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# Base-Catalyzed Three-Component Reaction of $\alpha$ -Cyanoacetates with Chalcones and Elemental Sulfur: Access to 2-Aminothiophenes Unobtainable via the Gewald Reaction

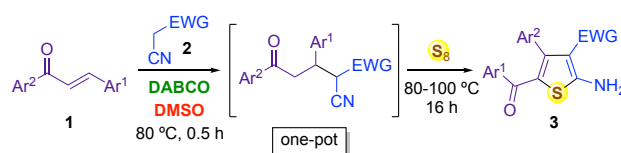
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- readily available substrates
- unobtainable products via Gewald synthesis
- substrate-defined regioselectivity
- chromatography-free purification for 39/41 examples

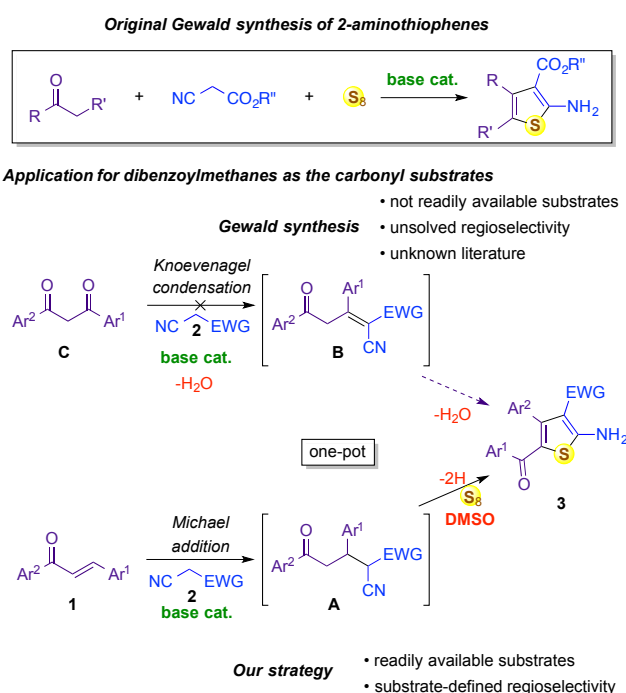
**ABSTRACT:** While Gewald reaction was well known for more than half a century as an excellent method providing bioactive 2-aminothiophenes from reactions of  $\alpha$ -cyanoacetates and carbonyl compounds and elemental sulfur, its application to dibenzoylmethanes as the carbonyl substrates was however unknown and experimentally proven unsuccessful. We proposed here a convenient approach to such series of compounds by a DABCO catalyzed, one-pot, two-step, three-component reaction of  $\alpha$ -cyanoacetate with chalcones and elemental sulfur. This catalytic strategy is highlighted by its excellent atom/step efficiency and high degree of structural diversification by simply choosing the suitable starting chalcones, which are unarguably much more readily available than dibenzoylmethanes.

## Introduction

2-Aminothiophene is an important heterocyclic scaffold in drug design and consequently is present in several commercialized drugs.<sup>1</sup> The development of new bioactive 2-aminothiophene derivatives<sup>2</sup>

greatly benefits from the Gewald reaction,<sup>3,4</sup> discovered for more than half a century, involves the condensation of an enolizable carbonyl compound (ketone or aldehyde bearing a methylenecarbonyl moiety) with an  $\alpha$ -cyanoacetate ester in the presence of elemental sulfur and a base (Scheme 1).

As a part of our project aiming at developing new bioactive 2-aminothiophene derivatives, we were interested in the synthesis of a series of **3**. Retrosynthetically, the scaffold of **3** was supposed to be synthesized via Gewald reaction starting with a Knoevenagel condensation of dibenzoylmethanes as the carbonyl components with  $\alpha$ -cyanoacetate esters (Scheme 1). Our unsuccessful attempts (*vide infra*, Scheme 4) confirmed the total absence of this kind of transformation reported in the literature. In the ideal case, even if this first step could provide the expected adducts **B** from Knoevenagel condensation of **C** with **2**, the second step of sulfurative cyclization of **B** with elemental sulfur would confront challenging differentiation between two benzoyl groups. Consequently, we proposed an approach, taking advantage of using also elemental sulfur as an inexpensive and user-friendly sulfur source,<sup>5</sup> and based on two following elementary reactions:



**Scheme 1. Our proposed strategy to dibenzoylmethane-derived Gewald 2-aminothiophenes**

- (i) Michael addition of  $\alpha$ -cyanoacetate esters **2** to chalcones **1** to provide **A**, and
- (ii) sulfurative cyclization of the resulting adduct **C** with elemental sulfur.

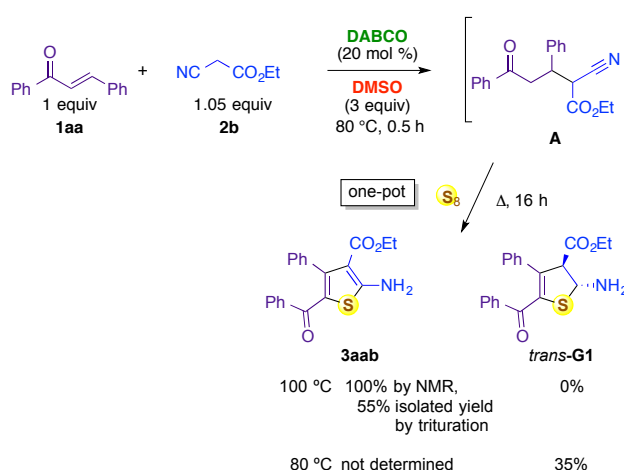
Since both step could be catalyzed by the same base, performing the reactions in one-pot manner would be the strategy of choice to maximize the reaction efficiency while avoiding unnecessary manipulations.

In terms of atom economy, the global transformation consists in a three-component combination with removal of only one hydrogen atom. Compared to the classical Gewald reaction which consists in a dehydration, the atom efficiency of our proposed pathway would be better.

## Results and Discussion

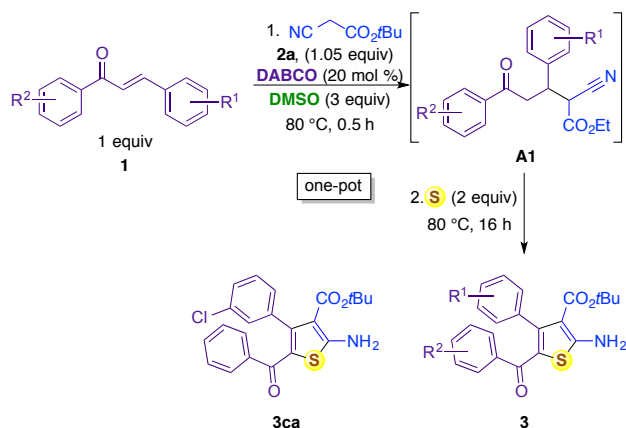
To test this idea, we set up a series of optimizing reactions starting with chalcone **1aa** and ethyl  $\alpha$ -cyanoacetate **2b** in slight excess. We found that the initial Michael addition could be efficiently accomplished in short reaction time (less than 30 min) at 80 °C with a catalytic amount (20 mol %) of DABCO as a base catalyst (Scheme 2). Previously, we found that similar reactions of chalcones with benzyl cyanides required DBU as a stronger base catalyst.<sup>6</sup> Despite the formation of a nearly equimolar mixture of two possible diastereomeric adducts **A**, they could be convergently transformed into 2-aminothiophene **3aab** in the subsequent step upon heating at 100 °C for 16 h. Performing the second step at 80 °C resulted in complex mixtures of incomplete transformation from which we could identify the presence of both Michael adducts *trans*-**G1** their sulfurative cyclizing product **3aab** without aromatization (*vide infra*, Scheme 5).<sup>7</sup>

Scheme 2. Initial three-component synthesis of **3aab**



It is noticeable that the sulfuration reaction of 1:1 adduct **A1** between *t*-butyl cyanoacetate **2a** with chalcone **1aa** and derivatives in general could be performed at lower temperature (80 °C) (Table 1, entry 1) than with ethyl ester **A** (100 °C) (Scheme 2).

**Table 1. Regio predefined synthesis of Gewald products 3<sup>a</sup>**

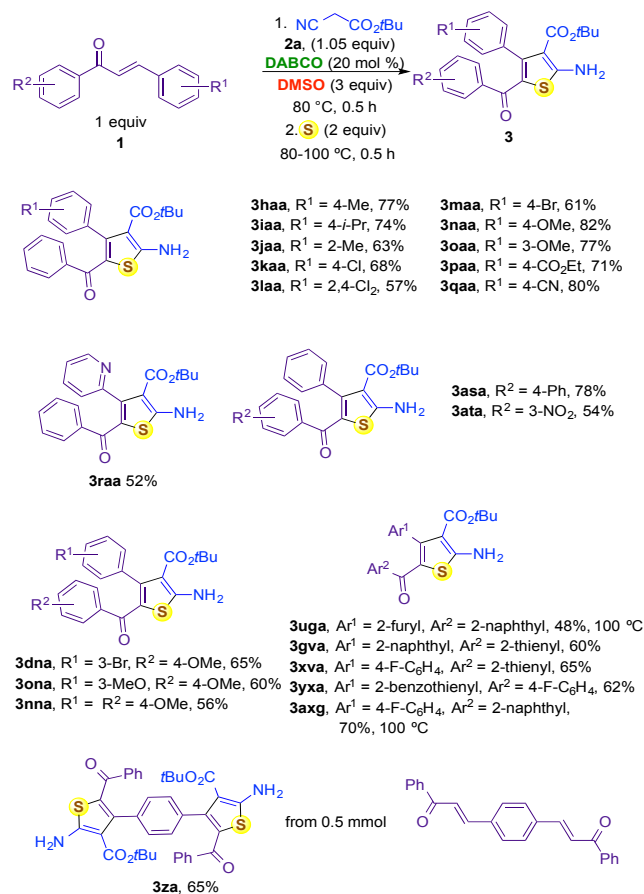


Entry <sup>a</sup>	<b>1</b>	R <sup>1</sup>	R <sup>2</sup>	<b>3</b>	yield (%)
1	<b>1aa</b>	H	H	<b>3aaa</b>	75
2	<b>1ab</b>	H	4-NO <sub>2</sub>	<b>3aba</b>	74
3	<b>1ba</b>	4-NO <sub>2</sub>	H	<b>3baa</b>	70
4	<b>1ac</b>	H	3-Cl	<b>3aca</b>	72
5	<b>1ca</b>	3-Cl	H	<b>3caa</b>	69
6	<b>1ad</b>	H	3-Br	<b>3ada</b>	65
7	<b>1da</b>	3-Br	H	<b>3daa</b>	63
8	<b>1ae</b>	H	2-Cl	<b>3aea</b>	63
9	<b>1ea</b>	2-Cl	H	<b>3eaa</b>	60
10	<b>1af</b>	H	2-Br	<b>3afa</b>	58
11	<b>1fa</b>	2-Br	H	<b>3faa</b>	55
12	<b>1ag</b>	H	3,4-C <sub>4</sub> H <sub>4</sub>	<b>3aga</b>	75
13	<b>1ga</b>	3,4-C <sub>4</sub> H <sub>4</sub>	H	<b>3gaa</b>	70

<sup>a</sup>Reaction conditions: chalcone **1** (1mmol), *t*-butyl cyanoacetate **2a** (1.05 mmol), DABCO (20 mol %, 0.2 mmol) and DMSO (0.2 mL, 3 mmol) 80 °C, 30 min; then S (64 mg, 2 mmol), 80 °C, 16 h.

