, 956, 927, 830, 806, 716, 692, 638, 587, 562, 507, 487, 430 cm^{-1}. MS (ESI): m/z = 232.1 [M + H]$^+$. Elemental analysis calcd. for $C_{13}H_{13}NOS$: C 67.50, H 5.66, N 6.06, found: C 67.36, H 5.59, N 5.97.

1-[3-Amino-5-(4-fluorophenyl)thiophen-2-yl]ethanone (6Fd): Yield 0.571 g, 81 %, yellow crystals, m.p. 122–123 °C. ^{1}H NMR (400 MHz, [D_6]DMSO): δ = 7.68 (dd, J_{HH} = 7.8, J_{HF} = 5.5 Hz, 2H, C_6H_4), 7.29–7.23 (m, 4H, C_6H_4, NH_2), 6.96 (s, 1H, thiophene), 2.26 (s, 3H, CH_3) ppm. ^{13}C NMR (126 MHz, [D_6]DMSO): δ = 189.7, 163.1 (d, J = 247.3 Hz), 156.0, 147.1, 129.8 (d, J = 3.0 Hz), 128.4 (d, J = 8.5 Hz), 116.8, 116.7 (d, J = 22.0 Hz), 109.0, 28.6 ppm. IR (ATR): $\tilde{\nu}$ = 3408, 3272, 3169, 1591, 1534, 1501, 1462, 1361, 1318, 1229, 1159, 1096, 1012, 957, 924, 833, 818, 799, 717, 690, 667, 632, 585, 559, 543, 515, 480, 435 cm^{-1}. MS (ESI): m/z = 236.1 [M + H]$^+$. Elemental analysis calcd. for $C_{12}H_{10}FNOS$: C 61.26, H 4.28, N 5.95, found: C 61.18, H 4.19, N 5.84.

1-{3-Amino-5-[3-(trifluoromethyl)phenyl]thiophen-2-yl}-ethanone (6Fe): Yield 0.769 g, 90 %, yellow crystals, m.p. 134–135 °C. ^{1}H NMR (400 MHz, [D_6]DMSO): δ = 8.04–7.85 (m, 2H, C_6H_4), 7.75 (d, J = 7.6 Hz, 1H, C_6H_4), 7.68 (t, J = 7.6 Hz, 1H, C_6H_4), 7.22 (s, 2H, NH_2), 7.15 (s, 1H, thiophene), 2.29 (s, 3H, CH_3) ppm. ^{13}C NMR (126 MHz, [D_6]DMSO): δ = 189.9, 155.8, 145.9, 134.2, 130.9, 130.5 (q, J = 31.6 Hz), 130.1, 126.1 (q, J = 3.7 Hz), 124.3 (q, J = 272.4 Hz), 122.4 (q, J = 3.7 Hz), 118.1, 109.6, 28.7 ppm. IR (ATR): $\tilde{\nu}$ = 3402, 3270, 3170, 1595, 1524, 1494, 1454, 1406, 1318, 1221, 1110, 1073, 1021, 972, 943, 894, 823, 794, 724, 686, 657, 634, 580, 550, 510, 492, 481, 432 cm^{-1}. MS (ESI): m/z = 286.0 [M + H]$^+$. Elemental analysis calcd. for $C_{13}H_{10}F_3NOS$: C 54.73, H 3.53, N 4.91, found: C 54.69, H 3.44, N 4.79.

1-[3-(5-Acetyl-4-aminothiophen-2-yl)phenyl]ethanone (6Ff): Yield 0.699 g, 90 %, yellow crystals, m.p. 154–155 °C. ^{1}H NMR (400 MHz, [D_6]DMSO): δ = 8.14 (t, J = 1.6 Hz, 1H, C_6H_4), 8.02–7.97 (m, 1H, C_6H_4), 7.94–7.90 (m, 1H, C_6H_4), 7.62 (t, J = 7.8 Hz, 1H, C_6H_4), 7.31–7.17 (br.s, 2H, NH_2), 7.12 (s, 1H, thiophene), 2.64 (s, 3H, CH_3), 2.30 (s, 3H, CH_3) ppm. ^{13}C NMR (101 MHz, [D_6]DMSO): δ = 197.5 (o), 189.4 (o), 155.4 (o), 146.4 (o), 137.5 (o), 133.0 (o), 130.0 (+), 129.8 (+), 129.0 (+), 124.8 (+), 117.0 (+), 108.8 (o), 28.2 (+), 26.8 (+) ppm. IR (ATR): $\tilde{\nu}$ = 3169, 1676, 1622, 1595, 1450, 1398, 1361, 1311, 1280, 1222, 1170, 1116, 1082, 944, 908, 833, 749, 707, 678, 644, 594, 560, 454, 420 cm^{-1}. MS (ESI): m/z = 260.1 [M + H]$^+$. Elemental analysis calcd. for $C_{14}H_{13}NO_2S$: C 64.84, H 5.05, N 5.40, found: C 64.70, H 5.00, N 5.41.

Methyl 3-(5-acetyl-4-aminothiophen-2-yl)benzoate (6Fg): Yield 0.544 g, 66 %, dark yellow crystals, m.p. 129–130 °C. ^{1}H NMR (500 MHz, [D_6]DMSO): δ = 8.10 (s, 1H, C_6H_4), 7.94 (d, J = 7.5 Hz, 1H, C_6H_4), 7.90 (d, J = 7.6 Hz, 1H, C_6H_4), 7.58 (t, J = 7.7 Hz, 1H, C_6H_4), 7.21 (s, 2H, NH_2), 7.07 (s, 1H, thiophene), 3.87 (s, 3H, OCH_3), 2.28 (s, 3H, CH_3) ppm. ^{13}C NMR (126 MHz, [D_6]DMSO): δ = 189.8, 166.0, 155.8, 146.5, 133.6, 131.0, 130.6, 130.3, 130.1, 126.2, 117.5, 109.3, 52.8, 28.7 ppm. IR (ATR): $\tilde{\nu}$ = 3427, 3320, 2950, 1716, 1593, 1524, 1485, 1461, 1436, 1398, 1361, 1282, 1214, 1111, 1002, 960, 935, 901, 873, 823, 751, 665, 640, 577, 548, 475, 436 cm^{-1}. MS (ESI): m/z = 276.1 [M + H]$^+$. Elemental analysis calcd. for $C_{14}H_{13}NO_3S$: C 61.07, H 4.76, N 5.09, found: C 60.94, H 4.68, N 4.99.

