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Synthesis, Molecular Engineering, and Photophysical Properties of Fluorescent Thieno[3,2-*b*]pyridine-5(4*H*)-ones

Dan-Bi Sung[†], Bohyun Mun[†], Sol Park[†,‡], Hyi-Seung Lee[†,‡], Jihoon Lee[†], Yeon-Ju Lee[†,‡], Hee Jae Shin[†,‡], and Jong Seok Lee[*,†,‡]

[†]Marine Natural Products Chemistry Laboratory, Korea Institute of Ocean Science and Technology (KIOST), Busan, Republic of Korea

[‡]Department of Marine Biotechnology, Korea University of Science and Technology, Republic of Korea

Supporting Information

ABSTRACT: We describe a synthetic approach for a set of fluorescent thieno[3,2-*b*]pyridine-5(4*H*)-one derivatives and their photophysical properties. These fluorophores are prepared by a series of reactions employing the Suzuki-Miyaura cross-coupling reaction and a regioselective aza-[3+3] cycloaddition of 3-aminothiophenes with *α,β*-unsaturated carboxylic acids. Our findings revealed that the photophysical properties are chemically tunable by an appropriate choice of functional group on the thieno[3,2-*b*]pyridine-5(4*H*)-one scaffold.

Fluorescence is undoubtedly an exceptional tool to monitor a system of interest at a molecular or supramolecular level in a non-destructive way.[1] Fluorescence technology has found extensive applications in various research areas such as biology, medicine, pharmaceutics, environment, and food science.[2] Over the last several decades, molecular fluorescence has witnessed a remarkable surge of a substantial number of small-molecule fluorophores with enhanced photophysical properties, which again facilitated the current culmination of fluorescence technology.[3] Small-molecule fluorophores offer several advantages over other fluorescent materials owing to their outstanding brightness despite the small size, excellent synthetic accessibility complemented by the inherent structural versatility, substantial flexibility to assemble components with a specific function, and high chemical stability. Currently, a variety of fluorescent core structures are available, which normally serve as the bases for the design of new fluorophores.[1,4] In general, organic fluorophores are considerably implemented in the molecular sensor design as a fluorescent reporter molecule.[5] This clearly indicates that they substantiate the ability of chemistry to solve various problems in nature. Thus, a wide pool of tailor-made molecular sensors has been developed based on a modest set of fluorescent core scaffolds.[1,4]

On the other hand, discovery of novel fluorophore scaffolds remains an unfulfilled task, which provides motivation to apply the innovations of contemporary organic chemistry to the synthesis of new fluorophore families with enhanced properties.[6] These efforts, together with our understanding of the properties of specific fluorophore scaffolds, will provide a well-defined design strategy for the development of state-of-the-art fluorescent molecular sensor.

In this communication, we present the design and synthesis of a series of fluorescent 2-arylthieno[3,2-*b*]pyridine-5(4*H*)-one derivatives [hereafter, collectively referred to as KIOST-Fluor (KF)] and investigation of the structure-fluorescence relationship. We sought to devise a concise and straightforward synthetic approach to a set of KF derivatives.[7]

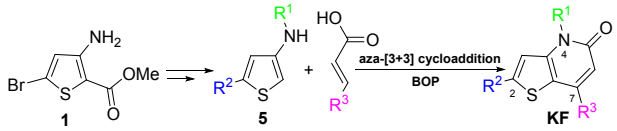
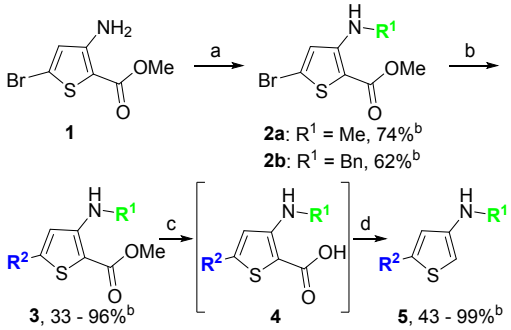


Figure 1. Synthetic strategy for KIOST-Fluor.

The key features in the synthesis of this class of fluorophore involve the Suzuki-Miyaura cross-coupling reaction, a silica gel-assisted decarboxylation, and most importantly, a (benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate (BOP)[8]-promoted regioselective aza-[3+3] cycloaddition[9] of 3-amino-5-arylthiophenes with various *α,β*-unsaturated carboxylic acids (Figure 1).

Scheme 1. Synthesis of Intermediate 5[a]



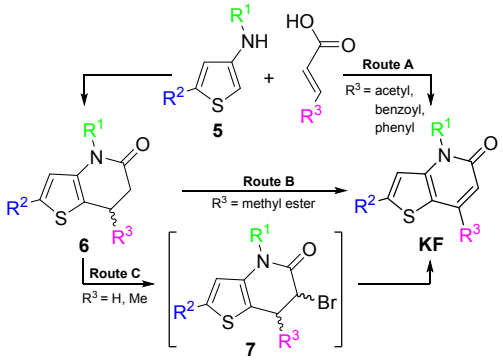
[a]Reagents and conditions: a. 1.4 eq. NaH, 1.3 eq. MeI (or 1.4 eq. BnBr), DMF, 0 ℃ to room temperature, 18 h; b. 5 mol% $Pd(PPh_3)_4$, 1.2 eq. boronic acid, 1.2 eq. Na_2CO_3, toluene/H_2O = 5 : 2, reflux; c. 1N KOH, EtOH, 70 ℃, 2 h; d. 500 wt% silica gel, EtOAc/MeOH, 60 ℃, 2 h. [b]Isolated yield.

As shown in Scheme 1, our synthesis commenced with the *N*-monosubstitution of the commercially available methyl 3-

amino-5-bromothiophene-2-carboxylate (**1**). Thus, the corresponding secondary amine **2** with the designated substituent (R^1 = methyl or benzyl group) was prepared efficiently by treating the starting material **1** with either methyl iodide or benzyl bromide in the presence of NaH in DMF at o ℃ (Scheme 1).

In order to induce fluorescence over a wide spectrum of emission wavelengths, the coupling between the electron-rich phenyl groups and the intermediate **2** was attempted, which was envisioned to finely tune the emission spectra of KF derivatives. Therefore, diverse phenyl groups with distinct electron-donating groups (R^2 group) were readily introduced to the intermediate **2** by the Suzuki-Miyaura cross-coupling reaction to furnish the corresponding 5-arylthiophene derivative **3** (Table S1 in SI). It is of interest that the key intermediate **5** was prepared in moderate to excellent yield by a sequential two-step process including hydrolysis in a mixture of 1 N KOH and EtOH at 70 ℃, directly followed by a silica gel-assisted mild decarboxylation of the resulting carboxylic acid **4** (Scheme 1, see Table S1 in SI for more details).