In order to demonstrate the utility of our strategy, we applied the optimized conditions to regiomeric 4- and 4'- nitrochalcones (**1ab** and **1ba** respectively), both of them could be conveniently obtained from a Claisen-Schmidt condensation of suitable benzaldehydes with acetophenones. As demonstrated in Table 1, entries 2-3, the corresponding 2-aminothiophenes **3aba** and **3baa** were formed in good yields with

both regioisomers. Further investigation showed that chalcones bearing a chloro, bromo or benzo group at different positions of the aromatic rings were all effective in the reaction, delivering the expected 2-aminothiophenes **3** with substrate-defined regiochemistry in moderate to high yields (entries 4-13).

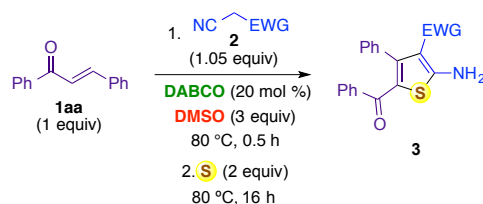


**Scheme 3. Reactions of chalcones 1 with cyanoacetate 2a**

Additional examples of chalcone substrates confirmed that the reaction conditions are not sensitive to the electronic nature of functional groups in both aromatic moieties (Scheme 3). A wide range of functional groups (alkyl, halo, methoxy) were found to tolerate, allowing access to a library of 2-aminothiophenes with different combinations of 3-aryl and 4-benzoyl substituents. Chalcone substrates **1pa**, **1qa** and **1at** which bear an electron-deficient group like ester, cyano or nitro substituent were all effective in the reaction, delivering 2-aminothiophenes **3paa**, **3qaa** and **3ata** in moderate to high yields. Products bearing hetaryl (furyl **3uga**, thienyl **3gva** and **3xva**, benzothienyl **3yxa**) or naphthyl (**3uga**, **3gva** and **3axg**) ring were smoothly obtained. Product **3za** issued from a two-fold reaction was also obtained in reasonable yield under the same reaction conditions. In some cases of substrates bearing 2-

naphthyl group, the reactions required heating at 100 °C to accomplish, which could be in part attributed to low solubilities in the reaction media of these substrates at 80 °C.

Finally, an array of acetonitrile substrates with different ester (CO<sub>2</sub>*n*Bu **2c** and CO<sub>2</sub>*i*Pr **2d**, Table 2, entries 1-2) and carboxamide groups (CONH*n*Bu **2e**, CONH*i*Pr **2f** and CONHBn **2g**, Table 2, entries 3-5) were further surveyed, and they were all quite compatible with the reaction, providing the corresponding products **3aac–3aag** in fair to excellent yields.



**Table 2. Reactions of chalcone 1aa with acetonitriles 2c-2g<sup>a</sup>**

Entry <sup>a</sup>	<b>2</b>	EWG	<b>3</b>	yield (%)
1	<b>2c</b>	CO <sub>2</sub> - <i>n</i> -Bu	<b>3aac</b>	72
2	<b>2d</b>	CO <sub>2</sub> - <i>i</i> -Pr	<b>3aad</b>	72
3	<b>2e</b>	CONH- <i>n</i> -Bu	<b>3aae</b>	80
4	<b>2f</b>	CONH- <i>i</i> -Pr	<b>3aaf</b>	81
5	<b>2g</b>	CONHBn	<b>3aag</b>	86

<sup>a</sup> Reaction conditions: chalcone **1aa** (208 mg, 1 mmol), acetonitrile **2** (1.05 mmol), DABCO (22 mg, 0.2 mmol, 20 mol %), and DMSO (0.2 mL, 3 mmol) 80 °C, 30 min; then S (64 mg, 2 mmol), 80 °C, 16 h.

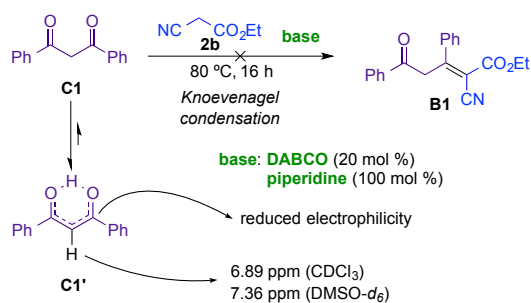
The structure of *N*-benzyl carboxamide product **3aag** was confirmed by X-ray crystallography.

We emphasized that, except for **3ata** and **3uga** (Scheme 3) that should be purified by column chromatography due to their high solubility in methanol, all the 2-aminothiophenes described in this manuscript were obtained from the reaction mixture by simple treatment with methanol followed by filtration.

To shed light on the difference in reactivity between the first step of the Gewald pathway and ours, we performed a Knoevenagel condensation of dibenzoylmethane **C1** with ethyl cyanoacetate **2b** under the

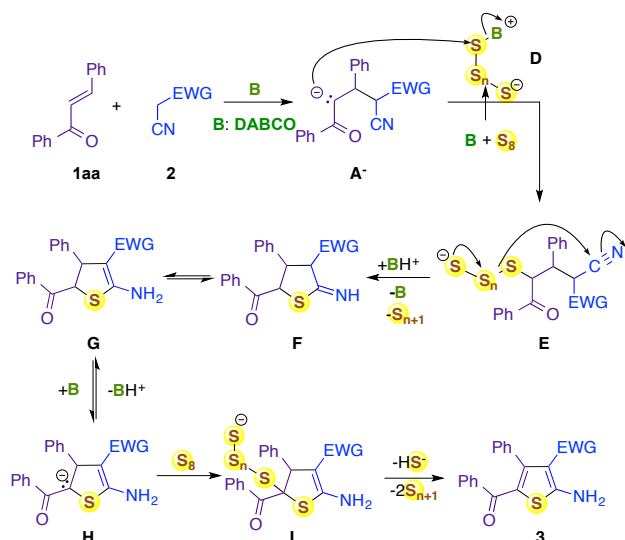
standard conditions catalyzed by DABCO (20 mol %) or piperidine in stoichiometric amount in reflux ethanol (Scheme 4).

While cyanoacetate **2b** suffered from degradation, **C1** remained unchanged and no trace of the expected condensed product **B1** could be observed.



**Scheme 4. Failed condensation of C1 with 2b**

Indeed, structural analysis of dibenzoylmethane **C1** showed that it exists in solution exclusively under enol form **C1'** as demonstrated by its  $^1\text{H}$  NMR spectra with a characteristic signal of enol C-H in common solvents such as  $\text{CDCl}_3$  or  $\text{DMSO-}d_6$  (6.89 ppm and 7.36 ppm respectively, see experimental). X-ray analysis of its structure confirmed once again its enol form stabilized by intramolecular hydrogen bonding.<sup>7</sup> Due to this structural particularity, the electrophilicity of both carbonyl groups in dibenzoylmethane is significantly lower than that of a typical ketone.



**Scheme 5. Proposed reaction mechanism**

On the other hand, the formation of C-C bond by attack of  $\alpha$ -cyanoacetate **2** to chalcone **1aa** leading to Michael adduct **A** is more favorable than to dibenzoylmethane **C1** due to both steric and electronic reasons (Scheme 5). The sulfuration step of the methylene moiety of **A** was suggested to be initiated by a nucleophilic attack of anionic form **A**<sup>-</sup> to S<sub>8</sub>/DABCO adduct **D**. Subsequent cyclization of the resulting adduct **E** via nucleophilic attack of the sulfide moiety on the cyano group would provide tetrahydrothiophene **F** existing in an equilibrium with dihydrothiophene **G**. Finally, oxidative aromatization of **G** to 2-aminothiophene **3** would proceed via sulfur assisted dehydrogenation initiated by a deprotonation to yield **H**. This step is more favored with *cis*-**G** due to steric effect. Indeed, *trans*-**G** could be isolated in high yields from an incomplete reaction mixture as the single diastereomer (Scheme 2).

In conclusion, we have proposed and realized a one-pot, two-step, three-component approach to Gewald 2-aminothiophenes derived from dibenzoylmethanes. While unobtainable via traditional Gewald method due to intrinsic low electrophilicity of the carbonyl moieties of dibenzoylmethanes, the expected 2-aminothiophenes products are now readily synthesized via reactions of  $\alpha$ -cyanoacetates with chalcones and elemental sulfur. The regiochemistry is readily controllable by simply choosing suitable chalcones. Moreover, the reactions conditions tolerate many functional groups as well as heterocycles. Most of the products were yielded with excellent atom efficiency and could be easily isolated in good yields by simple trituration with methanol and filtration. Based on these results, we believe that this strategy providing easy access to a library of densely functionalized 2-aminothiophenes with promising bioactivities will be very useful for drug-design and development.