General Method for Preparation of 5-Aryl-2-nitrothiophen-3-amines (6Ga–Gg), 3-Amino-5-phenylthiophene-2-carbonitriles (6Ha–Hg), Ethyl 3-(3-Amino-5-arylthiophen-2-yl)prop-2-enoates (6Ia–Ig), and 2-Arylthieno(3,2-b)pyridine-5,7(4*H*,6*H*)-diones (6Ja–Jg): Reactions were carried out under an atmosphere of nitrogen in flame or oven-dried glassware. The corresponding reagent (**5G**–**J**) (3.3 mmol) was added dropwise under stirring to a solution of sodium hydrosulfide (0.185 g, 3.3 mmol) in methanol (15 mL) at –5 °C. The mixture was then stirred at –5 °C within 1 h. Then a solution of MeONa (9 mL, 1 M) in methanol was added. After that solution of propanenitrile 3 (3 mmol) in methanol (5 mL) was added dropwise whilst stirring at –5 °C. The resulting mixture was stirred for 2 h at –5 °C and additional 2 h at ambient temperature. The solvent was evaporated under reduced pressure. Acetic acid (20 mL, ω = 2 %) was added to the residue. The product was filtered off and recrystallized from methanol. For the case of syntheses of **6Ia**–**Ig** and **6Ja**–**Jg** ethanol and EtONa were used instead of methanol and MeONa.

5-Phenyl-2-nitrothiophen-3-amine (6Ga): Yield 0.475 g, 72 %, yellow crystals, m.p. 222–223 °C. ^{1}H NMR (400 MHz, [D_6]DMSO): δ = 8.40–8.03 (br.s, 2H, NH_2), 7.73–7.67 (m, 2H, C_6H_5), 7.54–7.44 (m, 3H, C_6H_5), 7.02 (s, 1H, thiophene) ppm. ^{13}C NMR (101 MHz, [D_6]DMSO): δ = 152.0 (o), 149.6 (o), 131.4 (o), 130.6 (+), 129.4 (+), 126.0 (+), 120.2 (o), 115.0 (+) ppm. IR (ATR): $\tilde{\nu}$ = 3427, 3287, 3156, 1600, 1552, 1447, 1367, 1318, 1219, 1163, 1115, 1071, 1010, 998, 988, 908, 825, 762, 707, 684, 646, 514, 444 cm^{-1}. MS (ESI): m/z = 221.0 [M + H]$^+$. Elemental analysis calcd. for $C_{10}H_8N_2O_2S$: C 54.53, H 3.66, N 12.72, found: C 54.40, H 3.55, N 12.66.

5-(3-Methylphenyl)-2-nitrothiophen-3-amine (6Gb): Yield 0.393 g, 56 %, white crystals, m.p. 210–211 °C. ^{1}H NMR (400 MHz, [D_6]DMSO): δ = 8.27–8.07 (br.s, 2H, NH_2), 7.53–7.47 (m, 2H, C_6H_4), 7.38 (t, J = 7.9 Hz, 1H, C_6H_4), 7.31 (d, J = 7.5 Hz, 1H, C_6H_4), 7.00 (s, 1H, thiophene), 2.36 (s, 3H, CH_3) ppm. ^{13}C NMR (126 MHz, [D_6]DMSO): δ = 152.0 (o), 149.8 (o), 138.9 (o), 131.4 (+, two overlapped signals), 129.3 (+), 126.4 (+), 123.2 (+), 120.1 (o), 114.9 (+), 20.8 (+) ppm. IR (ATR): $\tilde{\nu}$ = 3416, 3302, 1610, 1553, 1501, 1445, 1387, 1305, 1261, 1223, 1119, 1033, 998, 965, 894, 831, 777, 745, 697, 681, 653, 557, 515, 458, 421 cm^{-1}. MS (ESI): m/z = 235.1 [M + H]$^+$. Elemental analysis calcd. for $C_{11}H_{10}N_2O_2S$: C 56.39, H 4.30, N 11.96, found: C 56.28, H 4.18, N 11.81.

5-(4-Methylphenyl)-2-nitrothiophen-3-amine (6Gc): Yield 0.569 g, 81 %, yellow crystals, m.p. 225–226 °C. ^{1}H NMR (400 MHz,

[D_6]DMSO): δ = 8.35–8.00 (br.s, 2H, NH_2), 7.60 (d, J = 8.0 Hz, 2H, C_6H_4), 7.31 (d, J = 7.9 Hz, 2H, C_6H_4), 6.97 (s, 1H, thiophene), 2.35 (s, 3H, CH_3) ppm. ^{13}C NMR (126 MHz, [D_6]DMSO): δ = 152.1 (o), 149.9 (o), 140.8 (o), 132.5 (o), 130.0 (+), 128.7 (o), 125.9 (+), 114.3 (+), 20.9 (+) ppm. IR (ATR): $\tilde{\nu}$ = 3437, 3308, 1605, 1554, 1525, 1445, 1389, 1313, 1150, 1116, 1016, 933, 900, 802, 787, 744, 702, 634, 592, 571, 485, 466, 410 cm^{-1}. Spectroscopic data are in agreement with those reported in the literature.[57]

5-(4-Fluorophenyl)-2-nitrothiophen-3-amine (6Gd): Yield 0.543 g, 76 %, yellow crystals, m.p. 290–291 °C. ^{1}H NMR (400 MHz, [D_6]DMSO): δ = 8.36–8.06 (m, 2H, NH_2), 7.77 (dd, J_{HH} = 7.7, J_{HF} = 5.7 Hz, 2H, C_6H_4), 7.34 (t, J = 8.4 Hz, 2H, C_6H_4), 6.98 (s, 1H, thiophene) ppm. ^{13}C NMR (126 MHz, [D_6]DMSO): δ = 163.3 (d, J = 249.0 Hz), 151.9, 148.4, 134.0, 128.5, 126.4 (d, J = 7.6 Hz), 120.2, 116.4 (d, J = 22.1 Hz) ppm. IR (ATR): $\tilde{\nu}$ = 3442, 3299, 3081, 1646, 1626, 1595, 1526, 1514, 1487, 1449, 1391, 1317, 1234, 1163, 1119, 1027, 1013, 970, 935, 886, 827, 803, 751, 692, 677, 492, 447 cm^{-1}. Spectroscopic data are in agreement with those reported in the literature.[57]