Scheme 2. Synthetic scheme of KIOST-Fluor



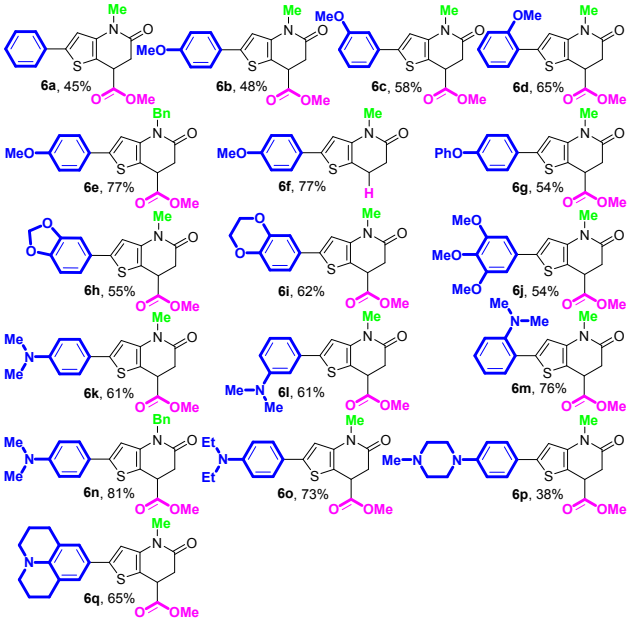


Figure 2. Structures and yields of intermediate **6.**

Subsequently, with intermediate **5** in hand, a BOP-promoted regioselective aza-[3+3] cycloaddition of the intermediate **5** was endeavoured with various *α,β*-unsaturated carboxylic acids (Scheme 2). Interestingly, KF derivatives were prepared via three different synthetic routes outlined in Scheme 1. For example, when R_3 was an electron-withdrawing group especially acetyl and benzoyl group, KF derivatives were obtained directly by concurrent dehydrogenation of the resulting 6,7-dihydrothieno[3,2-*b*]pyridin-5(4*H*)-one (**Route A**, Scheme 2). However, when R_3 was an ester group, preparation of the desired KIOST-Fluor required further treatment of the intermediate **6** under mild heating in DMF in the presence of K_2CO_3 at 70 ℃ (**Route B**, Scheme 2, Figure 2).

In contrast, no desired product was obtained when R^3 was an unactivated group such as H or Me. To overcome this limitation, a mild two-step process of halogenation and elimination was attempted. To our delight, monobromination using NBS followed by a subsequent elimination reaction successfully provided the desired products in good yields (**Route C**, Scheme 2).

With a set of various KF derivatives, we next measured their photophysical properties including absorptions, excitations, emissions, lifetimes, and quantum yields in dichloromethane and acetonitrile, respectively (Figure 4, see Figure S1 in SI for more details). The photophysical data of each compound are summarized in Table S2 in SI. Figure 3 shows images of representative KF's in dichloromethane when excited at 365 nm under a UV lamp.

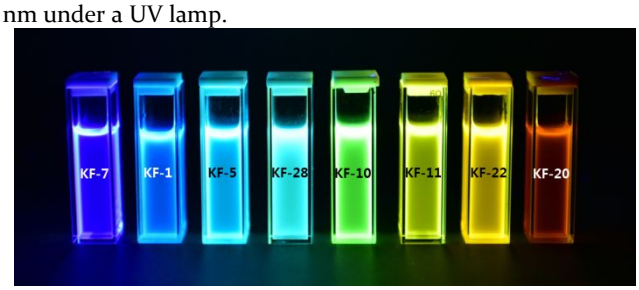


Figure 3. Images of representative KIOST-Fluors (KFs) in dichloromethane (excited at 365 nm under a UV lamp).

The thiophene-based fluorophores typically exhibit weak fluorescence emission due to significant spin-orbit coupling which is originated from the heavy atom effect of the sulfur mediated by charge transfer mixing.[11] This results in an efficient intersystem crossing to the triplet state and a highly efficient nonradiative transition between the triplet state and the ground state that induces relaxation without emission. It is especially noteworthy that the majority of KIOST-Fluors show strong fluorescence despite the fact that they are the fused-thiophenes. Therefore, the emission maxima of KIOST-Fluor showed a wide region of fluorescent emissions (λ_{em}: 426–678 nm in dichloromethane; λ_{em}: 424–610 nm in acetonitrile) along with large Stokes shifts (up to 232 nm in dichloromethane; up to 179 nm in acetonitrile) and high quantum yields (up to 99% in dichloromethane; up to 98% in acetonitrile). The fluorescence lifetime (τ) is the average time that a molecule remains in its excited state before returning to the ground state via emission of a photon. This intrinsic molecular property indicates the time available to collect information from the emission profile. The measured fluorescence lifetimes of the KF molecules range from 0.63 ns to 6.59 ns (see Table S2 in SI for more details).

Compared to **KF-1**, which contains a simple phenyl group at the C2 position, its electron-rich counter parts exhibited obvious bathochromic shifts (red shifts) in emission.

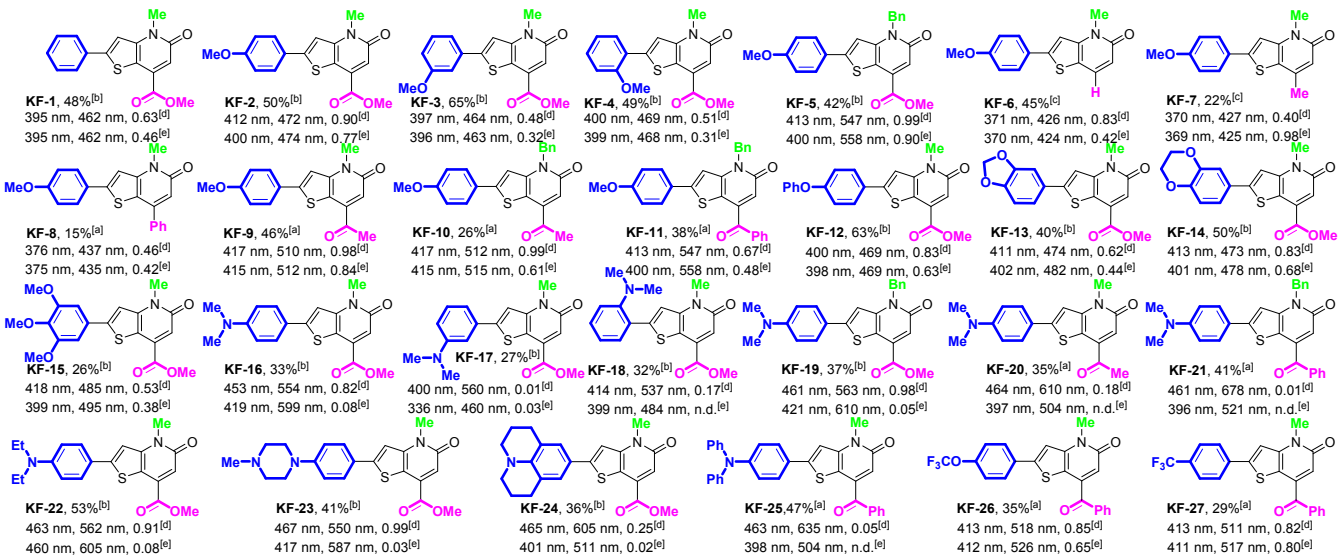


Figure 4. Structures and photophysical data of KIOST-Fluors. [a]**Route A** was applied. [b]**Route B** was applied. [c]**Route C** was applied. [d]Excitation maximum, emission maximum, and absolute quantum yield at 10 μM in CH_2Cl_2. [e]Excitation maximum, emission maximum, and absolute quantum yield at 10 μM in CH_3CN; n.d., not detected. The reliability of the integrating sphere system was confirmed by measuring absolute quantum yields of known fluorescent dyes [fluorescein: Φ_F = 0.92 (reported: 0.89); rhodamine 6G: Φ_F = 0.92 (reported: 0.92)][10]

For example, the emission maxima of KIOST-Fluor derivatives bearing an oxygen atom on the phenyl ring at the C2 position, as in the case of **KF-12**, **KF-2**, **KF-14**, **KF-13**, and **KF-15**, tended to gradually red-shift with increase in electron-donating ability of the R2 group, thus emitting at different wavelengths (469, 472, 473, 474, and 485 nm, respectively), while the absorption maxima remained relatively constant (398–404 nm).