## Experimental Section

### General Information

Reagents were obtained from commercial supplier and used without further purification. Analytical thin layer chromatography (TLC) was purchased from Merck KGaA (silica gel 60 F254). Visualization of the chromatogram was performed by UV light (254 nm) or KMnO<sub>4</sub> or vanilline stains. Flash column chromatography was carried out using kieselgel 35-70  $\mu$ m particle sized silica gel (230-400 mesh). NMR Chemical shifts are reported in ( $\delta$ ) ppm relative to tetramethylsilane (TMS) with the residual

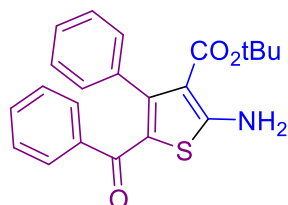
solvent as internal reference ( $\text{CDCl}_3$ ,  $\delta$  7.26 ppm for  $^1\text{H}$  and  $\delta$  77.0 ppm for  $^{13}\text{C}$ ). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants (Hz) and integration. Mass spectra were obtained using electron spray ionization (ESI). The HRMS data were measured on MALDI-TOF instrument. Chalcones **1** were known compounds, obtained from commercial supplier (**1aa**) or prepared according to previous literature report.<sup>9</sup> All compounds **2** were obtained from commercial supplier and used without further purification.

### General procedure

A mixture of chalcone **1** (1 mmol) nitrile **2** (1.05 mmol, 1.05 equiv), and DABCO (22 mg, 0.2 mmol, 20 mol %), and DMSO (0.2 mL, 3 mmol, 3 equiv) was stirred at 80 °C (aluminum block) for 30 min in a 7-mL tube. Sulfur (64 mg, 2 mmol, 2 equiv) was next added to the tube and the resulting mixture was stirred and heated at 80-100 °C (aluminum block) for 16 h. The reaction mixture was purified by trituration with methanol and filtration to afford the solid product (except for **3ata** and **3uga** which were purified by column chromatography on silica gel with eluent hexane:EtOAc 19:1).

### Characterization of the products

#### *tert*-Butyl 2-amino-5-benzoyl-4-phenylthiophene-3-carboxylate (**3aaa**)



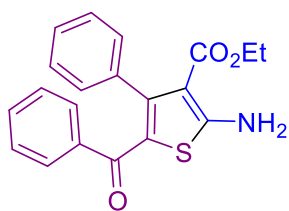
The reaction mixture was purified by trituration with methanol and filtration to afford the product as a pale yellow solid (299 mg, 75%).

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.30 – 7.21 (m, 2H), 7.20 – 7.10 (m, 1H), 7.07 – 6.91 (m, 7H), 6.68 (s, 2H), 1.08 (s, 9H).

$^{13}\text{C}$  { $^1\text{H}$ } NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  189.7, 166.8, 165.5, 148.3, 139.0, 136.7, 130.4, 129.8, 128.4, 127.3, 127.0, 127.0, 121.9, 110.4, 80.8, 27.7.

HRMS (ESI)  $m/z$ :  $[\text{M} + \text{Na}]^+$  Calcd for  $\text{C}_{22}\text{H}_{21}\text{NO}_3\text{SNa}$  402.1140; Found 402.1145.

#### Ethyl 2-amino-5-benzoyl-4-phenylthiophene-3-carboxylate (**3aab**)

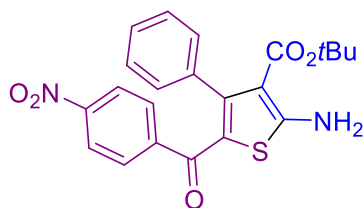


The reaction mixture was purified by trituration with methanol and filtration to afford the product as a pale yellow solid (193 mg, 55%).

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.31 (d,  $J = 7.4$  Hz, 2H), 7.18 (t,  $J = 7.4$  Hz, 1H), 7.03 (h,  $J = 8.0$  Hz, 8H), 6.83 (s, 2H-NH<sub>2</sub>), 3.95 (q,  $J = 7.1$  Hz, 2H), 0.80 (t,  $J = 7.1$  Hz, 3H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  189.8, 167.4, 165.8, 148.4, 138.9, 136.3, 130.5, 129.9 (2C), 128.4 (2C), 127.4 (2C), 127.2, 126.8 (2C), 122.2, 108.8, 59.8, 13.4.

HRMS (ESI)  $m/z$ :  $[\text{M} + \text{Na}]^+$  Calcd for  $\text{C}_{20}\text{H}_{17}\text{NO}_3\text{SNa}$  374.0827; Found 374.0833

***tert*-Butyl 2-amino-5-(4-nitrobenzoyl)-4-phenylthiophene-3-carboxylate (3aba)**



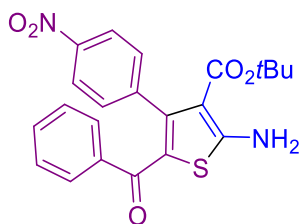
The reaction mixture was purified by trituration with methanol and filtration to afford the product as a pale yellow solid (313 mg, 74%).

$^1\text{H}$  NMR (500 MHz,  $\text{DMSO}-d_6$ )  $\delta$  8.36 (s, 2H-NH<sub>2</sub>), 7.80 (d,  $J = 8.7$  Hz, 2H), 7.28 (d,  $J = 8.6$  Hz, 2H), 7.02 – 6.87 (m, 5H), 1.00 (s, 9H).

$^{13}\text{C}\{^1\text{H}\}$  NMR (126 MHz,  $\text{DMSO}-d_6$ )  $\delta$  169.2, 164.8, 150.5, 147.6, 145.9, 136.4, 130.2 (2C), 129.1 (2C), 127.4, 127.2 (2C), 122.7 (2C), 120.4, 109.3, 80.2, 27.8.

HRMS (ESI)  $m/z$ :  $[\text{M} + \text{Na}]^+$  Calcd for  $\text{C}_{22}\text{H}_{20}\text{N}_2\text{O}_5\text{SNa}$  447.0991; Found 447.0993.

***tert*-Butyl 2-amino-5-benzoyl-4-(4-nitrophenyl)thiophene-3-carboxylate (3baa)**



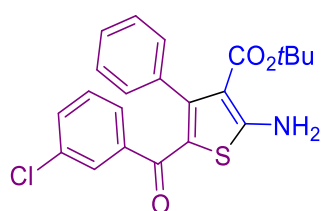
The reaction mixture was purified by trituration with methanol and filtration to afford the product as a pale yellow solid (297 mg, 70%).

$^1\text{H}$  NMR (500 MHz,  $\text{DMSO-}d_6$ )  $\delta$  8.26 (s, 2H-NH<sub>2</sub>), 7.97 – 7.86 (m, 2H), 7.36 – 7.30 (m, 2H), 7.30 – 7.20 (m, 3H), 7.12 (dd,  $J = 8.2, 7.3$  Hz, 2H), 1.03 (s, 9H).

$^{13}\text{C}\{^1\text{H}\}$  NMR (126 MHz,  $\text{DMSO-}d_6$ )  $\delta$  188.2, 168.4, 164.5, 146.6, 146.4, 145.0, 139.7, 131.4 (2C), 130.8, 128.3 (2C), 128.0 (2C), 122.3 (2C), 120.0, 108.3, 80.6, 44.6, 27.7.

HRMS (ESI)  $m/z$ :  $[\text{M} + \text{Na}]^+$  Calcd for  $\text{C}_{22}\text{H}_{20}\text{N}_2\text{O}_5\text{SNa}$  447.0991; Found 447.0995.

***tert*-Butyl 2-amino-5-(3-chlorobenzoyl)-4-phenylthiophene-3-carboxylate (3aca)**



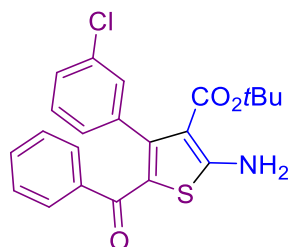
The reaction mixture was purified by trituration with methanol and filtration to afford the product as a pale yellow solid (297 mg, 72%).

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.13 (d,  $J = 7.7$  Hz, 1H), 7.11 (s, 1H), 7.08 (d,  $J = 8.0$  Hz, 1H), 7.06 – 7.00 (m, 3H), 7.00 – 6.93 (m, 3H), 6.74 (s, 2H), 1.08 (s, 9H).

$^{13}\text{C}\{^1\text{H}\}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  188.3, 167.3, 165.3, 149.0, 140.6, 136.4, 133.2, 130.2, 129.6 (2C), 128.8, 128.5, 127.3, 127.0 (2C), 126.1, 121.8, 110.5, 80.9, 27.7.

HRMS (ESI)  $m/z$ :  $[\text{M} + \text{Na}]^+$  Calcd for  $\text{C}_{22}\text{H}_{20}\text{ClNO}_3\text{SNa}$  436.0750; Found 436.0755.

***tert*-Butyl 2-amino-5-benzoyl-4-(3-chlorophenyl)thiophene-3-carboxylate (3caa)**



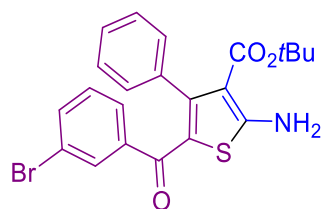
The reaction mixture was purified by trituration with methanol and filtration to afford the product as a pale yellow solid (285 mg, 69%).

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.30 – 7.25 (m, 2H), 7.23 – 7.17 (m, 1H), 7.09 (t,  $J = 7.7$  Hz, 2H), 7.03 (t,  $J = 1.7$  Hz, 1H), 7.00 (dt,  $J = 7.9, 1.6$  Hz, 1H), 6.91 (t,  $J = 7.8$  Hz, 1H), 6.85 (dt,  $J = 7.6, 1.3$  Hz, 1H), 6.72 (s, 2H), 1.13 (s, 9H).

$^{13}\text{C}\{^1\text{H}\}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  189.5, 167.0, 165.2, 146.3, 138.9, 138.5, 132.8, 130.7, 130.1, 128.3, 128.2 (2C), 127.9, 127.4 (2C), 127.0, 122.1, 110.0, 81.0, 27.8.

HRMS (ESI)  $m/z$ :  $[\text{M} + \text{Na}]^+$  Calcd for  $\text{C}_{22}\text{H}_{20}\text{ClNO}_3\text{SNa}$  436.0750; Found 436.0752.

***tert*-Butyl 2-amino-5-(3-bromobenzoyl)-4-phenylthiophene-3-carboxylate (3ada)**



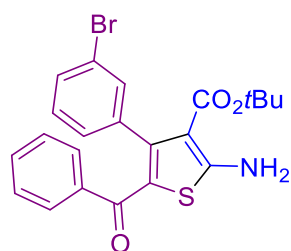
The reaction mixture was purified by trituration with methanol and filtration to afford the product as a pale yellow solid (297 mg, 65%).