2-Nitro-5-[3-(trifluoromethyl)phenyl]thiophen-3-amine (6Ge): Yield 0.527 g, 61 %, yellow crystals, m.p. 197–198 °C. ^{1}H NMR (400 MHz, [D_6]DMSO): δ = 8.3–8.12 (br.s, 2H, NH_2), 8.02–7.98 (m, 2H, C_6H_4), 7.86 (d, J = 7.6 Hz, 1H, C_6H_4), 7.78–7.70 (m, 1H, C_6H_4), 7.17 (s, 1H, thiophene) ppm. ^{13}C NMR (126 MHz, [D_6]DMSO): δ = 151.6 (o), 147.2 (o), 132.5 (o), 130.7 (+), 130.1 (+), 130.1 (q, J = 32.5 Hz, o), 126.9 (q, J = 3.6 Hz, +), 123.7 (q, J = 272.6 Hz, o), 122.4 (q, J = 3.8 Hz, +), 120.7 (o), 116.8 (+) ppm. IR (ATR): $\tilde{\nu}$ = 3418, 3307, 1625, 1563, 1510, 1446, 1395, 1314, 1229, 1166, 1071, 960, 887, 832, 799, 746, 717, 689, 664, 510, 420 cm^{-1}. MS (ESI): m/z = 289.0 [M + H]$^+$. Elemental analysis calcd. for $C_{11}H_7F_3N_2O_2S$: C 45.84, H 2.45, N 9.72, found: C 45.75, H 2.37, N 9.66.

5-[(3-Acetylphenyl)phenyl]-2-nitrothiophen-3-amine (6Gf): Yield 0.511 g, 65 %, off-yellow crystals, m.p. 180–181 °C. ^{1}H NMR (400 MHz, [D_6]DMSO): δ = 8.35–8.12 (br.s, 2H, NH_2), 7.77 (s, 1H, C_6H_4), 7.68 (d, J = 7.9 Hz, 1H, C_6H_4), 7.55 (d, J = 8.5 Hz, 1H, C_6H_4), 7.31 (t, J = 7.8 Hz, 1H, C_6H_4), 7.00 (s, 1H, thiophene), 2.62 (s, 3H, CH_3) ppm. ^{13}C NMR (126 MHz, [D_6]DMSO): δ = 197.5, 148.9, 140.5, 137.6, 132.5, 130.0, 129.9, 126.1, 123.0, 119.9, 116.7, 26.9 ppm. IR (ATR): $\tilde{\nu}$ = 3285, 3169, 1676, 1622, 1597, 1569, 1450, 1398, 1361, 1312, 1277, 1222, 1170, 1118, 1082, 1028, 944, 908, 832, 792, 749, 707, 678, 645, 594, 561, 454, 412 cm^{-1}. MS (ESI): m/z = 263.0 [M + H]$^+$. Elemental analysis calcd. for $C_{12}H_{10}N_2O_3S$: C 54.95, H 3.84, N 10.68, found: C 54.90, H 3.76, N 10.65.

Methyl 3-(4-amino-5-nitrothiophen-2-yl)benzoate (6Gg): Yield 0.584 g, 70 %, yellow-brown crystals, m.p. 200–201 °C. ^{1}H NMR (400 MHz, [D_6]DMSO): δ = 8.43–8.22 (br.s, 2H, NH_2), 8.13 (s, 1H, C_6H_4), 8.03 (d, J = 7.7 Hz, 1H, C_6H_4), 7.95–7.90 (m, 1H, C_6H_4), 7.57–7.49 (m, 1H, C_6H_4), 7.04 (s, 1H, thiophene), 3.92 (s, 3H, CH_3) ppm. ^{13}C NMR (126 MHz, [D_6]DMSO): δ = 166.6, 157.7, 146.5, 132.6, 131.8, 130.6, 130.2, 130.0, 125.9, 116.5, 115.6, 52.4 ppm. IR (ATR): $\tilde{\nu}$ = 3425, 3314, 1721, 1627, 1562, 1448, 1398, 1287, 1222, 1114, 1081, 998, 831, 811, 789, 751, 669, 638, 622, 502, 456 cm^{-1}. MS (ESI): m/z = 279.0 [M + H]$^+$. Elemental analysis calcd. for $C_{12}H_{10}N_2O_4S$: C 51.79, H 3.62, N 10.07, found: C 51.86, H 3.60, N 10.11.

3-Amino-5-phenylthiophene-2-carbonitrile (6Ha): Yield 0.378 g, 63 %, cream colored crystals, m.p. 179–180 °C. ^{1}H NMR (400 MHz, [D_6]DMSO): δ = 7.62–7.58 (m, 2H, C_6H_5), 7.48–7.36 (m, 3H, C_6H_5), 6.94 (s, 1H, thiophene), 6.57 (s, 2H, NH_2) ppm. ^{13}C NMR (126 MHz, [D_6]DMSO): δ = 158.4, 148.6, 132.6, 129.9, 129.8, 126.1, 116.3, 116.2, 75.3 ppm. Spectroscopic data are in agreement with those reported in the literature.[29b]

3-Amino-5-(3-methylphenyl)thiophene-2-carbonitrile (6Hb): Yield 0.417 g, 65 %, buff colored crystals, m.p. 163–164 °C. ^{1}H NMR (400 MHz, [D_6]DMSO): δ = 7.44–7.37 (m, 2H, C_6H_4), 7.30 (t, J = 7.4 Hz, 1H, C_6H_4), 7.17 (d, J = 7.0 Hz, 1H, C_6H_4), 7.00 (s, 1H, thiophene), 6.61 (s, 2H, NH_2), 2.36 (s, 3H, CH_3) ppm. ^{13}C NMR (126 MHz, [D_6]DMSO): δ = 156.7, 147.0, 134.1, 131.4, 129.3, 126.4, 123.2, 120.4, 117.3, 115.5, 75.6, 20.8 ppm. IR (ATR): $\tilde{\nu}$ = 3428, 3347, 2187, 1632, 1559, 1521, 1464, 1438, 1407, 1380, 1217, 1181, 1101, 1017, 800, 717, 676, 634, 557, 538, 511, 465 cm^{-1}. MS (ESI): m/z = 215.1 [M + H]$^+$. Elemental analysis calcd. for $C_{12}H_{10}N_2S$: C 67.26, H 4.70, N 13.07, found: C 67.07, H 4.62, N 13.10.