In addition, a similar trend was observed in a series of nitrogen atom-containing derivatives such as **KF-16**, **KF-22**, **KF-23**, and **KF-24** as they fluoresced at 554, 562, 550, and 605 nm, respectively, with the absorption maxima ranging from 420 to 454 nm. As other examples, two different sets of KIOST-Fluors (one includes **KF-27**, **KF-26**, and **KF-25** and the other includes **KF-11** and **KF-21** separately) demonstrated the same trend in emission wavelengths.

Considering the regioisomeric effects of specific auxochromes such as methoxy and dimethylamino groups on the fluorescence property, a series of *ortho*-, *meta*-, and *para*-substituted KF derivatives (for methoxy group, see: **KF-4**, **KF-3**, **KF-2**; for dimethylamino group, see: **KF-18**, **KF-17**, **KF-16**) were prepared and compared with respect to the quantum yield and the absorption/emission maxima. As a result, it can be concluded that the para substitution provides improved photophysical properties including high quantum yield and significant bathochromic shift in the emission wavelengths (**KF-2** and **KF-16**).

The brightness of a fluorophore is given by the multiplication of its molar extinction coefficient (ε) with its quantum yield (Φ). When a benzyl group was introduced at the R^1 position as a replacement of a methyl group (compounds **KF-2**/ **KF-5** and **KF-9**/ **KF-10**), a normally higher molar extinction coefficient (ε), and thus, a much greater brightness was obtained with the exception of **KF-16**/ **KF-19**, which had a similar brightness. With regard to the impact of R^3 substituent, an increase in electron-withdrawing ability from H (**KF-6**) to methyl (**KF-7**), phenyl (**KF-8**), methyl ester (**KF-2**), and acetyl (**KF-9**) with larger conjugations resulted in bathochromic shifts in the emission wavelengths from 426, 427, 437, 472, and 510 nm, respectively.

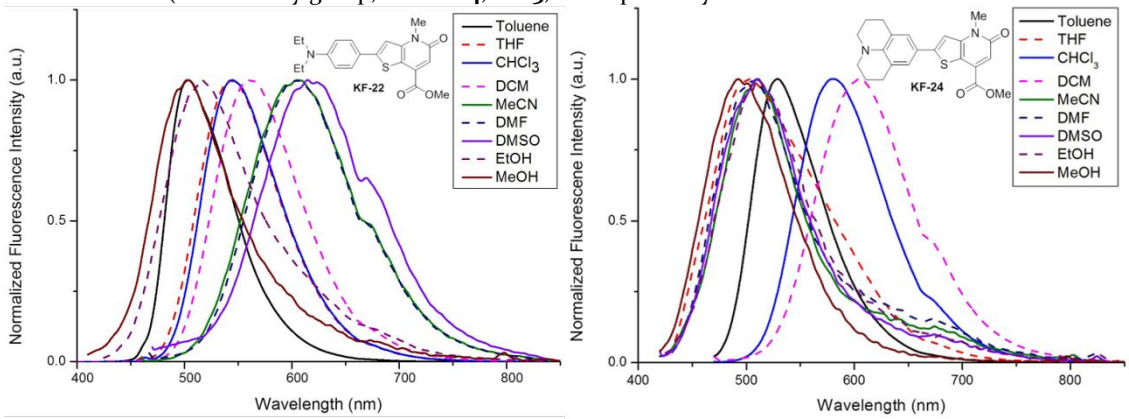


Figure 5. Normalized fluorescence spectra of compounds **KF-22** and **KF-24**. Spectra are normalized with respect to peak intensities.

The same bathochromic shifts were observed in both **KF-16**/ **KF-20** and **KF-19**/ **KF-21**. Therefore, it is reasonable to assume that the photophysical properties of the KIOST-Fluor can be fine-tuned by a proper combination of an electron-donating R^2 and an electron-withdrawing R^3 substituent. Next, we measured the solvatochromic properties of selected KIOST-Fluors such as **KF-2**, **KF-22**, and **KF-24** (Fig. 5, see Figure S2 and Table S3 in SI for compound **KF-2**). Interestingly, **KF-22** showed a broad range of emission wavelengths in the visible region with increase in solvent polarity (positive solvatochromism) from 504 to 615 nm, while **KF-2** had a spectrally narrow emission window from 472 to 484 nm (see Figure S2 and Table S3 in SI). This result indicates that compared to **KF-22**, **KF-2** is relatively insensitive to solvent polarity. Notably, a julolidine derivative, **KF-24**, exhibited red shifts only in toluene, chloroform, and dichloromethane. However, its emission wavelengths were remarkably blue-shifted (hypsochromic shift) in polar solvents, which suggests a negative solvatochromic character of the **KF-24** (Figure 5).[12]

Finally, carboxylic acid derivatives **KF-28** and **KF-29** were prepared by simple hydrolysis of **KF-2** and **KF-22**, respectively, and their photophysical properties were evaluated under various pH conditions (from pH 1.0 to 7.0: see Table S4 and Figure S3 in SI for more details).[13] **KF-28** bearing a *p*-methoxy group on the C2-phenyl ring exhibited a gradual increase in fluorescence intensity with increasing pH, indicating photoinduced proton transfer where the emitting form is carboxylate form of **KF-28** because excitation of **KF-28** is followed by excited-state deprotonation. Therefore, the fluorescence spectrum is unchanged. In contrast to **KF-28**, **KF-29** demonstrated a significant increase in fluorescence intensity in response to decrease in pH. This outstanding enhancement in fluorescence intensity supposedly originated from the inhibition of fluorescent quenching via photoinduced electron transfer (PET) due to the protonation of the *p*-diethylamino group on the C2-phenyl ring (Table S4 and Figure S3 in SI).

In conclusion, we have demonstrated the design and synthesis of a set of fluorescent thieno[3,2-*b*]pyridine-5(4*H*)-ones [KIOST-Fluor (KF)] via the Suzuki-Miyaura cross-coupling reaction and a regioselective aza-[3+3] cycloaddition of 3-aminothiophenes with *α,β*-unsaturated carboxylic acids promoted by BOP. The photophysical properties of these fluorophores can be readily fine-tuned by varying the electron-donating R^2 and electron-withdrawing R^3 substituents.

It is anticipated that these compounds will readily find application as a tool for physical, chemical, material, and biomedical investigations. Studies are ongoing to understand the fundamental principles of the fluorophores and derive novel fluorophores with more improved photophysical properties for their subsequent application to many long-standing problems.

EXPERIMENTAL SECTION

General Information. All melting points were recorded on a micro melting point apparatus and are uncorrected. All anhydrous solvents, boronic acids and other chemical reagents were of reagent grade quality and used without further purification unless otherwise noted. The organic reactions were monitored by thin layer chromatography (TLC) with 0.25-mm pre-coated silica gel plates (Kieselgel $60F_{254}$). Flash column chromatography was performed on silica gel (70-230 mesh) using distilled organic solvents.