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.46 (t,  $J = 6.8$  Hz, 2H), 7.36 (d,  $J = 6.9$  Hz, 1H), 7.31 (d,  $J = 8.0$  Hz, 2H), 7.21 (d,  $J = 8.0$  Hz, 2H), 7.00 (s, 2H), 6.67 (s, 2H), 1.09 (s, 9H).

$^{13}\text{C}\{^1\text{H}\}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  189.3, 166.8, 165.5, 148.3, 143.0, 140.5, 137.7, 136.8, 129.9 (2C), 128.9, 128.8, 127.7, 127.1, 127.0, 126.9, 126.1, 122.2, 110.4, 80.8, 27.7.

HRMS (ESI)  $m/z$ :  $[\text{M} + \text{Na}]^+$  Calcd for  $\text{C}_{22}\text{H}_{20}\text{BrNO}_3\text{SNa}$  480.0245; Found 480.0243.

***tert*-Butyl 2-amino-5-benzoyl-4-(3-bromophenyl)thiophene-3-carboxylate (3daa)**



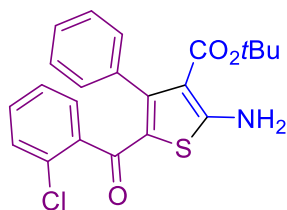
The reaction mixture was purified by trituration with methanol and filtration to afford the product as a pale yellow solid (288 mg, 63%).

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.29 – 7.25 (m, 2H), 7.24 – 7.18 (m, 2H), 7.14 (ddd,  $J = 7.9, 1.9, 1.2$  Hz, 1H), 7.11 – 7.06 (m, 2H), 6.89 (dt,  $J = 7.6, 1.3$  Hz, 1H), 6.84 (t,  $J = 7.8$  Hz, 1H), 6.70 (s, 2H), 1.13 (s, 9H).

$^{13}\text{C}\{^1\text{H}\}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  189.5, 166.9, 165.2, 146.2, 138.9, 138.7, 132.9, 130.7, 129.9, 128.5, 128.3, 128.2 (2C), 127.5 (2C), 122.1, 121.0, 110.0, 81.1, 27.8.

HRMS (ESI)  $m/z$ :  $[\text{M} + \text{Na}]^+$  Calcd for  $\text{C}_{22}\text{H}_{20}\text{BrNO}_3\text{SNa}$  480.0245; Found 480.0248.

***tert*-Butyl 2-amino-5-(2-chlorobenzoyl)-4-phenylthiophene-3-carboxylate (3aea)**



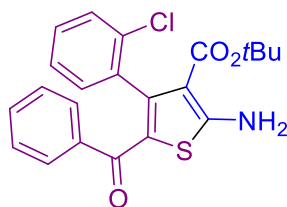
The reaction mixture was purified by trituration with methanol and filtration to afford the product as a pale yellow solid (260 mg, 63%).

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.00 – 6.90 (m, 5H), 6.88 – 6.83 (m, 4H), 1.01 (s, 9H).

$^{13}\text{C}\{^1\text{H}\}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  187.3, 168.3, 165.3, 150.0, 139.5, 135.8, 130.4, 129.6, 129.1, 128.8 (2C), 128.5, 127.0, 126.8 (2C), 125.9, 122.9, 111.0, 80.7, 27.6.

HRMS (ESI)  $m/z$ :  $[\text{M} + \text{Na}]^+$  Calcd for  $\text{C}_{22}\text{H}_{20}\text{ClNO}_3\text{SNa}$  436.0750; Found 436.0758.

***tert*-Butyl 2-amino-5-benzoyl-4-(2-chlorophenyl)thiophene-3-carboxylate (3eaa)**



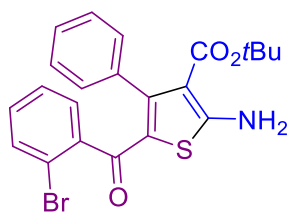
The reaction mixture was purified by trituration with methanol and filtration to afford the product as a pale yellow solid (248 mg, 60%).

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.35 (dq,  $J = 4.8, 1.3, 0.0$  Hz, 2H), 7.17 (t,  $J = 7.4$  Hz, 1H), 7.12 (d,  $J = 8.0$  Hz, 1H), 7.07 (t,  $J = 7.6$  Hz, 2H), 6.96 (td,  $J = 7.8, 1.9$  Hz, 1H), 6.89 (dd,  $J = 7.6, 1.8$  Hz, 1H), 6.87 – 6.82 (m, 1H), 6.72 (s, 2H), 1.10 (s, 9H).

$^{13}\text{C}\{^1\text{H}\}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  189.4, 166.6, 165.2, 144.6, 139.2, 136.3, 133.7, 131.3, 130.6, 128.6, 128.5, 127.9 (2C), 127.4 (2C), 125.6, 122.4, 110.1, 80.7, 27.7.

HRMS (ESI)  $m/z$ :  $[\text{M} + \text{Na}]^+$  Calcd for  $\text{C}_{22}\text{H}_{20}\text{ClNO}_3\text{SNa}$  436.0750; Found 436.0755.

***tert*-Butyl 2-amino-5-(2-bromobenzoyl)-4-phenylthiophene-3-carboxylate (3afa)**



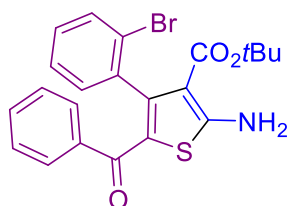
The reaction mixture was purified by trituration with methanol and filtration to afford the product as a pale yellow solid (265 mg, 58%).

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.16 (dd,  $J = 7.7, 1.3$  Hz, 1H), 7.00 – 6.96 (m, 2H), 6.94 – 6.87 (m, 6H), 6.86 (dd,  $J = 4.6, 2.2$  Hz, 1H), 6.82 (dd,  $J = 4.4, 2.2$  Hz, 1H), 1.01 (s, 9H).

$^{13}\text{C}\{^1\text{H}\}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  188.1, 168.4, 165.3, 150.0, 141.3, 135.8, 129.7, 128.8 (2C), 128.6, 127.0, 126.8 (2C), 126.4, 122.5, 119.3, 111.0, 80.7, 27.6.

HRMS (ESI)  $m/z$ :  $[\text{M} + \text{Na}]^+$  Calcd for  $\text{C}_{22}\text{H}_{20}\text{BrNO}_3\text{SNa}$  480.0245; Found 480.0252.

***tert*-Butyl 2-amino-5-benzoyl-4-(2-bromophenyl)thiophene-3-carboxylate (3faa)**



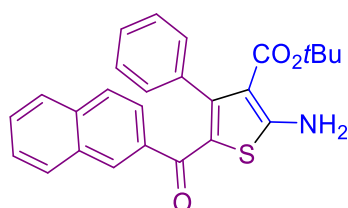
The reaction mixture was purified by trituration with methanol and filtration to afford the product as a pale yellow solid (251 mg, 55%).

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.41 – 7.36 (m, 2H), 7.32 (dt,  $J = 7.5, 1.0$  Hz, 1H), 7.22 – 7.14 (m, 1H), 7.08 (t,  $J = 7.7$  Hz, 2H), 6.93 – 6.84 (m, 3H), 6.71 (s, 2H), 1.10 (s, 9H).

$^{13}\text{C}\{^1\text{H}\}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  189.8, 166.6, 165.1, 139.3, 138.2, 131.7, 131.3, 130.5, 128.6, 127.9 (2C), 127.4 (2C), 126.2, 110.0, 80.7, 27.7.

HRMS (ESI)  $m/z$ :  $[\text{M} + \text{Na}]^+$  Calcd for  $\text{C}_{22}\text{H}_{20}\text{BrNO}_3\text{SNa}$  480.0245; Found 480.0247.

***tert*-Butyl 5-(2-naphthoyl)-2-amino-4-phenylthiophene-3-carboxylate (3aga)**



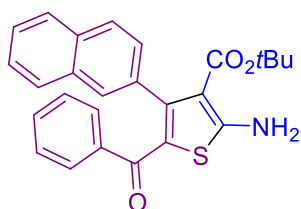
The reaction mixture was purified by trituration with methanol and filtration to afford the product as a pale yellow solid (321 mg, 75%).

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.78 (s, 1H), 7.69 (d,  $J = 8.1$  Hz, 1H), 7.64 (d,  $J = 8.2$  Hz, 1H), 7.52 (d,  $J = 8.5$  Hz, 1H), 7.47 – 7.43 (m, 1H), 7.42 (dd,  $J = 3.7, 1.5$  Hz, 1H), 7.41 – 7.39 (m, 1H), 7.06 – 6.97 (m, 2H), 6.84 (t,  $J = 7.7$  Hz, 2H), 6.76 – 6.70 (m, 1H), 6.66 (s, 2H), 1.08 (s, 9H).

$^{13}\text{C}\{^1\text{H}\}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  189.6, 166.8, 165.5, 148.4, 136.8, 136.2, 134.2, 131.7, 129.8, 129.5 (2C), 128.8, 127.5, 127.3, 127.3, 126.9 (2C), 126.7, 126.0, 124.7, 122.0, 110.4, 80.8, 27.7.

HRMS  $m/z$  calculated  $[\text{M}+\text{Na}]^+$ :  $\text{C}_{26}\text{H}_{23}\text{NO}_3\text{SNa}$  452.1296; Found 452.1299.

***tert*-Butyl 2-amino-5-benzoyl-4-(naphthalen-2-yl)thiophene-3-carboxylate (3gaa)**



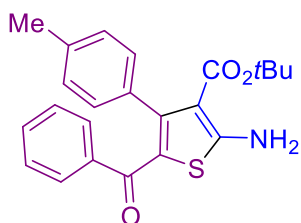
The reaction mixture was purified by trituration with methanol and filtration to afford the product as a pale yellow solid (300 mg, 70%).

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.66 (d,  $J = 7.9$  Hz, 1H), 7.58 – 7.48 (m, 2H), 7.42 – 7.31 (m, 3H), 7.24 – 7.13 (m, 3H), 6.87 – 6.75 (m, 3H), 6.72 (s, 2H), 0.96 (s, 9H).

$^{13}\text{C}\{^1\text{H}\}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  189.9, 167.0, 165.4, 148.3, 139.0, 134.1, 132.4, 129.9, 129.1, 127.9 (2C), 127.6, 127.2, 127.1 (2C), 126.3, 125.7, 125.6, 122.3, 110.3, 80.9, 27.7.

HRMS (ESI)  $m/z$ :  $[\text{M} + \text{Na}]^+$  Calcd for  $\text{C}_{26}\text{H}_{23}\text{NO}_3\text{SNa}$  452.1296; Found 452.1302.