3-Amino-5-(4-methylphenyl)thiophene-2-carbonitrile (6Hc): Yield 0.507 g, 79 %, buff colored crystals, m.p. 184–185 °C. ^{1}H NMR (400 MHz, [D_6]DMSO): δ = 7.48 (d, J = 8.2 Hz, 2H, C_6H_4), 7.25 (d, J = 7.9 Hz, 2H, C_6H_4), 6.88 (s, 1H, thiophene), 6.53 (s, 2H, NH_2), 2.32 (s, 3H, CH_3). ppm. ^{13}C NMR (101 MHz, [D_6]DMSO): δ = 157.9 (o), 148.3 (o), 139.1 (o), 129.8 (+), 129.4 (o), 125.5 (+), 115.8 (o), 115.2 (+), 74.2 (o), 20.8 (+) ppm. IR (ATR): $\tilde{\nu}$ = 3428, 3347, 2187, 1632, 1559, 1521, 1464, 1438, 1407, 1380, 1217, 1181, 1101, 1017, 800, 717, 676, 634, 557, 538, 511, 465 cm^{-1}. Spectroscopic data are in agreement with those reported in the literature.[27g]

3-Amino-5-(4-fluorophenyl)thiophene-2-carbonitrile (6Hd): Yield 0.536 g, 82 %, cream colored crystals, m.p. 200–201 °C. ^{1}H NMR (500 MHz, [D_6]DMSO): δ = 7.79–7.60 (m, 2H, C_6H_4), 7.30 (t, J = 8.7 Hz, 2H, C_6H_4), 6.91 (s, 1H, thiophene), 6.58 (s, 2H, NH_2) ppm. ^{13}C NMR (101 MHz, [D_6]DMSO): δ = 163.1 (d, J = 247.3 Hz), 157.8, 147.3, 131.2 (d, J = 3.0 Hz), 129.8 (d, J = 8.5 Hz), 118.1 (d, J = 22.0 Hz), 116.4, 108.6, 75.1. IR (ATR): $\tilde{\nu}$ = 3240, 2194, 1628, 1570, 1502, 1444, 1328, 1233, 1164, 1073, 1018, 968, 917, 890, 815, 723, 688, 514, 453 cm^{-1}. MS (ESI): m/z = 219.0 [M + H]$^+$. Elemental analysis calcd. for $C_{11}H_7FN_2S$: C 60.54, H 3.23, N 12.84, found: C 60.45, H 3.20, N 12.87.

3-Amino-5-[3-(trifluoromethyl)phenyl]thiophene-2-carbonitrile (6He): Yield 0.482 g, 60 %, cream colored crystals, m.p. 160–161 °C. ^{1}H NMR (400 MHz, [D_6]DMSO): δ = 7.96–7.86 (m, 2H, C_6H_4), 7.82–7.74 (m, 1H, C_6H_4), 7.72–7.66 (m, 1H, C_6H_4), 7.10 (s, 1H, thiophene), 6.61 (s, 2H, NH_2) ppm. ^{13}C NMR (101 MHz, [D_6]DMSO): δ = 157.8 (o), 145.9 (o), 133.1 (o), 130.6 (+), 130.0 (q, J = 31.8 Hz, o), 129.7 (+), 125.8 (q, J = 3.3 Hz, +), 123.8 (q, J = 272.5 Hz, o), 121.9 (q, J = 3.7 Hz, +), 117.3 (+), 115.4 (o), 75.6 (o) ppm. IR (ATR): $\tilde{\nu}$ = 3452, 3355, 3241, 2191, 1628, 1568, 1500, 1481, 1443, 1417, 1329, 1233, 1168, 1119, 1073, 1020, 1000, 968, 917, 890, 819, 796, 723, 688, 654, 511, 497 cm^{-1}. MS (ESI): m/z = 269.0 [M + H]$^+$. Elemental analysis calcd. for $C_{12}H_7F_3N_2S$: C 53.73, H 2.63, N 10.44, found: C 53.65, H 2.70, N 10.40.

3-Amino-5-(3-acetylphenyl)thiophene-2-carbonitrile (6Hf): Yield 0.457 g, 63 %, cream colored crystals, m.p. 154–155 °C. ^{1}H NMR (400 MHz, [D_6]DMSO): δ = 8.08 (s, 1H, C_6H_4), 7.99 (d, J = 7.9 Hz, 1H, C_6H_4), 7.86 (d, J = 8.5 Hz, 1H, C_6H_4), 7.63–7.60 (m, 1H, C_6H_4), 7.06 (s, 1H, thiophene), 6.61 (s, 2H, NH_2), 2.64 (s, 3H, CH_3) ppm. ^{13}C NMR (101 MHz, [D_6]DMSO): δ = 197.5 (o), 157.9 (o), 146.9 (o), 137.5 (o), 132.5 (o), 130.0 (+), 129.8 (+), 129.0 (+), 124.8 (+), 116.6 (+), 115.5 (o), 75.2 (o), 26.8 (+) ppm. IR (ATR): $\tilde{\nu}$ = 3445, 3352, 3240, 2926, 2191, 1685, 1628, 1600, 1568, 1495, 1442, 1409, 1353, 1291, 1277, 1210, 1177, 1102, 1080, 1021, 946, 892, 814, 791, 703, 677, 632, 585, 507, 422 cm^{-1}. MS (ESI): m/z = 243.1 [M + H]$^+$. Elemental analysis calcd. for $C_{13}H_{10}N_2OS$: C 64.44, H 4.16, N 11.56, found: C 64.38, H 4.13, N 11.57.