^1H and ^{13}C Spectra were recorded on Varian Unity-Inova 500 MHz and Bruker 600 MHz spectrometer. Chemical shifts are reported as δ (ppm) values relative to chloroform ($CDCl_3$, δ 7.26) and dimethylsulfoxide (DMSO-d_6, δ 2.50) and coupling constant was noted by Hz units. High resolution mass spectroscopy (HRMS) data were obtained by a magnetic sector-electric sector double focusing mass analyzer in Korea Basic Science Institute (KBSI) in electron ionization (EI) mode or fast atom bombardment (FAB) mode. Photophysical properties (UV-vis spectra, emission, excitation, quantum yield and molecular coefficient) were obtained using UV-Vis Shimadzu UV1650PC and Fluorescence spectrophotometer Scinco FS-2 (1 cm quartz cell). Fluorescence lifetimes were recorded on Edinburgh instruments using a 375 nm laser source in Korea Advanced Institute of Science and Technology (KAIST)-Analysis Center for Research Advancement (KARA).

General Procedure for the Synthesis of 2a-2b

To a solution of methyl 3-amino-5-bromothiophene-2-carboxylate **1** (1.00 g, 4.24 mmol, 1.0 equiv.) in DMF (40 mL), NaH (60% in mineral oil dispersion, 237 mg, 11.9 mmol, 1.4 equiv.) was added at 0 °C. After stirring for 10 min, methyl iodide (343 μL, 5.51 mmol, 1.3 equiv.) was added and warmed up to room temperature. The reaction was stirred for 18 h at room temperature. For quenching the reaction, water (50 mL) was added and extracted with EtOAc (50 mL) at three times. The organic layer was dried over Na_2SO_4, filtered and evaporated in vacuo. The crude was purified by flash column chromatography (Hexane/EtOAc = 30/1, v/v) on silica to afford the product **2a**.

*Methyl 5-bromo-3-(methylamino)thiophene-2-carboxylate (**2a**)* Compound **2a** was obtained as a white solid (783 mg, 3.13 mmol, 74%). ^1H NMR (600 MHz, CDCl3) δ 6.67 (br s, 1H), 6.63 (s, 1H), 3.78 (s, 3H), 2.93 (d, J = 5.5 Hz, 3H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 164.4, 156.5, 121.8, 119.5, 99.2, 51.3, 31.7; Data are consistent with those reported in the literature.[14]

Methyl 3-(benzylamino)-5-bromothiophene-2-carboxylate (***2b***). Compound **2b** was obtained as a white solid (1.71 g, 5.24 mmol, 62%) starting from benzyl bromide (1.59 g, 9.32 mmol, 1.1 equiv.). m.p: 76-77 °C; ^1H NMR (600 MHz, $CDCl_3$) δ 7.31-7.29 (m, 2H), 7.25-7.20 (m, 3H), 6.54 (d, J = 1.2 Hz, 1H), 4.38 (d, J = 4.2 Hz, 2H), 3.75 (s, 3H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 164.3, 155.4, 138.5, 128.9, 127.6, 127.0, 121.8, 119.9, 100.1, 51.3, 49.0; HRMS (EI): *m/z* calcd for $C_{13}H_{12}BrNO_2S$ $[M]^+$ 324.9772, found 324.9774.

General Procedure for the Synthesis of 3a-3s

To a solution of **2a** (250 mg, 1.00 mmol, 1.0 equiv.) in toluene (2.5 mL, 0.25 M), phenyl boronic acid (146 mg, 1.20 mmol, 1.2 equiv.), $Pd(PPh_3)_4$ (50.9 mg, 0.050 mmol, 0.05 equiv.) and sodium carbonate (127 mg, 1.20 mmol, 1.2 equiv.) in distilled water (1 mL) were added. And then, the reaction was heated to 110 °C and stirred for 5 h. After completion of the reaction, water (5 mL) was added. The crude was extracted with EtOAc (4 mL) at three times. The organic layer was dried over Na_2SO_4, filtered and evaporated *in vacuo*. The residue was

purified by flash column chromatography (Hexane/EtOAc = 4/1, v/v) on silica to afford the product **3a**.

Methyl 3-(methylamino)-5-phenylthiophene-2-carboxylate (***3a***). Compound **3a** was obtained as a pale yellow solid (128 mg, 0.517 mmol, 52%) starting from **2a** (250 mg, 1.00 mmol, 1.0 equiv.). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.64-7.62 (m, 2H), 7.41-7.39 (m, 2H), 7.34-7.34 (m, 1H), 6.85 (s, 1H), 6.68 (br s, 1H), 3.83 (s, 3H), 3.02 (s, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 165.3, 157.5, 149.8, 133.7, 129.00, 128.99, 126.1, 111.7, 97.5, 51.1, 31.7; Data are consistent with those reported in the literature.[15]

Methyl 5-(4-methoxyphenyl)-3-(methylamino)thiophene-2-carboxylate (***3b***). Compound **3b** was obtained as a pale yellow solid (404 mg, 1.46 mmol, 61%) starting from **2a** (600 mg, 2.40 mmol, 1.0 equiv.), 4-methoxyphenylboronic acid (437 mg, 1.84 mmol, 1.2 equiv.), $Pd(PPh_3)_4$ (139 mg, 0.12 mmol, 0.05 equiv.), 0.4 M sodium carbonate (7.2 mL) and toluene (9.6 mL). m.p: 138-139 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.56 (dd, *J* = 6.9 Hz and *J* = 2.1 Hz, 2H), 6.92 (dd, *J* = 6.9 Hz and *J* = 2.1 Hz, 2H), 6.75 (s, 1H), 3.84 (s, 3H), 3.82 (s, 3H), 3.02 (s, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 165.4, 160.5, 157.7, 150.0, 127.5, 126.5, 114.4, 110.7, 96.7, 55.5, 51.1, 31.8; HRMS (EI): *m/z* calcd for $C_{14}H_{15}NO_3S$ $[M]^+$ 277.0773, found 277.0772.

Methyl 5-(3-methoxyphenyl)-3-(methylamino)thiophene-2-carboxylate (***3c***). Compound **3c** was obtained as a yellow solid (218 mg, 0.786 mmol, 66%) starting from **2a** (300 mg, 1.20 mmol, 1.0 equiv.), 3-methoxyphenylboronic acid (219 mg, 1.44 mmol, 1.2 equiv.), $Pd(PPh_3)_4$ (69.3 mg, 0.06 mmol, 0.05 equiv.), 0.4 M sodium carbonate (3 mL) and toluene (4.8 mL). m.p: 49-50 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 (t, *J* = 8.0 Hz, 1H), 7.22 (dt, *J* = 7.5 Hz and *J* = 1.1 Hz, 1H), 7.14 (t, *J* = 2.0 Hz, 1H), 6.90 (dd, *J* = 2.5 Hz and *J* = 8.0 Hz, 1H), 6.84 (s, 1H), 6.66 (br s, 1H), 3.85 (s, 3H), 3.82 (s, 3H), 3.02 (d, *J* = 5.5 Hz, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 165.4, 157.6, 151.2, 150.9, 134.5, 129.7, 114.6, 113.3, 111.7, 110.0, 97.2, 51.2, 40.7, 31.8; HRMS (EI): *m/z* calcd for $C_{14}H_{15}NO_3S$ $[M]^+$ 277.0773, found 277.0775.