***tert*-Butyl 2-amino-5-benzoyl-4-(*p*-tolyl)thiophene-3-carboxylate (3haa)**



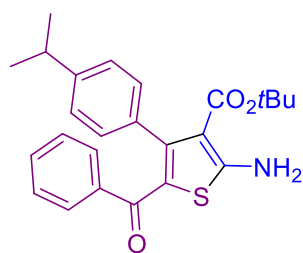
The reaction mixture was purified by trituration with methanol and filtration to afford the product as a pale yellow solid (303 mg, 77%).

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ) 7.25 (d,  $J = 7.6$  Hz, 2H), 7.16 (t,  $J = 7.4$  Hz, 1H), 7.04 (t,  $J = 7.6$  Hz, 2H), 6.92 (dt,  $J = 8.1, 4.1$  Hz, 1H), 6.86 (d,  $J = 7.5$  Hz, 1H), 6.83 (d,  $J = 3.8$  Hz, 2H), 6.71 (s, 2H), 2.10 (s, 3H), 1.05 (s, 9H).

$^{13}\text{C}\{^1\text{H}\}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  189.5, 167.1, 165.5, 148.2, 139.4, 136.9, 135.8, 130.2, 129.5, 129.0, 127.7 (2C), 127.3, 127.2 (2C), 124.6, 121.6, 110.2, 80.5, 27.7, 20.1.

HRMS (ESI)  $m/z$ :  $[\text{M} + \text{Na}]^+$  Calcd for  $\text{C}_{23}\text{H}_{23}\text{NO}_3\text{SNa}$  416.1296; Found 416.1298.

***tert*-Butyl 2-amino-5-benzoyl-4-(4-isopropylphenyl)thiophene-3-carboxylate (3iaa)**



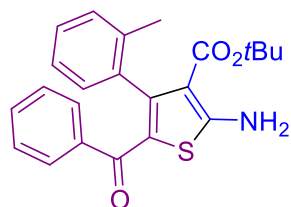
The reaction mixture was purified by trituration with methanol and filtration to afford the product as a pale yellow solid (311 mg, 74%).

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.20 (d,  $J = 7.2$  Hz, 2H), 7.10 (t,  $J = 7.4$  Hz, 1H), 6.97 (t,  $J = 7.7$  Hz, 2H), 6.86 (d,  $J = 8.1$  Hz, 2H), 6.81 (d,  $J = 8.1$  Hz, 2H), 6.69 (s, 2H), 2.71 (p,  $J = 6.9$  Hz, 1H), 1.11 (d,  $J = 6.9$  Hz, 6H), 1.08 (s, 9H).

$^{13}\text{C}\{^1\text{H}\}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  190.0, 167.0, 165.5, 148.8, 147.6, 139.1, 134.0, 130.1 (2C), 129.8 (2C), 128.3 (2C), 127.2(2C), 124.9 (2C), 122.2, 110.4, 80.7, 33.9, 27.7, 23.9.

HRMS (ESI)  $m/z$ :  $[\text{M} + \text{Na}]^+$  Calcd for  $\text{C}_{25}\text{H}_{27}\text{NO}_3\text{SNa}$  444.1609; Found 444.1615.

***tert*-Butyl 2-amino-5-benzoyl-4-(*o*-tolyl)thiophene-3-carboxylate (3jaa)**



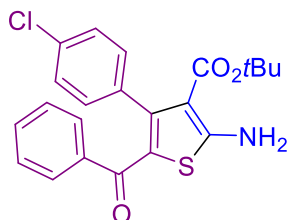
The reaction mixture was purified by trituration with methanol and filtration to afford the product as a pale yellow solid (248 mg, 63%).

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.25 (d,  $J = 7.9$  Hz, 2H), 7.17 (t,  $J = 7.4$  Hz, 1H), 7.01 (t,  $J = 7.7$  Hz, 2H), 6.86 (d,  $J = 8.0$  Hz, 2H), 6.79 (d,  $J = 7.9$  Hz, 2H), 6.60 (s, 2H), 2.18 (s, 3H), 1.11 (s, 9H).

$^{13}\text{C}\{^1\text{H}\}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  189.7, 166.7, 165.5, 148.6, 139.1, 136.6, 133.7, 130.0, 129.6 (2C), 128.4 (2C), 127.6 (2C), 127.3 (2C), 121.8, 110.5, 80.8, 27.7, 21.0.

HRMS (ESI)  $m/z$ :  $[\text{M} + \text{Na}]^+$  Calcd for  $\text{C}_{23}\text{H}_{23}\text{NO}_3\text{SNa}$  416.1296; Found 416.1301.

***tert*-Butyl 2-amino-5-benzoyl-4-(4-chlorophenyl)thiophene-3-carboxylate (3kaa)**



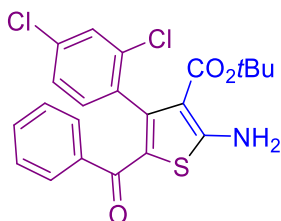
The reaction mixture was purified by trituration with methanol and filtration to afford the product as a pale yellow solid (280 mg, 68%).

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.33 – 7.19 (m, 3H), 7.08 (t,  $J = 7.7$  Hz, 2H), 6.99 (d,  $J = 8.4$  Hz, 2H), 6.93 (d,  $J = 8.4$  Hz, 2H), 6.68 (s, 2H), 1.13 (s, 9H).

$^{13}\text{C}\{^1\text{H}\}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  189.4, 166.9, 165.2, 146.9, 139.0, 135.3, 133.1, 131.0 (2C), 130.5, 128.3 (2C), 127.5 (2C), 127.1 (2C), 121.9, 109.8, 81.1, 27.8.

HRMS (ESI)  $m/z$ :  $[\text{M} + \text{Na}]^+$  Calcd for  $\text{C}_{22}\text{H}_{20}\text{ClNO}_3\text{SNa}$  436.0750; Found 436.0762.

***tert*-Butyl 2-amino-5-benzoyl-4-(2,4-dichlorophenyl)thiophene-3-carboxylate (3laa)**



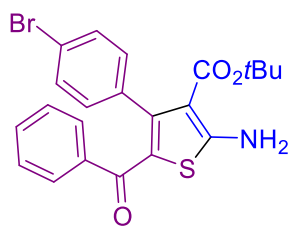
The reaction mixture was purified by trituration with methanol and filtration to afford the product as a pale yellow solid (457 mg, 57%).

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.35 (d,  $J = 7.2$  Hz, 2H), 7.27 (s, 1H), 7.16 (d,  $J = 1.8$  Hz, 1H), 7.13 (t,  $J = 7.7$  Hz, 2H), 6.85 (d,  $J = 1.8$  Hz, 1H), 6.82 (d,  $J = 8.2$  Hz, 1H), 6.73 (s, 2H), 1.15 (s, 9H).

$^{13}\text{C}\{^1\text{H}\}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  189.1, 166.8, 164.9, 143.4, 139.2, 135.0, 134.4, 133.7, 131.9, 130.6, 128.4, 127.8 (2C), 127.6 (2C), 125.9, 122.3, 109.9, 81.1, 27.7.

HRMS (ESI)  $m/z$ :  $[\text{M} + \text{Na}]^+$  Calcd for  $\text{C}_{22}\text{H}_{19}\text{Cl}_2\text{NO}_3\text{SNa}$  470.0360; Found 470.0367.

***tert*-Butyl 2-amino-5-benzoyl-4-(4-bromophenyl)thiophene-3-carboxylate (3maa)**



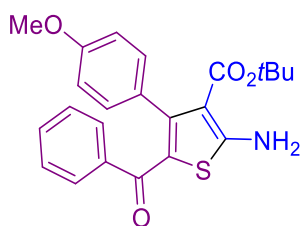
The reaction mixture was purified by trituration with methanol and filtration to afford the product as a pale yellow solid (279 mg, 61%).

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.25 (d,  $J = 8.1$  Hz, 3H), 7.14 (d,  $J = 8.3$  Hz, 2H), 7.08 (t,  $J = 7.8$  Hz, 2H), 6.87 (d,  $J = 8.3$  Hz, 2H), 6.67 (s, 2H), 1.13 (s, 9H).

$^{13}\text{C}\{^1\text{H}\}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  166.9, 165.2, 146.9, 139.0, 135.8, 131.3 (2C), 130.5, 130.1 (2C), 128.3 (2C), 127.6 (2C), 121.2, 110.1, 81.2, 27.8.

HRMS (ESI)  $m/z$ :  $[\text{M} + \text{Na}]^+$  Calcd for  $\text{C}_{22}\text{H}_{20}\text{BrNO}_3\text{SNa}$  480.0245; Found 480.0251.

***tert*-Butyl 2-amino-5-benzoyl-4-(4-methoxyphenyl)thiophene-3-carboxylate (3naa)**



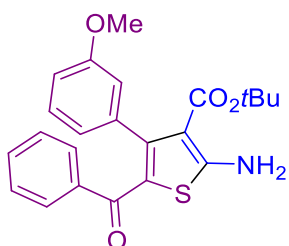
The reaction mixture was purified by trituration with methanol and filtration to afford the product as a pale yellow solid (335 mg, 82%).

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.34 (d,  $J = 8.8$  Hz, 2H), 7.05 (p,  $J = 6.4, 5.2$  Hz, 5H), 6.60 (s, 2H), 6.54 (d,  $J = 8.8$  Hz, 2H), 3.73 (s, 3H), 1.10 (s, 9H).

$^{13}\text{C}\{^1\text{H}\}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  188.4, 166.1, 165.5, 161.7, 147.2, 137.0, 131.4, 130.9 (2C), 129.8 (2C), 127.1 (2C), 126.9, 121.6, 112.7 (2C), 110.2, 80.7, 55.3, 27.7.

HRMS (ESI)  $m/z$ :  $[\text{M} + \text{Na}]^+$  Calcd for  $\text{C}_{23}\text{H}_{23}\text{NO}_4\text{SNa}$  432.1245; Found 432.1252.

***tert*-Butyl 2-amino-5-benzoyl-4-(3-methoxyphenyl)thiophene-3-carboxylate (3oaa)**



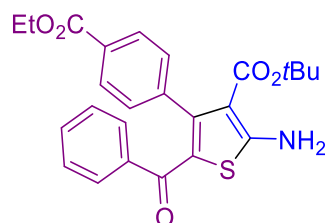
The reaction mixture was purified by trituration with methanol and filtration to afford the product as a pale yellow solid (315 mg, 77%).