Methyl 3-(4-Amino-5-cyanothiophen-2-yl)benzoate (6Hg): Yield 0.503 g, 65 %, cream colored crystals, m.p. 180–181 °C. ^{1}H NMR (400 MHz, [D_6]DMSO): δ = 8.07 (s, 1H, C_6H_4), 7.97 (d, J = 7.7 Hz, 1H,

C_6H_4), 7.87 (t, J = 9.0 Hz, 1H, C_6H_4), 7.64–7.56 (m, 1H, C_6H_4), 7.05 (s, 1H, thiophene), 6.61 (s, 2H, NH_2), 3.89 (s, 3H, CH_3) ppm. ^{13}C NMR (101 MHz, [D_6]DMSO): δ = 165.6 (o), 157.9 (o), 146.5 (o), 132.5 (o), 130.6 (o), 130.2 (+), 130.0 (+), 129.7 (+), 125.7 (+), 116.6 (+), 115.5 (o), 75.3 (o), 52.4 (+) ppm. IR (ATR): $\tilde{\nu}$ = 3361, 3243, 2955, 2191, 1721, 1634, 1606, 1572, 1495, 1443, 1411, 1289, 1227, 1115, 1080, 1020, 999, 817, 748, 678, 662, 510, 418 cm^{-1}. MS (ESI): m/z = 259.1 [M + H]$^+$. Elemental analysis calcd. for $C_{13}H_{10}N_2O_2S$: C 60.45, H 3.90, N 10.85, found: C 60.31, H 3.81, N 10.70.

Ethyl (2*E*)-3-(3-Amino-5-phenylthiophen-2-yl)prop-2-enoate (6Ia): Yield 0.606 g, 74 %, yellow crystals, m.p. 156–157 °C. ^{1}H NMR (400 MHz, [D_6]DMSO): δ = 7.98 (d, J = 15.0 Hz, 1H, CH=), 7.59 (d, J = 7.4 Hz, 2H, C_6H_5), 7.45–7.35 (m, 3H, C_6H_5), 6.92 (s, 1H, thiophene), 6.33 (s, 2H, NH_2), 5.63 (d, J = 15.0 Hz, 1H, CH=), 4.13 (q, J = 7.0 Hz, 2H, CH_2), 1.24 (t, J = 7.1 Hz, 3H, CH_3). ppm. ^{13}C NMR (101 MHz, [D_6]DMSO): δ = 166.7 (o), 152.4 (o), 144.6 (o), 135.8 (+), 132.9 (o), 129.1 (+), 128.7 (+), 125.3 (+), 117.3 (+), 107.7 (o), 107.2 (+), 59.2 (–), 14.4 (+) ppm. IR (ATR): $\tilde{\nu}$ = 3372, 3203, 2975, 2901, 1687, 1674, 1590, 1552, 1498, 1463, 1423, 1412, 1368, 1319, 1224, 1178, 1074, 1026, 972, 954, 908, 839, 759, 723, 688, 634, 519, 460 cm^{-1}. MS (ESI): m/z = 274.1 [M + H]$^+$. Elemental analysis calcd. for $C_{15}H_{15}NO_2S$: C 65.91, H 5.53, N 5.12, found: C 65.79, H 5.44, N 5.05.

Ethyl (2*E*)-3-[3-Amino-5-(3-methylphenyl)thiophen-2-yl]prop-2-enoate (6Ib): Yield 0.560 g, 65 %, yellow crystals, m.p. 145–146 °C. ^{1}H NMR (500 MHz, [D_6]DMSO): δ = 7.97 (d, J = 15.0 Hz, 1H, CH=), 7.45–7.34 (m, 2H, C_6H_4), 7.30 (t, J = 7.4 Hz, 1H, C_6H_4), 7.17 (d, J = 7.0 Hz, 1H, C_6H_4), 6.85 (s, 1H, thiophene), 6.29 (s, 2H, NH_2), 5.59 (d, J = 15.0 Hz, 1H, CH=), 4.12 (q, J = 7.1 Hz, 2H, CH_2), 2.27 (s, 3H, CH_3), 1.22 (t, J = 7.1 Hz, 3H, OCH_3) ppm. ^{13}C NMR (126 MHz, [D_6]DMSO): δ = 166.8, 152.4, 144.9, 138.4, 135.8, 130.2, 129.4, 129.1, 125.9, 122.6, 116.8, 107.3, 106.8, 59.2, 20.9, 14.4 ppm. IR (ATR): $\tilde{\nu}$ = 2978, 2920, 1979, 1709, 1603, 1456, 1373, 1175, 1093, 1035, 823, 783, 695, 594, 512, 435 cm^{-1}. MS (ESI): m/z = 288.1 [M + H]$^+$. Elemental analysis calcd. for $C_{16}H_{17}NO_2S$: C 66.87, H 5.96, N 4.84, found: C 66.87, H 5.84, N 4.79.

Ethyl (2*E*/*Z*)-3-[3-Amino-5-(4-methylphenyl)thiophen-2-yl]prop-2-enoate (6Ic): Yield 0.491 g, 57 %, yellow crystals, m.p. 174–175 °C. ^{1}H NMR (400 MHz, [D_6]DMSO) (*E*/*Z* = 0.94:0.06): δ = 7.97 (d, J = 15.0 Hz, 1H, CH=), 7.47 (d, J = 8.2 Hz, 1.9H, C_6H_4), 7.23 (d, J = 7.9 Hz, 2H, C_6H_4), 7.15 (d, J = 8.1 Hz, 0.15H, C_6H_4), 6.86 (s, 1H, thiophene), 6.30 (s, 1.9H, NH_2), 6.15 (s, 0.12H, NH_2), 5.59 (d, J = 15.0 Hz, 0.92H, CH=), 5.26 (d, J = 12.2 Hz, 0.06H, CH=), 4.12 (q, J = 7.1 Hz, 2H, CH_2), 2.31 (s, 2.84H, CH_3), 2.28 (s, 0.2H, CH_3), 1.23 (t, J = 7.1 Hz, 3H, CH_3) ppm. ^{13}C NMR (126 MHz, [D_6]DMSO): δ = 166.8 (o), 166.5 (o), 155.6 (o), 152.5 (o), 144.9 (o), 141.3 (o), 138.4 (o), 135.8 (+), 132.4 (o), 130.2 (o), 129.7 (+), 129.3 (+), 127.5 (+), 125.2 (+), 116.8 (+), 116.4 (o), 107.3 (o), 106.8 (+), 101.3 (+), 59.2 (–), 20.8 (+), 14.4 (+) ppm. IR (ATR): $\tilde{\nu}$ = 3383, 3323, 1684, 1589, 1550, 1510, 1459, 1367, 1318, 1236, 1169, 1113, 1026, 972, 954, 834, 805, 715, 692, 636, 540, 517, 476 cm^{-1}. MS (ESI): m/z = 288.1 [M + H]$^+$. Elemental analysis calcd. for $C_{16}H_{17}NO_2S$: C 66.87, H 5.96, N 4.87, found: C 66.75, H 5.89, N 4.92.