*Methyl 5-(2-methoxyphenyl)-3-(methylamino)thiophene-2-carboxylate (**3d**)*. Compound **3d** was obtained as a pale yellow liquid (217 mg, 0.782 mmol, 65%) starting from **2a** (300 mg, 1.20 mmol, 1.0 equiv.), 2-methoxyphenylboronic acid (219 mg, 1.44 mmol, 1.2 equiv.), $Pd(PPh_3)_4$ (69.3 mg, 0.06 mmol, 0.05 equiv.), 0.4 M sodium carbonate (3 mL) and toluene (4.8 mL). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67 (dd, *J* = 7.5 Hz and *J* = 1.5 Hz, 1H), 7.32 (t, *J* = 7.8 Hz, 1H), 7.05 (s, 1H), 7.02-6.98 (m, 2H), 6.70 (br s, 1H), 3.95 (s, 3H), 3.83 (s, 3H), 3.03 (s, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 165.6, 156.7, 156.6, 145.5, 130.0, 128.7, 122.5, 121.1, 113.9, 111.9, 98.7, 55.8, 51.2, 31.8; HRMS (EI): *m/z* calcd for $C_{14}H_{15}NO_3S$ $[M]^+$ 277.0773, found 277.0775.

*Methyl 3-(methylamino)-5-(4-phenoxyphenyl)thiophene-2-carboxylate (**3e**)*. Compound **3e** was obtained as a pale yellow solid (220 mg, 0.648 mmol, 81%) starting from **2a** (200 mg, 0.800 mmol, 1.0 equiv.), (4-phenoxyphenyl)boronic acid (205 mg, 0.960 mmol, 1.2 equiv.), $Pd(PPh_3)_4$ (46.2 mg, 0.0400 mmol, 0.05 equiv.), 0.4 M sodium carbonate (2 mL) and toluene (3.2 mL). m.p: 75-76 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.60-7.58 (m, 2H), 7.38-7.36 (m, 2H), 7.15 (tt, *J* = 7.5 Hz and *J* = 1.2 Hz, 1H), 7.07-7.05 (m, 2H), 7.03-7.00 (m, 2H), 6.79 (s, 1H), 3.83 (s, 3H), 3.03 (s, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 165.4, 158.4, 157.6, 156.6, 149.4, 130.0, 128.7, 127.6, 124.0, 119.5, 118.9, 111.3, 97.1, 51.2, 31.8; HRMS (EI): *m/z* calcd for $C_{19}H_{17}NO_3S$ $[M]^+$ 339.0929, found 339.0932.

*Methyl 5-(benzo[d][1,3]dioxol-5-yl)-3-(methylamino)thiophene-2-carboxylate (**3f**)*. Compound **3f** was obtained as a pale yellow solid (319 mg, 1.09 mmol, 68%) starting from **2a** (400 mg, 1.60 mmol, 1.0 equiv.), benzo[*d*][1,3]dioxol-5-ylboronic acid (318 mg, 1.92 mmol, 1.2 equiv.), $Pd(PPh_3)_4$ (92.4 mg, 0.0800 mmol, 0.05 equiv.), 0.4 M sodium carbonate (4.8 mL) and toluene (6.4 mL). m.p: 124-125 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.14 (dd, *J* = 8.4 Hz and *J* = 1.8 Hz, 1H), 7.09 (d, *J* = 1.8 Hz, 1H), 6.82 (d, *J* = 7.8 Hz, 1H), 6.73 (s, 1H), 6.00 (s, 2H), 3.82 (s, 3H), 3.02 (s, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 165.4, 157.6, 149.9, 148.6, 148.3, 128.1, 120.3, 111.2, 108.8, 106.6, 101.6, 96.9, 51.2, 31.8; HRMS (EI): *m/z* calcd for $C_{14}H_{13}NO_4S$ $[M]^+$ 291.0565, found 291.0567.

*Methyl 5-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-3-(methylamino)thiophene-2-carboxylate (**3g**)*. Compound **3g** was obtained as a pale yellow sticky solid (274 mg, 0.897 mmol, 90%) starting from **2a** (250 mg, 1.00 mmol, 1.0 equiv.), (2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)boronic acid (216 mg, 1.20 mmol, 1.2 equiv.), $Pd(PPh_3)_4$ (57.0 mg, 0.0500 mmol, 0.05 equiv.), 0.4 M sodium carbonate (2 mL) and toluene (2.5 mL). m.p: 50-51 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.11 (d, *J* = 2.4 Hz, 1H), 7.08 (dd, *J* = 8.4 Hz and *J* = 2.4 Hz, 1H), 6.83 (d, *J* = 8.4 Hz, 1H), 6.70 (s, 1H), 6.64 (br s, 1H), 4.22 (s, 4H), 3.79 (s, 3H), 2.97 (d, *J* = 4.8 Hz, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 165.2, 157.5, 149.5, 144.5, 143.6, 127.2, 119.3, 117.6, 114.8, 110.8, 96.6, 64.4, 64.3, 50.9, 31.5; HRMS (EI): *m/z* calcd for $C_{15}H_{15}NO_4S$ $[M]^+$ 305.0722, found 305.0720.

Methyl 3-(methylamino)-5-(3,4,5-trimethoxyphenyl)thiophene-2-carboxylate (***3h***). Compound **3h** was obtained as a yellow solid (438 mg, 1.30 mmol, 67%) starting from **2a** (485 mg, 1.94 mmol, 1.0 equiv.), (3,4,5-trimethoxyphenyl)boronic acid (493 mg, 2.33 mmol, 1.2 equiv.), $Pd(PPh_3)_4$ (112 mg, 0.100 mmol, 0.05 equiv.), 0.4 M sodium carbonate (5.8 mL) and toluene (7.8 mL). m.p: 135-136 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.82 (s, 2H), 6.77 (s, 1H), 3.91 (s, 6H), 3.91 (s, 3H), 3.83 (s, 3H), 3.05 (s, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 165.3, 157.3, 153.7, 150.1, 139.2, 129.5, 111.7, 103.7, 93.0, 61.1, 56.4, 51.3, 31.9; HRMS (EI): *m/z* calcd for $C_{14}H_{13}NO_4S$ $[M]^+$ 337.0984, found 337.0987.

*Methyl 5-(4-(dimethylamino)phenyl)-3-(methylamino)thiophene-2-carboxylate (**3i**)*. Compound **3i** was obtained as a pale red solid (194 mg, 0.668 mmol, 56%) starting from **2a** (300 mg, 1.20 mmol, 1.0 equiv.), (4-(dimethylamino)phenyl)boronic acid (237 mg, 1.43 mmol, 1.2 equiv.), $Pd(PPh_3)_4$ (69.3 mg, 0.0600 mmol, 0.05 equiv.), 0.4 M sodium carbonate (2 mL) and DMF (4.8 mL). m.p: 130-132 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.52 (d, *J* = 9.0 Hz, 2H), 6.71 (s, 1H), 6.70 (d, *J* = 9.0 Hz, 2H), 3.81 (s, 3H), 3.02 (d, *J* = 5.4 Hz, 3H), 3.01 (s, 6H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 165.5, 158.1, 151.3, 151.0, 127.2, 121.7, 112.2, 109.2, 95.5, 51.1, 40.4, 31.8; HRMS (EI): *m/z* calcd for $C_{15}H_{18}N_2O_2S$ $[M]^+$ 290.1089, found 290.1092.