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.30 – 7.22 (m, 2H), 7.16 (t,  $J = 7.4$  Hz, 1H), 7.02 (t,  $J = 7.7$  Hz, 2H), 6.92 (t,  $J = 7.9$  Hz, 1H), 6.73 (s, 2H-NH<sub>2</sub>), 6.61 (d,  $J = 7.5$  Hz, 1H), 6.55 (dd,  $J = 8.2, 2.3$  Hz, 1H), 6.50 (s, 1H), 3.62 (s, 3H), 1.11 (s, 9H).

$^{13}\text{C}\{^1\text{H}\}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  189.8, 167.0, 165.4, 158.4, 148.1, 139.1, 137.9, 130.4, 128.2 (2C), 128.0, 127.3 (2C), 122.6, 122.0, 115.3, 113.2, 110.3, 80.7, 55.2, 27.8.

HRMS (ESI)  $m/z$ :  $[\text{M} + \text{Na}]^+$  Calcd for  $\text{C}_{23}\text{H}_{23}\text{NO}_4\text{SNa}$  432.1245; Found 432.1248.

***tert*-Butyl 2-amino-5-benzoyl-4-(4-(ethoxycarbonyl)phenyl)thiophene-3-carboxylate (3paa)**



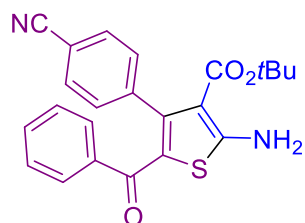
The reaction mixture was purified by trituration with methanol and filtration to afford the product as a pale yellow solid (320 mg, 71%).

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.72 (d,  $J = 8.3$  Hz, 2H), 7.28 (dd,  $J = 7.1, 1.2$  Hz, 2H), 7.18 (t,  $J = 7.5$  Hz, 1H), 7.09 (d,  $J = 8.3$  Hz, 2H), 7.04 (t,  $J = 7.7$  Hz, 2H), 6.77 (s, 2H-NH<sub>2</sub>), 4.34 (q,  $J = 7.1$  Hz, 2H), 1.37 (t,  $J = 7.1$  Hz, 3H), 1.07 (s, 9H).

$^{13}\text{C}\{^1\text{H}\}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  189.2, 167.0, 166.4, 165.1, 147.1, 141.9, 139.0, 130.7, 129.7 (2C), 128.9, 128.32 (2C), 128.27 (2C), 127.5 (2C), 121.5, 110.0, 81.1, 60.9, 27.7, 14.3.

HRMS (ESI)  $m/z$ :  $[\text{M} + \text{Na}]^+$  Calcd for  $\text{C}_{25}\text{H}_{25}\text{NO}_5\text{SNa}$  474.1351; Found 474.1357.

***tert*-Butyl 2-amino-5-benzoyl-4-(4-cyanophenyl)thiophene-3-carboxylate (3qaa)**



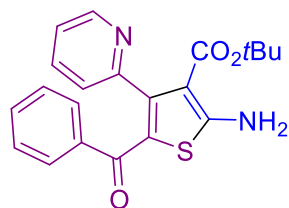
The reaction mixture was purified by trituration with methanol and filtration to afford the product as a pale yellow solid (323 mg, 80%).

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.36 (d,  $J = 8.1$  Hz, 2H), 7.29 (d,  $J = 7.7$  Hz, 3H), 7.15 (d,  $J = 8.1$  Hz, 2H), 7.11 (t,  $J = 7.8$  Hz, 2H), 6.74 (s, 2H-NH<sub>2</sub>), 1.10 (s, 9H).

$^{13}\text{C}$  { $^1\text{H}$ } NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  188.8, 167.0, 164.8, 145.8, 142.3, 138.9, 131.1, 130.8 (2C), 130.4 (2C), 128.3 (2C), 127.7 (2C), 121.5, 118.8, 110.6, 109.8, 81.4, 27.8.

HRMS (ESI)  $m/z$ :  $[\text{M} + \text{Na}]^+$  Calcd for  $\text{C}_{23}\text{H}_{20}\text{N}_2\text{O}_3\text{SNa}$  427.1092; Found 427.1097.

***tert*-Butyl 2-amino-5-benzoyl-4-(pyridin-2-yl)thiophene-3-carboxylate (3raa)**



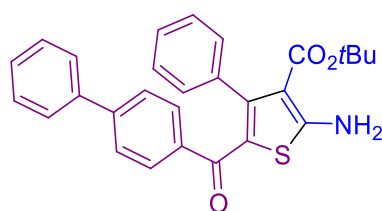
Brown solid (197 mg, 52%).

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.44 (dd,  $J = 3.5, 1.8$  Hz, 1H), 7.32 (d,  $J = 7.5$  Hz, 2H), 7.29 (t,  $J = 8.4, 6.8$  Hz, 1H), 7.18 (t,  $J = 7.4$  Hz, 1H), 7.07 (t,  $J = 7.7$  Hz, 2H), 6.98 (dd,  $J = 7.6, 3.7$  Hz, 2H), 6.76 (s, 2H-NH<sub>2</sub>), 1.08 (s, 9H).

$^{13}\text{C}$  { $^1\text{H}$ } NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  188.9, 167.1, 165.0, 155.4, 148.2, 139.1, 135.0, 130.5, 128.4 (2C), 127.5 (2C), 125.2, 122.5, 122.0, 110.3, 80.7, 27.8.

HRMS (ESI)  $m/z$ :  $[\text{M} + \text{Na}]^+$  Calcd for  $\text{C}_{21}\text{H}_{20}\text{N}_2\text{O}_3\text{SNa}$  403.1092; Found 403.1098.

***tert*-Butyl 5-([1,1'-biphenyl]-4-carbonyl)-2-amino-4-phenylthiophene-3-carboxylate (3asa)**



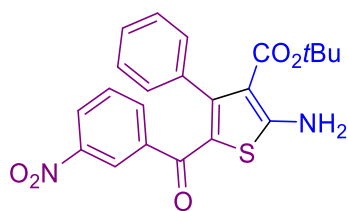
The reaction mixture was purified by trituration with methanol and filtration to afford the product as a pale yellow solid (355 mg, 78%).

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.27 (t,  $J = 8.7$  Hz, 2H), 7.21 (d,  $J = 7.5$  Hz, 1H), 7.09 – 6.98 (m, 5H), 6.93 (t,  $J = 7.7$  Hz, 1H), 6.78 (s, 2H-NH<sub>2</sub>), 1.11 (s, 9H).

$^{13}\text{C}$  { $^1\text{H}$ } NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  188.2, 167.3, 165.3, 149.0, 140.8, 136.3, 133.1, 131.4, 129.6 (2C), 129.0, 127.3, 127.1 (2C), 126.5, 121.8, 121.3, 110.5, 80.9, 27.7.

HRMS (ESI)  $m/z$ :  $[\text{M} + \text{Na}]^+$  Calcd for  $\text{C}_{28}\text{H}_{25}\text{NO}_3\text{SNa}$  478.1453; Found 478.1457.

***tert*-Butyl 2-amino-5-(3-nitrobenzoyl)-4-phenylthiophene-3-carboxylate (3ata)**



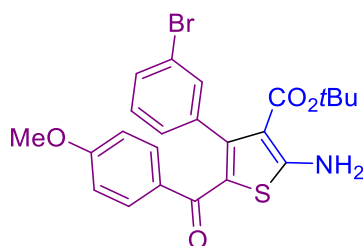
The crude mixture was purified by column chromatography on silica gel (hexane:AcOEt 19:1) to afford the product as a brown yellow solid (229 mg, 54%).

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.94 (ddd,  $J = 8.2, 2.3, 1.1$  Hz, 1H), 7.87 – 7.81 (m, 1H), 7.58 (dt,  $J = 7.6, 1.3$  Hz, 1H), 7.23 (t,  $J = 7.9$  Hz, 1H), 6.98 – 6.94 (m, 2H), 6.92 (td,  $J = 4.9, 4.5, 1.5$  Hz, 3H), 6.88 (s, 2H-NH<sub>2</sub>), 1.06 (s, 9H).

$^{13}\text{C}\{^1\text{H}\}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  187.2, 168.0, 165.2, 149.6, 146.7, 140.3, 136.2, 135.5, 129.9 (2C), 128.6, 127.4, 127.1 (2C), 124.5, 123.6, 110.6, 81.1, 27.7.

HRMS (ESI)  $m/z$ :  $[\text{M} + \text{Na}]^+$  Calcd for  $\text{C}_{22}\text{H}_{20}\text{N}_2\text{O}_5\text{SNa}$  447.0991; Found 447.0997.

***tert*-Butyl 2-amino-4-(3-bromophenyl)-5-(4-methoxybenzoyl)thiophene-3-carboxylate (3dna)**



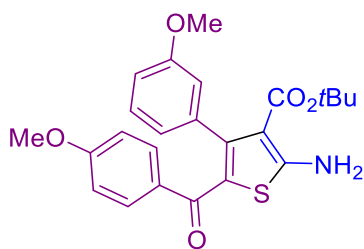
The reaction mixture was purified by trituration with methanol and filtration to afford the product as a pale yellow solid (316 mg, 65%).

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.33 (d,  $J = 8.7$  Hz, 2H), 7.24 (s, 1H), 7.19 (d,  $J = 7.7$  Hz, 1H), 6.93 (d,  $J = 7.6$  Hz, 1H), 6.89 (t,  $J = 7.6$  Hz, 1H), 6.63 (s, 2H-NH<sub>2</sub>), 6.61 (d,  $J = 8.7$  Hz, 2H), 3.77 (s, 3H), 1.15 (s, 9H).

$^{13}\text{C}\{^1\text{H}\}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  188.3, 166.3, 165.2, 161.9, 139.1, 133.0, 131.3, 130.8 (2C), 129.8, 128.6, 128.4, 121.0, 112.9 (2C), 109.7, 81.0, 55.4, 27.8.

HRMS (ESI)  $m/z$ :  $[\text{M} + \text{Na}]^+$  Calcd for  $\text{C}_{23}\text{H}_{22}\text{BrNO}_4\text{SNa}$  510.0351; Found 510.0353.