Ethyl (2*E*)-3-[3-Amino-5-(4-fluorophenyl)thiophen-2-yl]prop-2-enoate (6Id): Yield 0.750 g, 86 %, yellow crystals, m.p. 148–149 °C. ^{1}H NMR (400 MHz, [D_6]DMSO): δ = 7.98 (d, J = 15.0 Hz, 1H, CH=), 7.63 (dd, J_{HH} = 8.8 Hz, J_{HF} = 5.3 Hz, 2H, 3,5H-C_6H_4), 7.32–7.17 (m, 2H, C_6H_4), 6.88 (s, 1H, thiophene), 6.33 (s, 2H, NH_2), 5.62 (d, J = 15.0 Hz, 1H, CH=), 4.13 (q, J = 7.1 Hz, 2H, CH_2), 1.23 (t, J = 7.1 Hz, 3H, CH_3) ppm. ^{13}C NMR (101 MHz, [D_6]DMSO): δ = 166.7 (o), 162.2 (d, J = 246.5 Hz, o), 152.4 (o), 143.5 (o), 135.7 (+), 129.54 (d, J = 3.1 Hz, o), 127.4 (d, J = 8.3 Hz, +), 117.5 (+), 116.1 (d, J = 22.0 Hz, +), 107.7 (o), 107.2 (+), 59.2 (–), 14.3 (+) ppm. IR (ATR): $\tilde{\nu}$ = 3474, 3359, 3214, 2982, 1687, 1675, 1596, 1554, 1509, 1465, 1437, 1404, 1368, 1317, 1234, 1181, 1159, 1097, 1023, 972, 952, 835, 815, 716, 691, 576, 561, 516, 494 cm^{-1}. MS (ESI): m/z = 292.1 [M + H]$^+$. Elemental analysis calcd. for $C_{15}H_{14}FNO_2S$: C 61.84, H 4.84, N 4.81, found: C 61.76, H 4.77, N 4.71.

Ethyl (2*E*)-3-{3-Amino-5-[3-(trifluoromethyl)phenyl]thiophen-2-yl}prop-2-enoate (6Ie): Yield 0.583 g, 57 %, yellow crystals, m.p. 120–121 °C. ^{1}H NMR (500 MHz, [D_6]DMSO): δ = 7.97 (d, J = 15.0 Hz, 1H, CH=), 7.74 (d, J = 7.2 Hz, 1H, C_6H_4), 7.71 (s, 1H, C_6H_4), 7.63–7.43 (m, 2H, C_6H_4), 6.91 (s, 1H, thiophene), 6.32 (s, 2H, NH_2), 5.62 (d, J = 15.0 Hz, 1H, CH=), 4.12 (q, J = 7.0 Hz, 2H, CH_2), 1.23 (t, J = 7.1 Hz, 3H, CH_3) ppm. ^{13}C NMR (126 MHz, [D_6]DMSO): δ = 166.9, 152.6, 144.8, 134.3, 130.7, 130.2 (q, J = 33.6 Hz), 129.6, 126.6, 125.3 (q, J = 3.4 Hz), 124.2 (q, J = 276.4 Hz), 121.8 (q, J = 4.3 Hz), 118.5, 107.7, 107.2, 59.2, 14.4 ppm. IR (ATR): $\tilde{\nu}$ = 3296, 1593, 1558, 1532, 1489, 1332, 1311, 1111, 999, 973, 960, 915, 894, 859, 839, 793, 753, 715, 683, 613, 493, 436 cm^{-1}. MS (ESI): m/z = 342.1. [M + H]$^+$. Elemental analysis calcd. for $C_{16}H_{14}F_3NO_2S$: C 56.30, H 4.13, N 4.10, found: C 56.14, H 4.09, N 4.01.

Ethyl (2*E*/*Z*)-3-[5-(3-Acetylphenyl)-3-aminothiophen-2-yl]prop-2-enoate (6If): Yield 0.642 g, 68 %, yellow crystals, m.p. 127–128 °C. ^{1}H NMR (400 MHz, [D_6]DMSO) (*E*/*Z** = 0.75:0.25): δ = 8.10 (s, 0.25H, 2H-C_6H_4), 8.08 (s, 0.75H, 2H-C_6H_4), 7.99 (d, J = 15.1 Hz, 0.75H, =CH), 7.94 (d, J = 7.7 Hz, 1H, C_6H_4), 7.84 (d, J = 7.9 Hz, 1H, C_6H_4), 7.59 (t, J = 7.8 Hz, 1H, C_6H_4), 7.24 (d, J = 12.2 Hz, 0.25H, =CH), 7.04 (s, 0.75H, thiophene), 7.03 (s, 0.25H, thiophene), 6.34 (s, 1.5H, NH_2), 6.21 (s, 0.5H, NH_2), 5.67 (d, J = 15.1 Hz, 0.75H, =CH), 5.33 (d, J = 12.2 Hz, 0.25H, =CH), 4.13 (q, J = 7.1 Hz, 2H, CH_2), 2.63 (s, 3H, CH_3), 1.24 (t, J = 7.1 Hz, 3H, CH_3) ppm. ^{13}C NMR (101 MHz, [D_6]DMSO): δ = 197.6 (o), 166.7 (o), 166.5* (o), 154.8* (o), 152.3 (o), 145.9* (o), 143.4 (o), 137.5 (o), 137.4* (o), 135.6 (+), 134.2* (+), 133.9* (o), 133.3 (o), 129.7* (+), 129.6 (+), 128.35 (+), 128.30* (+), 124.4 (+), 124.2* (+), 118.2 (+), 116.1* (+), 108.2 (o), 108.0* (o), 107.7 (+), 104.3* (+), 59.3 (–), 59.0* (–), 26.8 (+), 14.4 (+), 14.3* (+) ppm. IR (ATR): $\tilde{\nu}$ = 3446, 3349, 3228, 2988, 1678, 1586, 1557, 1494, 1464, 1428, 1367, 1324, 1272, 1233, 1170, 1110, 1030, 980, 940, 841, 786, 716, 677, 588, 521, 468 cm^{-1}. MS (ESI): m/z = 316.1 [M + H]$^+$. Elemental analysis calcd. for $C_{17}H_{17}NO_3S$: C 64.74, H 5.43, N 4.44, found: C 64.80, H 5.45, N 4.42.