*Methyl 5-(3-(dimethylamino)phenyl)-3-(methylamino)thiophene-2-carboxylate (**3j**)*. Compound **3j** was obtained as a yellow solid (250 mg, 0.861 mmol, 72%) starting from **2a** (300 mg, 1.20 mmol, 1.0 equiv.), (3-(dimethylamino)phenyl)boronic acid (237 mg, 1.43 mmol, 1.2 equiv.), $Pd(PPh_3)_4$ (69.3 mg, 0.0600 mmol, 0.05 equiv.), 0.4 M sodium carbonate (2 mL) and toluene (4.8 mL). m.p: 102-103 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.26 (t, *J* = 8.1 Hz, 1H), 7.00 (dd, *J* = 7.2 Hz and *J* = 1.2 Hz, 1H), 6.93 (t, *J* = 2.4 Hz, 1H), 6.84 (s, 1H), 6.74 (dd, *J* = 8.4 Hz and *J* = 2.4 Hz, 1H), 6.67 (br s, 1H), 3.83 (s, 3H), 3.04 (d, *J* = 5.4 Hz, 3H), 3.00 (s, 6H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 165.4, 157.6, 151.2, 150.9, 134.5, 129.7, 114.6, 113.3, 111.7, 110.0, 97.2, 51.2, 40.7, 31.8; HRMS (EI): *m/z* calcd for $C_{15}H_{18}N_2O_2S$ $[M]^+$ 290.1089, found 290.1087.

*Methyl 5-(2-(dimethylamino)phenyl)-3-(methylamino)thiophene-2-carboxylate (**3k**)*. Compound **3k** was obtained as a yellow liquid (174 mg, 0.599 mmol, 75%) starting from **2a** (200 mg, 0.800 mmol, 1.0 equiv.), (2-(dimethylamino)phenyl)boronic acid (158 mg, 0.960 mmol, 1.2 equiv.), $Pd(PPh_3)_4$ (46.0 mg, 0.0400 mmol, 0.05 equiv.), 0.4 M sodium carbonate (1 mL) and DMF (3.2 mL). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.56 (dd, *J* = 7.8 Hz and *J* = 1.2 Hz, 1H), 7.28 (td, *J* = 7.8 Hz and *J* = 1.4 Hz, 1H), 7.14 (dd, *J* = 7.8 Hz and *J* = 1.2 Hz, 1H), 7.05 (td, *J* = 7.2 Hz and *J* = 1.2 Hz, 1H), 6.99 (s, 1H), 6.64-6.63 (m, 1H), 3.83 (s, 3H), 3.02 (d, *J* = 5.4 Hz, 3H), 2.68 (s, 6H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 165.8, 156.7, 151.9, 147.9, 129.6, 129.4, 128.0, 123.0, 119.9, 113.5, 98.8, 51.0, 44.3, 31.7; HRMS (EI): *m/z* calcd for $C_{15}H_{18}N_2O_2S$ $[M]^+$ 290.1089, found 290.1093.

*Methyl 5-(4-(diethylamino)phenyl)-3-(methylamino)thiophene-2-carboxylate (**3l**)*. Compound **3l** was obtained as an orange liquid (490 mg, 1.54 mmol, 96%) starting from **2a** (400 mg, 1.60 mmol, 1.0 equiv.), *N*,*N*-diethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (528 mg, 1.92 mmol, 1.2 equiv.), $Pd(PPh_3)_4$ (92.3 mg, 0.0800 mmol, 0.05 equiv.), 0.4 M sodium carbonate (2 mL) and toluene (6.4 mL). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49 (d, *J* = 9.0 Hz, 2H), 6.70 (s, 1H), 6.65 (d, *J* = 9.0 Hz, 2H), 3.82 (s, 3H), 3.37 (q, *J* = 7.3 Hz, 4H), 3.03 (d, *J* = 5.0 Hz, 3H), 1.19 (t, *J* = 7.0 Hz, 6H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 165.4, 158.0, 151.4, 148.4, 127.3, 120.6, 111,4, 108.7, 95.1, 50.9, 44.5, 31.7, 12.7; HRMS (EI): *m/z* calcd for $C_{17}H_{22}N_2O_2S$ $[M]^+$ 318.1402, found 318.1405.

*Methyl 3-(methylamino)-5-(4-(4-methylpiperazin-1-yl)phenyl)thiophene-2-carboxylate (**3m**)*. Compound **3m** was obtained as a brown solid (113 mg, 0.327 mmol, 82%) starting from **2a** (100 mg, 0.400 mmol, 1.0 equiv.), 4-(4-methyl)-piperazinylboronic acid (145 mg, 0.480 mmol, 1.2 equiv.), $Pd(PPh_3)_4$ (23.0 mg, 0.0200 mmol, 0.05 equiv.), 0.4 M sodium carbonate (0.5 mL) and DMF (1.6 mL). m.p: 153-154 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.53 (d, *J* = 8.4 Hz, 2H), 6.91 (d, *J* = 8.4 Hz, 2H), 6.74 (s, 1H), 6.67 (br s, 1H), 3.81 (s, 3H), 3.28 (t, *J* = 5.1 Hz, 4H), 3.02 (d, *J* = 5.4 Hz, 3H), 2.57 (t, *J* = 5.1 Hz, 4H), 2.36 (s, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 165.5, 157.9, 151.7, 150.5, 127.1, 124.6, 115.5, 110.0, 96.2, 55.0, 51.1, 48.4, 46.3, 31.8; HRMS (EI): *m/z* calcd for $C_{18}H_{23}N_3O_2S$ $[M]^+$ 345.1511, found 345.1508.

Methyl 3-(methylamino)-5-(2,3,6,7-tetrahydro-1H,5H-pyrido[3,2,1-ij]quinolin-9-yl)thiophene-2-carboxylate (**3n**). To a solution of **2a** (100 mg, 0.400 mmol, 1.0 equiv.) in dioxane:H_2O (3:1, 1.6 mL), (2,3,6,7-tetrahydro-1*H*,5*H*-pyrido[3,2,1-*ij*]quinolin-9-yl)boronic acid (96.0 mg, 0.440 mmol, 1.2 equiv.), $Pd(OAc)_2$ (9.00 mg, 0.0400 mmol, 0.1 equiv.), 1,1`-bis(diphenylphospino)ferrocene (dppf, 22.2 mg, 0.0400 mmol, 0.1 equiv.) and Cs_2CO_3 (260 mg, 0.800 mmol, 2.0 equiv.) were added. And then, the reaction was heated to reflux for 18 h. For quenching the reaction, water (2 mL) was added. The crude was extracted with DCM (3 mL) at three times. The organic layer was dried over Na_2SO_4, filtered and evaporated in vacuo. The mixture was purified by flash column chromatography (Hexane/EtOAc = 3/1, v/v) on silica to obtain **3n** as a red-orange sticky liquid (45.0 mg, 0.131 mmol, 33%). m.p: 157-159 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.08 (s, 2H), 6.65 (s, 1H), 3.80 (s, 3H), 3.19 (t, *J* = 5.7 Hz, 4H), 3.01 (d, *J* = 4.8 Hz, 3H), 2.76 (t, *J* = 6.6 Hz, 4H), 2.00-1.95 (m, 4H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 165.4, 158.1, 151.8, 143.8, 124.8, 121.3, 120.6, 108.6, 94.6, 50.9, 50.0, 31.7, 27.8, 21.9; HRMS (EI): *m/z* calcd for $C_{19}H_{22}N_2O_2S$ $[M]^+$ 342.1402, found 342.1404.