***tert*-Butyl 2-amino-5-(4-methoxybenzoyl)-4-(3-methoxyphenyl)thiophene-3-carboxylate (3ona)**



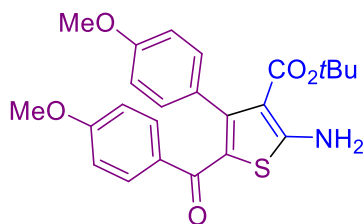
The reaction mixture was purified by trituration with methanol and filtration to afford the product as a pale yellow solid (263 mg, 60%).

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.39 – 7.31 (m, 2H), 6.97 (t,  $J = 7.9$  Hz, 1H), 6.69 (s, 2H-NH<sub>2</sub>), 6.65 (d,  $J = 7.6$  Hz, 1H), 6.60 (dd,  $J = 8.2, 2.0$  Hz, 1H), 6.57 – 6.49 (m, 2H), 3.73 (s, 3H), 3.64 (s, 3H), 1.12 (s, 9H).

$^{13}\text{C}\{^1\text{H}\}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  188.6, 166.4, 165.4, 161.7, 158.5, 147.1, 138.2, 131.5, 130.7 (2C), 128.1, 122.7, 121.6, 115.4, 113.0, 112.7 (2C), 110.0, 80.7, 55.3, 55.2, 27.8.

HRMS (ESI)  $m/z$ :  $[\text{M} + \text{Na}]^+$  Calcd for  $\text{C}_{24}\text{H}_{25}\text{NO}_5\text{SNa}$  462.1351; Found 462.1358.

***tert*-Butyl 2-amino-5-(4-methoxybenzoyl)-4-(4-methoxyphenyl)thiophene-3-carboxylate (3na)**



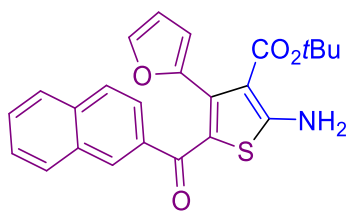
The reaction mixture was purified by trituration with methanol and filtration to afford the product as a pale yellow solid (246 mg, 56%).

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.31 (d,  $J = 8.6$  Hz, 2H), 6.93 (d,  $J = 8.5$  Hz, 2H), 6.59 (s, 2H-NH<sub>2</sub>), 6.58 (d,  $J = 8.5$  Hz, 2H), 6.55 (d,  $J = 8.6$  Hz, 2H), 3.73 (s, 3H), 3.69 (s, 3H), 1.15 (s, 9H).

$^{13}\text{C}\{^1\text{H}\}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  188.6, 166.2, 165.5, 161.6, 158.8, 147.2, 131.5, 131.1 (2C), 130.9 (2C), 129.4, 121.7, 112.7 (2C), 112.6 (2C), 110.1, 80.7, 55.3, 27.9.

HRMS (ESI)  $m/z$ :  $[\text{M} + \text{Na}]^+$  Calcd for  $\text{C}_{24}\text{H}_{25}\text{NO}_5\text{SNa}$  462.1351; Found 462.1357.

***tert*-Butyl 5-(2-naphthoyl)-2-amino-4-(furan-2-yl)thiophene-3-carboxylate (3uga)**



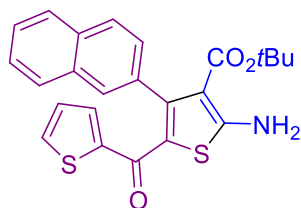
The product was purified by column chromatography on silica gel (hexane:AcOEt 19:1). Pale yellow solid (201 mg, 48%).

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.86 (d,  $J = 1.6$  Hz, 1H), 7.72 (d,  $J = 8.1$  Hz, 1H), 7.69 (d,  $J = 8.1$  Hz, 1H), 7.59 (d,  $J = 8.5$  Hz, 1H), 7.46 (dd,  $J = 8.5, 1.7$  Hz, 1H), 7.43 – 7.40 (m, 1H), 7.38 (ddd,  $J = 8.1, 6.8, 1.4$  Hz, 1H), 7.01 – 6.78 (m, 1H), 6.58 (s, 2H-NH<sub>2</sub>), 5.78 (dd,  $J = 3.4, 0.8$  Hz, 1H), 5.71 – 5.49 (m, 1H), 1.22 (s, 9H).

$^{13}\text{C}\{^1\text{H}\}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  189.4, 166.2, 165.1, 146.4, 141.7, 136.0, 134.5, 132.2, 129.4, 129.0, 127.6, 127.5, 127.4, 126.2, 124.5, 115.9, 112.2, 110.4, 109.7, 80.9, 28.2.

HRMS (ESI)  $m/z$ :  $[\text{M} + \text{Na}]^+$  Calcd for  $\text{C}_{24}\text{H}_{21}\text{NO}_4\text{SNa}$  442.1089; Found 442.1093.

***tert*-Butyl 2-amino-4-(naphthalen-2-yl)-5-(thiophene-2-carbonyl)thiophene-3-carboxylate (3gva)**



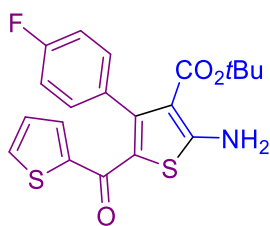
Brown solid (261 mg, 60%).

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.78 (dd,  $J = 6.1, 2.9$  Hz, 1H), 7.75 – 7.67 (m, 2H), 7.62 (s, 1H), 7.45 – 7.41 (m, 2H), 7.38 (dd,  $J = 8.4, 1.7$  Hz, 1H), 7.28 (ddd,  $J = 11.8, 4.4, 1.0$  Hz, 2H), 6.67 (dd,  $J = 4.9, 3.9$  Hz, 1H), 6.63 (s, 2H-NH<sub>2</sub>), 0.99 (s, 9H).

$^{13}\text{C}\{^1\text{H}\}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  179.8, 165.7, 165.4, 147.7, 144.0, 134.9, 132.8, 132.5, 132.5, 132.0, 128.1, 127.9, 127.8, 127.5, 126.9, 126.6, 125.8, 125.7, 119.5, 110.5, 81.0, 27.7.

HRMS (ESI)  $m/z$ :  $[\text{M} + \text{Na}]^+$  Calcd for  $\text{C}_{24}\text{H}_{21}\text{NO}_3\text{S}_2\text{Na}$  458.0861; Found 458.0866.

***tert*-Butyl 2-amino-4-(4-fluorophenyl)-5-(thiophene-2-carbonyl)thiophene-3-carboxylate (3xva)**



Brown solid (262 mg, 65%).

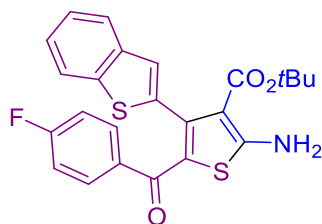
$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.45 (dd,  $J = 4.9, 0.9$  Hz, 1H), 7.29 (dd,  $J = 3.8, 0.9$  Hz, 1H), 7.18 – 7.09 (m, 2H), 6.92 (t,  $J = 8.7$  Hz, 2H), 6.85 (dd,  $J = 4.8, 3.9$  Hz, 1H), 6.65 (s, 2H-NH<sub>2</sub>), 1.16 (s, 6H).

$^{13}\text{C}\{^1\text{H}\}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  179.55, 165.79, 165.26, 162.21 (d,  $J = 246.1$  Hz), 146.74, 144.15, 133.41 (d,  $J = 3.4$  Hz), 132.72, 132.38, 130.91 (d,  $J = 8.1$  Hz), 127.17, 119.12, 114.25 (d,  $J = 21.6$  Hz), 110.26, 27.84.

$^{19}\text{F}$  NMR (471 MHz,  $\text{CDCl}_3$ )  $\delta$  -115.30.

HRMS (ESI)  $m/z$ :  $[\text{M} + \text{Na}]^+$  Calcd for  $\text{C}_{20}\text{H}_{18}\text{FNO}_3\text{S}_2\text{Na}$  426.0610; Found 426.0617.

***tert*-Butyl 2-amino-4-(benzo[b]thiophen-2-yl)-5-(4-fluorobenzoyl)thiophene-3-carboxylate (3yxa)**



Brown solid (281 mg, 62%).

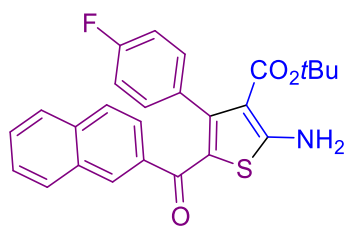
$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.77 (d,  $J = 8.3$  Hz, 1H), 7.67 (d,  $J = 7.9$  Hz, 1H), 7.52 (s, 1H), 7.38 (q,  $J = 1.5$  Hz, 1H), 7.35 – 7.30 (m, 1H), 7.18 (dd,  $J = 8.7, 5.4$  Hz, 2H), 6.89 (t,  $J = 8.8$  Hz, 2H), 6.67 (s, 2H-NH<sub>2</sub>), 1.17 (s, 9H).

$^{13}\text{C}\{^1\text{H}\}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  180.47, 166.09, 165.24, 162.21 (d,  $J = 246.4$  Hz), 147.30, 143.60, 141.66, 138.68, 133.40 (d,  $J = 3.4$  Hz), 130.77 (d,  $J = 8.1$  Hz), 129.68, 126.79, 125.41, 124.78, 122.60, 119.03, 114.32 (d,  $J = 21.6$  Hz), 110.52, 81.17, 27.84.

$^{19}\text{F}$  NMR (471 MHz,  $\text{CDCl}_3$ )  $\delta$  -115.15.

HRMS (ESI)  $m/z$ :  $[\text{M} + \text{Na}]^+$  Calcd for  $\text{C}_{24}\text{H}_{20}\text{FNO}_3\text{S}_2\text{Na}$  476.0766; Found 476.0769.

***tert*-Butyl 5-(2-naphthoyl)-2-amino-4-(4-fluorophenyl)thiophene-3-carboxylate (3axg)**



The reaction mixture was purified by trituration with methanol and filtration to afford the product as a pale yellow solid (313 mg, 70%).

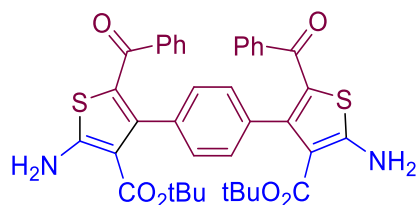
$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.77 (d,  $J = 8.3$  Hz, 1H), 7.67 (d,  $J = 7.9$  Hz, 1H), 7.52 (s, 1H), 7.38 (q,  $J = 1.5$  Hz, 1H), 7.35 – 7.30 (m, 1H), 7.18 (dd,  $J = 8.7, 5.4$  Hz, 2H), 6.89 (t,  $J = 8.8$  Hz, 2H), 6.67 (s, 2H-NH<sub>2</sub>), 1.17 (s, 9H).