Methyl 3-{4-Amino-5-[(1*E*)-3-ethoxy-3-oxoprop-1-en-1-yl]thiophen-2-yl}benzoate (6Ig): Yield 0.605 g, 61 %, yellow crystals, m.p. 79–80 °C. ^{1}H NMR (400 MHz, [D_6]DMSO): δ = 8.09 (s, 1H, 2H-C_6H_4), 8.05–7.75 (m, 3H, C_6H_4, CH=), 7.64–7.54 (br.s, 1H, C_6H_4), 7.02 (s, 1H, thiophene), 6.35 (s, 2H, NH_2), 5.68 (d, J = 14.7 Hz, 1H, CH=), 4.15–4.12 (m, 2H, CH_2), 3.89 (s, 3H, OCH_3), 1.28–1.20 (br.s, 3H, CH_3) ppm. ^{13}C NMR (101 MHz, [D_6]DMSO): δ = 166.7 (o), 165.7 (o), 152.3 (o), 143.0 (o), 135.6 (+), 133.3 (o), 130.5 (o), 129.8 (+), 129.7 (+), 129.0 (+), 125.4 (+), 118.2 (+), 108.2 (o), 107.8 (+), 59.3 (–), 52.3 (+), 14.3 (+) ppm. IR (ATR): $\tilde{\nu}$ = 3435, 3344, 3231, 2981, 2950, 2905, 1703, 1679, 1592, 1558, 1466, 1427, 1366, 1324, 1282, 1239, 1178, 1109, 964, 837, 806, 750, 730, 677, 637, 587, 523, 470 cm^{-1}. MS (ESI): m/z = 332.1 [M + H]$^+$. Elemental analysis calcd. for $C_{17}H_{17}NO_4S$: C 61.62, H 5.17, N 4.23, found: C 61.53, H 5.09, N 4.18.

2-Phenylthieno(3,2-b)pyridine-5,7(4*H*,6*H*)-dione (6Ja): Yield 0.620 g, 85 %, white crystals, m.p. > 355 °C. ^{1}H NMR (400 MHz, [D_6]DMSO): δ = 11.91–11.48 (br.s, 2H), 7.76–7.66 (m, 2H, C_6H_5), 7.51–7.44 (m, 2H, C_6H_5), 7.43–7.37 (m, 1H, C_6H_5), 7.28 (s, 1H, thiophene), 5.64 (s, 1H, CH) ppm. ^{13}C NMR (151 MHz, [D_6]DMSO): δ = 146.2, 129.3, 125.7 ppm. IR (ATR): $\tilde{\nu}$ = 3017, 3002, 2807, 1668, 1622, 1586, 1519, 1472, 1436, 1386, 1351, 1319, 1224, 1184, 1161, 1136, 1107, 1015, 998, 861, 808, 748, 719, 706, 676, 599, 534, 443, 428 cm^{-1}. MS (ESI): m/z = 244.0 [M + H]$^+$. Elemental analysis calcd. for $C_{13}H_9NO_2S$:

C 64.18, H 3.73, N 5.76, found: C 64.05, H 3.62, N 5.60. ^{1}H NMR spectrum is in agreement with those reported in the literature.[58]

2-(3-Methylphenyl)thieno(3,2-b)pyridine-5,7(4*H*,6*H*)-dione (6Jb): Yield 0.439 g, 57 %, cream colored crystals, m.p. > 348 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 11.61 (s, 1H, NH), 11.47 (s, 1H, OH), 7.52 (s, 1H, C_6H_4), 7.49 (d, J = 7.9 Hz, 1H, C_6H_4), 7.35 (t, J = 7.6 Hz, 1H, C_6H_4), 7.27–7.17 (m, 2H, C_6H_4, thiophene), 5.59 (s, 1H, CH) ppm. ^{13}C NMR (151 MHz, [D$_6$]DMSO): δ = 164.2, 146.3, 138.7, 132.7, 129.7, 129.2, 126.1, 122.9, 119.4, 112.7, 95.6, 20.9 ppm. IR (ATR): $\tilde{\nu}$ = 3020, 2857, 1662, 1616, 1581, 1476, 1447, 1374, 1344, 1311, 1218, 1122, 943, 800, 743, 696, 637, 557, 522, 469, 445, 428 cm^{-1}. MS (ESI): m/z = 258.1 [M + H]$^+$. Elemental analysis calcd. for $C_{14}H_{11}NO_2S$: C 65.35, H 4.31, N 5.44, found: C 65.20, H 4.22, N 5.36.

2-(4-Methylphenyl)thieno(3,2-b)pyridine-5,7(4*H*,6*H*)-dione (6Jc): Yield 0.532 g, 69 %, cream colored crystals, m.p. 250–252 °C (dec.). ^{1}H NMR (600 MHz, [D$_6$]DMSO): δ = 11.58 (s, 1H), 11.45 (s, 1H), 7.59 (d, J = 8.1 Hz, 2H, C_6H_4), 7.28 (d, J = 7.8 Hz, 2H, C_6H_4), 7.20 (s, 1H, thiophene), 5.58 (s, 1H, CH), 2.34 (s, 3H, CH_3) ppm. ^{13}C NMR (151 MHz, [D$_6$]DMSO): δ = 164.7, 146.8, 139.2, 130.6, 130.5, 130.4, 128.2, 127.0, 126.1, 112.8, 96.0, 21.3 ppm. IR (ATR): $\tilde{\nu}$ = 2852, 1662, 1615, 1575, 1475, 1447, 1343, 1309, 1217, 1121, 1019, 942, 799, 742, 695, 636, 557, 523, 469, 427 cm^{-1}. MS (ESI): m/z = 258.1 [M + H]$^+$. Elemental analysis calcd. for $C_{14}H_{11}NO_2S$: C 65.35, H 4.31, N 5.44, found: C 65.20, H 4.24, N 5.31.