Methyl 5-(4-(diphenylamino)phenyl)-3-(methylamino)thiophene-2-carboxylate (***3o***). Compound **3o** was obtained as a yellow solid (728 mg, 1.76 mmol, 88%) starting from **2a** (500 mg, 2.00 mmol, 1.0 equiv.), (4-(diphenylamino)phenyl)boronic acid (693 mg, 2.40 mmol, 1.2 equiv.), $Pd(PPh_3)_4$ (116 mg, 0.100 mmol, 0.05 equiv.), 0.4 M sodium carbonate (3 mL) and toluene (8 mL). m.p: 69-71 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.94-7.47 (m, 2H), 7.30-7.27 (m, 4H), 7.14-7.12 (m, 4H), 7.08-7.04 (m, 4H), 6.77 (s, 1H), 3.82 (s, 3H), 3.02 (s, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 165.4, 157.7, 150.0, 148.8, 147.3, 129.5, 127.2, 126.9, 125.1, 123.7, 122.8, 110.6, 96.7, 51.2, 31.8; HRMS (EI): *m/z* calcd for $C_{25}H_{22}N_2O_2S$ $[M]^+$ 414.1402, found 414.1404.

Methyl 3-(methylamino)-5-(4-(trifluoromethoxy)phenyl)thiophene-2-carboxylate (***3p***). Compound **3p** was obtained as a yellow solid (365 mg, 1.10 mmol, 69%) starting from **2a** (400 mg, 1.60 mmol, 1.0 equiv.), (4-(trifluoromethoxy)phenyl)boronic acid (395 mg, 1.92 mmol, 1.2 equiv.), $Pd(PPh_3)_4$ (92.0 mg, 0.0800 mmol, 0.05 equiv.), 0.4 M sodium carbonate (4.8 mL) and toluene (6.4 mL). m.p: 68-70 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.64 (d, *J* = 8.4 Hz, 2H), 7.24 (d, *J* = 8.4 Hz, 2H), 6.83 (s, 1H), 3.83 (s, 3H), 3.03 (s, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 165.3, 157.4, 149.7 (q, $J_{C\text{-}F}$ = 1.9 Hz), 148.1, 132.6, 127.6, 121.5, 120.6 (q, $J_{C\text{-}F}$ = 256.1 Hz), 112.3, 98.2, 51.3, 31.8; ^{19}F{^{1}H} NMR (600 MHz, $CDCl_3$) δ -57.8; HRMS (EI): *m/z* calcd for $C_{14}H_{12}F_3NO_3S$ $[M]^+$ 331.0490, found 331.0490.

Methyl 3-(methylamino)-5-(4-(trifluoromethyl)phenyl)thiophene-2-carboxylate (***3q***). Compound **3q** was obtained as a pale yellow solid (345 mg, 1.09 mmol, 68%) starting from **2a** (400 mg, 1.60 mmol, 1.0 equiv.), (4-(trifluoromethyl)phenyl)boronic acid (365 mg, 1.92 mmol, 1.2 equiv.), $Pd(PPh_3)_4$ (92.0 mg, 0.0800 mmol, 0.05 equiv.), 0.4 M sodium carbonate (4.8 mL) and toluene (6.4 mL). m.p: 93-95 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.72 (d, *J* = 8.4 Hz, 2H), 7.64 (d, *J* = 8.4 Hz, 2H), 6.91 (s, 1H), 3.84 (s, 3H), 3.04 (s, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 165.3, 157.3, 147.6, 137.2, 130.7, (q, $J_{C\text{-}F}$ = 32.5 Hz), 126.3, 126.1 (q, $J_{C\text{-}F}$ = 3.7 Hz), 124.1 (q, $J_{C\text{-}F}$ = 270.6 Hz), 112.9, 98.8, 51.4, 31.8; ^{19}F{^{1}H} NMR (600 MHz, $CDCl_3$) δ -62.7; HRMS (EI): *m/z* calcd for $C_{14}H_{12}F_3NO_2S$ $[M]^+$ 315.0541, found 315.0543.

Methyl 3-(benzylamino)-5-(4-methoxyphenyl)thiophene-2-carboxylate (***3r***). Compound **3r** was obtained as a yellow solid

(392 mg, 1.11 mmol, 73%) starting from **2b** (500 mg, 1.53 mmol, 1.0 equiv.), 4-methoxyphenylboronic acid (280 mg, 1.84 mmol, 1.2 equiv.), $Pd(PPh_3)_4$ (88.6 mg, 0.0800 mmol, 0.05 equiv.), 0.4 M sodium carbonate (4 mL) and toluene (6.1 mL). m.p: 100-102 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.50 (dd, *J* = 6.6 Hz and *J* = 1.8 Hz, 2H), 7.37-7.33 (m, 4H), 7.29-7.26 (m, 1H), 7.22 (br s, 1H), 6.89 (dd, *J* = 6.6 Hz and *J* = 2.4 Hz, 2H), 6.70 (s, 1H), 4.53 (d, *J* = 6.0 Hz, 2H), 3.84 (s, 3H), 3.82 (s, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 165.5, 160.5, 156.7, 150.0, 139.0, 128.9, 127.49, 127.45, 127.1, 126.4, 114.4, 111.2, 97.5, 55.5, 51.2, 49.1; HRMS (EI): *m/z* calcd for $C_{20}H_{19}NO_3S$ [M]$^+$ 353.1086, found 353.1088.

Methyl 3-(benzylamino)-5-(4-(dimethylamino)phenyl)thiophene-2-carboxylate (***3s***). Compound **3s** was obtained as a pale red solid (371 mg, 1.01 mmol, 66%) starting from **2b** (500 mg, 1.53 mmol, 1.0 equiv.), (4-(dimethylamino)phenyl)boronic acid (304 mg, 1.84 mmol, 1.2 equiv.), $Pd(PPh_3)_4$ (88.6 mg, 0.0800 mmol, 0.05 equiv.), 0.4 M sodium carbonate (2 mL) and toluene (6.1 mL). m.p: 135-136 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.46-7.44 (m, 2H), 7.37-7.33 (m, 4H), 7.28-7.25 (m, 2H), 6.67-6.66 (m, 3H), 4.53 (d, *J* = 6.0 Hz, 2H), 3.83 (s, 3H), 2.99 (s, 6H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 165.5, 157.0, 151.3, 151.0, 139.2, 128.8, 127.4, 127.2, 121.6, 112.2, 109.8, 96.3, 51.1, 49.1, 40.4; HRMS (EI): *m/z* calcd for $C_{21}H_{22}N_2O_2S$ [M]$^+$ 366.1402, found 366.1405.

General Procedure for the Synthesis of 5a-5s

To a solution of **3a** (150 mg, 0.600 mmol, 1.0 equiv.) in ethanol (4 mL, 0.25 M), 1 N KOH (2 mL) was added. The reaction was heated to 70 °C and stirred for 1 h. After completion of the reaction, the solvent was evaporated. The crude was used without further purification. And then, silicagel (750 mg, 500 wt % of substrate) was added in EtOAc (2 mL) and MeOH (2 mL) solution (1:1). The reaction was heated 60 °C and stirred for 2 h. After completion of the reaction, the silicagel was filtered and the organic layer was evaporated *in vacuo*. The residue was purified by flash column chromatography (Hexane/EtOAc = 3/1, v/v) on silica to afford the product **5a**.