$^{13}\text{C}\{^1\text{H}\}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  180.47, 166.09, 165.24, 162.21 (d,  $J = 246.4$  Hz), 147.30, 143.60, 141.66, 138.68, 133.40, 130.77 (d,  $J = 8.1$  Hz) (2C), 129.68, 126.79, 125.41, 124.78, 122.60, 119.03, 114.32 (d,  $J = 21.6$  Hz) (2C), 110.52, 81.17, 27.84.

$^{19}\text{F}$  NMR (471 MHz,  $\text{CDCl}_3$ )  $\delta$  -115.57.

HRMS (ESI)  $m/z$ :  $[\text{M} + \text{Na}]^+$  Calcd for  $\text{C}_{26}\text{H}_{22}\text{FNO}_3\text{SNa}$  470.1202; Found 470.1206.

#### Di-*tert*-butyl 4,4'-(1,4-phenylene)bis(2-amino-5-benzoylthiophene-3-carboxylate) (3za)



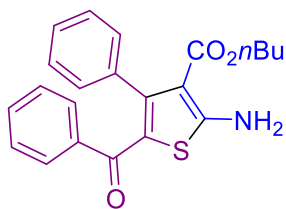
The reaction mixture was purified by trituration with methanol and filtration to afford the product as a pale yellow solid (459 mg, 65%).

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.71 (d,  $J = 6.9$  Hz, 4H), 7.41 – 7.31 (m, 10H), 6.44 (s, 4H-NH<sub>2</sub>), 1.41 (s, 18H).

$^{13}\text{C}\{^1\text{H}\}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  188.0, 164.8, 164.5, 147.5, 139.3, 134.9, 131.8 (2C), 129.1 (4C), 129.0 (4C), 127.9 (4C), 119.8, 110.5, 81.6, 28.2.

HRMS (ESI)  $m/z$ :  $[\text{M} + \text{Na}]^+$  Calcd for  $\text{C}_{38}\text{H}_{36}\text{N}_2\text{O}_6\text{S}_2\text{Na}$  703.1912; Found 730.1921.

#### Butyl 2-amino-5-benzoyl-4-phenylthiophene-3-carboxylate (3aac)



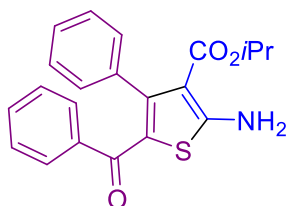
The reaction mixture was purified by trituration with methanol and filtration to afford the product as a pale yellow solid (273 mg, 72%).

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.27 (dt,  $J = 8.5, 1.5$  Hz, 2H), 7.19 – 7.09 (m, 1H), 7.08 – 6.89 (m, 7H), 6.77 (s, 2H-NH<sub>2</sub>), 3.89 (t,  $J = 6.4$  Hz, 2H), 1.10 (dq,  $J = 8.2, 6.5$  Hz, 2H), 0.85 (dt,  $J = 14.5, 7.4$  Hz, 2H), 0.68 (t,  $J = 7.3$  Hz, 3H).

$^{13}\text{C}\{^1\text{H}\}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  189.8, 167.3, 166.1, 148.1, 138.8, 136.2, 130.5, 129.9, 128.4, 127.4, 127.2, 126.8, 122.3, 108.8, 63.9, 30.1, 18.9, 13.6.

HRMS (ESI)  $m/z$ :  $[\text{M} + \text{Na}]^+$  Calcd for  $\text{C}_{22}\text{H}_{21}\text{NO}_3\text{SNa}$  402.1140; Found 402.1150.

#### Isopropyl 2-amino-5-benzoyl-4-phenylthiophene-3-carboxylate (3aad)



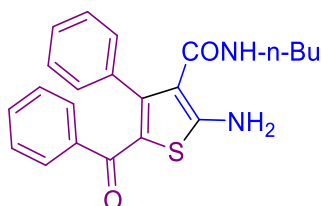
The reaction mixture was purified by trituration with methanol and filtration to afford the product as a pale yellow solid (263 mg, 72%).

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.30 – 7.27 (m, 2H), 7.23 – 7.12 (m, 1H), 7.04 – 6.96 (m, 7H), 6.76 (s, 2H-NH<sub>2</sub>), 4.86 (hept,  $J = 6.2$  Hz, 1H), 0.83 (d,  $J = 6.3$  Hz, 6H).

$^{13}\text{C}\{^1\text{H}\}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  189.8, 167.2, 165.4, 148.4, 138.9, 136.4, 130.5, 129.9 (2C), 128.4 (2C), 127.3 (2C), 127.1, 126.8 (2C), 122.2, 109.3, 67.4, 21.3.

HRMS (ESI)  $m/z$ :  $[\text{M} + \text{Na}]^+$  Calcd for  $\text{C}_{21}\text{H}_{19}\text{NO}_3\text{SNa}$  388.0983; Found 388.0991.

#### 2-Amino-5-benzoyl-*N*-Butyl-4-phenylthiophene-3-carboxamide (3aae)



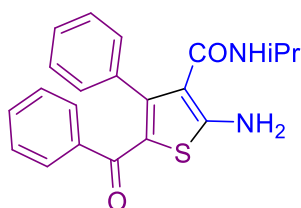
The reaction mixture was purified by trituration with methanol and filtration to afford the product as a pale yellow solid (302 mg, 80%).

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.35 – 7.28 (m, 2H), 7.24 – 7.13 (m, 6H), 7.07 (t,  $J = 7.7$  Hz, 2H), 4.85 (s, 1H-NH), 3.01 (q,  $J = 6.7$  Hz, 2H), 1.06 – 0.99 (m, 2H), 0.98 – 0.91 (m, 2H), 0.73 (t,  $J = 7.2$  Hz, 3H).

$^{13}\text{C}\{^1\text{H}\}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  188.9, 166.1, 165.8, 145.8, 139.4, 135.4, 130.6, 129.9 (2C), 128.6, 128.5 (2C), 128.3 (2C), 127.5 (2C), 120.9, 111.2, 38.6, 30.8, 19.8, 13.5.

HRMS (ESI)  $m/z$ :  $[\text{M} + \text{Na}]^+$  Calcd for  $\text{C}_{22}\text{H}_{22}\text{N}_2\text{O}_2\text{SNa}$  401.1300; Found 401.1310.

### 2-Amino-5-benzoyl-*N*-isopropyl-4-phenylthiophene-3-carboxamide (3aaf)



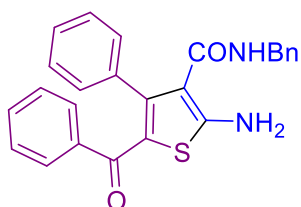
The reaction mixture was purified by trituration with methanol and filtration to afford the product as a pale yellow solid (295 mg, 81%).

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.34 (d,  $J = 7.5$  Hz, 2H), 7.20 (q,  $J = 8.0$  Hz, 4H), 7.15 (d,  $J = 7.4$  Hz, 2H), 7.08 (t,  $J = 7.6$  Hz, 2H), 6.97 (s, 2H), 4.66 (d,  $J = 7.5$  Hz, 1H-NH), 3.87 (h,  $J = 6.8$  Hz, 1H), 0.74 (d,  $J = 6.5$  Hz, 6H).

$^{13}\text{C}\{^1\text{H}\}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  188.9, 166.0, 164.9, 145.9, 139.4, 135.4, 130.6, 129.9 (2C), 128.6, 128.5 (2C), 128.3 (2C), 127.5 (2C), 120.8, 111.4, 40.7, 22.2.

HRMS (ESI)  $m/z$ :  $[\text{M} + \text{Na}]^+$  Calcd for 387.1143  $\text{C}_{21}\text{H}_{20}\text{N}_2\text{O}_2\text{SNa}$ ; Found 387.1152

### 2-Amino-5-benzoyl-*N*-benzyl-4-phenylthiophene-3-carboxamide (3aag)



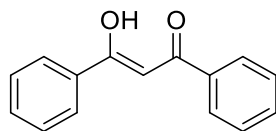
The reaction mixture was purified by trituration with methanol and filtration to afford the product as a pale yellow solid (354 mg, 86%).

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.25 – 7.21 (m, 2H), 7.13 – 7.08 (m, 4H), 7.04 – 6.92 (m, 10H), 6.81 – 6.76 (m, 2H), 5.10 (t,  $J = 5.4$  Hz, 1H), 4.12 (d,  $J = 5.4$  Hz, 2H).

$^{13}\text{C}\{^1\text{H}\}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  188.9, 166.4, 165.6, 145.7, 139.3, 137.4, 135.1, 130.6, 129.8 (2C), 128.6, 128.5 (2C), 128.4, 128.3 (2C), 127.5 (2C), 127.4, 127.2, 121.0, 110.9, 59.5, 43.3.z

HRMS (ESI)  $m/z$ :  $[\text{M} + \text{Na}]^+$  Calcd for  $\text{C}_{25}\text{H}_{20}\text{N}_2\text{O}_2\text{SNa}$  435.1143; Found 435.1151.

### (Z)-3-Hydroxy-1,3-diphenylprop-2-en-1-one (C1)



$^1\text{H}$  NMR (500 MHz, Chloroform- $d$ )  $\delta$  8.06 – 7.91 (m, 4H), 7.56 (t,  $J = 7.3$  Hz, 2H), 7.50 (t,  $J = 7.5$  Hz, 4H), 6.87 (s, 1H).

$^1\text{H}$  NMR (500 MHz, DMSO- $d_6$ )  $\delta$  8.04 (d,  $J = 7.8$  Hz, 4H), 7.51 (t,  $J = 7.3$  Hz, 2H), 7.43 (t,  $J = 7.6$  Hz, 4H), 7.21 (s, 1H).

## ASSOCIATED CONTENT

### Supporting information

The Supporting Information is available free of charge on the

ACS Publications website at DOI: 10.1021/acs.joc.xxxxxxx.

Copies of  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra data for all new compounds. X-ray crystallographic data for **3aab**, **3aag** and **3aca** (CCDC 2062860, 2062861 and 2062862, respectively).

This material is available free of charge via the Internet at <http://pubs.acs.org>.

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