2-(4-Fluorophenyl)thieno(3,2-b)pyridine-5,7(4*H*,6*H*)-dione (6Jd): Yield 0.603 g, 77 %, white crystals, m.p. 240–243 °C (dec.). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 11.63 (s, 1H), 11.51 (s, 1H), 7.77 (dd, J_{HH} = 8.9 Hz, J_{HF} = 5.3 Hz, 2H, C_6H_4), 7.31 (t, J = 8.9 Hz, 2H, C_6H_4), 7.23 (s, 1H, thiophene), 5.60 (s, 1H, CH) ppm. IR (ATR): $\tilde{\nu}$ = 2803, 1661, 1585, 1471, 1411, 1381, 1347, 1318, 1223, 1159, 1098, 1012, 946, 813, 740, 696, 659, 557, 523, 489, 448, 433, 417 cm^{-1}. MS (ESI): m/z = 262.0 [M + H]$^+$. Elemental analysis calcd. for $C_{13}H_8FNO_2S$: C 59.76, H 3.09, N 5.36, found: C 59.62, H 2.99, N 5.31.

2-[3-(Trifluoromethyl)phenyl]thieno(3,2-b)pyridine-5,7(4*H*,6*H*)-dione (6Je): Yield 0.532 g, 57 %, cream colored crystals, m.p. 260–262 °C (dec.). ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 11.81 (s, 1H, NH), 11.72 (s, 1H, OH), 8.03–7.99 (m, 2H, C_6H_4), 7.76 (d, J = 7.7 Hz, 1H, C_6H_4), 7.71 (t, J = 7.9 Hz, 1H, C_6H_4), 7.46 (s, 1H, thiophene), 5.76 (s, 1H, CH) ppm. ^{13}C NMR (151 MHz, [D$_6$]DMSO): δ = 164.8 (o), 161.7 (o), 144.4 (o), 144.2 (o), 134.4 (o), 131.0 (+), 130.6 (q, J = 32.0 Hz, o), 130.3 (+), 125.8 (q, J = 3.6 Hz, +), 124.4 (q, J = 272.6 Hz, o), 122.5 (q, J = 3.6 Hz, +), 115.0 (+), 111.5 (q, J = 3.3 Hz, o), 96.6 (+) ppm. IR (ATR): $\tilde{\nu}$ = 2802, 1661, 1615, 1585, 1512, 1475, 1439, 1422, 1380, 1327, 1251, 1225, 1167, 1116, 1096, 1071, 1000, 968, 889, 793, 740, 711, 686, 656, 533, 500, 451, 436, 421, 410 cm^{-1}. MS (ESI): m/z = 312.0 [M + H]$^+$. Elemental analysis calcd. for $C_{14}H_8F_3NO_2S$: C 54.02, H 2.59, N 4.50, found: C 53.93, H 2.52, N 4.39.

2-(3-Acetylphenyl)thieno(3,2-b)pyridine-5,7(4*H*,6*H*)-dione (6Jf): Yield 0.633 g, 74 %, cream colored crystals, m.p. 230–232 °C (dec.). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 12.00–11.22 (m, 2H, NH, OH), 8.17 (s, 1H, C_6H_4), 8.09–7.82 (m, 2H, C_6H_4), 7.62 (t, J = 7.8 Hz, 1H, C_6H_4), 7.38 (s, 1H, thiophene), 5.63 (s, 1H, CH), 2.65 (s, 3H, CH_3) ppm. ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 197.6, 164.2, 161.2, 144.9, 143.7, 137.6, 133.2, 130.1, 129.8, 128.6, 124.9, 113.8, 95.9, 26.9 ppm. IR (ATR): $\tilde{\nu}$ = 3020, 2857, 1662, 1616, 1581, 1476, 1447, 1374, 1344, 1311, 1218, 1122, 943, 800, 743, 696, 637, 557, 522, 469, 445, 428 cm^{-1}. MS (ESI): m/z = 286.1 [M + H]$^+$. Elemental analysis calcd. for $C_{15}H_{11}NO_3S$: C 63.14, H 3.89, N 4.91, found: C 62.99, H 3.80, N 4.80.

Methyl 3-[5,7-Dioxo-4,5,6,7-tetrahydrothieno(3,2-b)pyridin-2-yl]benzoate (6Jg): Yield 0.596 g, 66 %, cream colored crystals, m.p. 345–348 °C (dec.). ^{1}H NMR (600 MHz, [D$_6$]DMSO): δ = 11.82–11.42 (br.s, 2H, NH, OH), 8.17 (t, J = 1.6 Hz, 1H, C_6H_4), 8.08–7.98 (m, 1H, C_6H_4), 7.98–7.94 (m, 1H, C_6H_4), 7.75–7.54 (m, 1H, C_6H_4), 7.34 (s, 1H, thiophene), 5.61 (s, 1H, CH), 3.90 (s, 3H, CH_3) ppm. ^{13}C NMR (151 MHz, [D$_6$]DMSO): δ = 165.71, 164.3, 144.5, 133.3, 130.7, 130.3, 130.0, 129.4, 125.8, 113.8, 96.0, 52.5 ppm. IR (ATR): $\tilde{\nu}$ = 2951, 2809, 1723, 1668, 1622, 1580, 1511, 1479, 1375, 1346, 1287, 1219, 1134, 996, 951, 897, 796, 748, 736, 685, 620, 532, 445, 425 cm^{-1}. MS (ESI): m/z = 302.0 [M + H]$^+$. Elemental analysis calcd. for $C_{15}H_{11}NO_4S$: C 59.79, H 3.68, N 4.65, found: C 59.60, H 3.52, N 4.53.

Keywords: Meerwein arylation · Arenediazonium salts · Thiophene · Heterocycle synthesis · Thorpe–Ziegler cyclization

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