N-methyl-5-phenylthiophen-3-amine (***5a***). Compound **5a** was obtained as a white solid (105 mg, 0.555 mmol, 92%) starting from **3a** (150 mg, 0.600 mmol, 1.0 equiv.). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.59-7.57 (m, 2H), 7.37 (td, *J* = 7.2 Hz and *J* = 1.8 Hz, 2H), 7.28 (tt, *J* = 7.2 Hz and *J* = 1.5 Hz, 1H), 6.86 (d, *J* = 1.8 Hz, 1H), 5.95 (d, *J* = 1.8 Hz, 1H), 3.48 (br s, 1H), 2.85 (s, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 150.3, 143.6, 134.7, 128.9, 127.6, 125.6, 116.0, 95.0, 32.7; Data are consistent with those reported in the literature.[7a]

5-(4-Methoxyphenyl)-N-methylthiophen-3-amine (***5b***). Compound **5b** was obtained as a pale yellow solid (130 mg, 0.593 mmol, 89%) starting from **3b** (185 mg, 0.667 mmol, 1.0 equiv.). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.48 (dd, *J* = 6.6 Hz and *J* = 1.8 Hz, 2H), 6.91 (dd, *J* = 6.6 Hz and *J* = 2.4 Hz, 2H), 6.74 (d, *J* = 1.8 Hz, 1H), 5.87 (d, *J* = 1.8 Hz, 1H), 3.83 (s, 3H), 2.84 (s, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 159.3, 150.3, 143.6, 127.6, 126.9, 115.1, 114.3, 94.0, 55.5, 32.8; Data are consistent with those reported in the literature.[7a]

5-(3-Methoxyphenyl)-N-methylthiophen-3-amine (***5c***). Compound **5c** was obtained as a brown oil (122 mg, 0.556 mmol, 85%) starting from **3c** (182 mg, 0.656 mmol, 1.0 equiv.). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 (t, *J* = 7.8 Hz, 1H), 7.27 (d, *J* = 7.5 Hz, 1H), 7.23 (s, 1H), 6.93 (dd, *J* = 2.5 Hz and *J* = 8.0 Hz, 1H), 6.89 (d, *J* = 1.8 Hz, 1H), 5.99 (d, *J* = 2.0 Hz, 1H), 3.90 (s, 3H), 3.71 (br s, 1H), 2.87 (s, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 159.8, 150.2, 142.9, 135.8, 129.7, 117.9, 116.1, 112.7, 111.0, 94.5, 55.1, 32.4; HRMS (EI): *m/z* calcd for $C_{12}H_{13}NOS$ [M]$^+$ 219.0718, found 219.0717.

5-(2-Methoxyphenyl)-N-methylthiophen-3-amine (***5d***). Compound **5d** was obtained as a dark green oil (139 mg, 0.634 mmol, 86%) starting from **3d** (204 mg, 0.736 mmol, 1.0 equiv.). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62 (dd, *J* = 7.5 Hz and *J* = 1.5 Hz, 1H), 7.26 (td, *J* = 7.9 Hz and *J* = 1.8 Hz, 1H), 7.09 (d, *J* = 1.5 Hz, 1H), 7.01-6.96 (m, 2H), 6.00 (d, *J* = 1.5 Hz, 1H), 3.90 (s, 3H), 3.63 (br s, 1H), 2.84 (s, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 155.8, 149.6, 138.7, 128.28, 128.25, 123.4, 120.8, 118.5, 111.6, 95.6, 55.5, 32.7; HRMS (EI): *m/z* calcd for $C_{12}H_{13}NOS$ [M]$^+$ 219.0718, found 219.0716.

N-Methyl-5-(4-phenoxyphenyl)thiophen-3-amine (***5e***). Compound **5e** was obtained as a pale yellow solid (33.2 mg, 0.118 mmol, 72%) starting from **3e** (56.0 mg, 0.165 mmol, 1.0 equiv.). m.p: 84-85 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.53 (dd, *J* = 6.6 Hz and *J* = 1.8 Hz, 2H), 7.38-7.36 (m, 2H), 7.14 (tt, *J* = 7.2 Hz and *J* = 1.1 Hz, 1H), 7.07-7.05 (m, 2H), 7.01 (dd, *J* = 6.6 Hz and *J* = 1.8 Hz, 2H), 6.79 (d, *J* = 1.8 Hz, 1H), 5.91 (d, *J* = 1.2 Hz. 1 H), 2.85 (s, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 157.1, 156.9, 150.3, 143.0, 129.95, 129.90, 127.0, 123.5, 119.14, 119.06, 115.6, 94.5, 32.7; HRMS (EI): *m/z* calcd for $C_{17}H_{15}NOS$ [M]$^+$ 281.0874, found 281.0871.

5-(Benzo[d][1,3]dioxol-5-yl)-N-methylthiophen-3-amine (***5f***). Compound **5f** was obtained as a pale green solid (16.3 mg, 0.0699 mmol, 73%) starting from **3f** (28.0 mg, 0.0961 mmol, 1.0 equiv.). m.p: 65-66 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.05-7.03 (m, 2H), 6.80 (d, *J* = 2.4 Hz, 1H), 6.72 (s, 1H), 5.97 (s, 2H), 5.86 (s, 1H), 3.63 (br s, 1H), 2.83 (s, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 150.2, 148.1, 147.3, 143.5, 129.1, 119.4, 115.5, 108.7, 106.4, 101.3, 94.2, 32.7; HRMS (EI): *m/z* calcd for $C_{12}H_{11}NO_2S$ [M]$^+$ 233.0511, found 233.0508.

5-(2,3-Dihydrobenzo[b][1,4]dioxin-6-yl)-N-methylthiophen-3-amine (***5g***). Compound **5g** was obtained as a brown oil (160 mg, 0.647 mmol, 77%) starting from **3g** (256 mg, 0.838 mmol, 1.0 equiv.). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.09-7.04 (m, 2H), 6.85 (d, *J* = 8.5 Hz, 1H), 6.72 (d, *J* = 2.0 Hz, 1H), 5.86 (d, *J* = 1.5 Hz, 1H), 4.27 (s, 4H), 3.61 (br s, 1H), 2.83 (s, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 150.2, 143.7, 143.3, 143.2, 128.5 119.0, 117.6, 115.3, 114.5, 94.1, 64.53, 64.50, 32.7; HRMS (EI): *m/z* calcd for $C_{13}H_{13}NO_2S$ [M]$^+$ 247.0667, found 247.0668.

N-Methyl-5-(3,4,5-trimethoxyphenyl)thiophen-3-amine (***5h***). Compound **5h** was obtained as a brown oil (298 mg, 1.07 mmol, 90%) starting from **3h** (400 mg, 1.19 mmol, 1.0 equiv.). ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.77 (d, *J* = 1.8 Hz, 1H), 6.75 (s, 2H), 5.89 (d, *J* = 1.8 Hz, 1H), 3.89 (s, 6H), 3.86 (s, 3H), 2.83 (s, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 153.4, 150.2, 143.5, 137.8, 130.5, 115.9, 103.1, 94.7, 61.0, 56.2, 32.7; HRMS (EI): *m/z* calcd for $C_{14}H_{17}NO_3S$ [M]$^+$ 279.0929, found 279.0930.

5-(4-(Dimethylamino)phenyl)-N-methylthiophen-3-amine (***5i***). Compound **5i** was obtained as a red-brown solid (600 mg, 2.58 mmol, 62%) starting from **3i** (1.20 g, 4.13 mmol, 1.0 equiv.). m.p: 125-127 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.44 (d, *J* =

9.0 Hz, 2H), 6.71-6.70 (m, 3H), 5.81 (s, 1H), 2.98 (s, 6H), 2.84 (s, 3H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 150.2, 150.1, 144.5, 126.6, 123.3, 114.0, 112.6, 93.0, 40.6, 32.8; HRMS (EI): *m/z* calcd for $C_{13}H_{16}N_2S$ $[M]^+$ 232.1034, found 232.1033.

5-(3-(Dimethylamino)phenyl)-N-methylthiophen-3-amine (***5j***). Compound **5j** was obtained as a brown liquid (109 mg, 0.469 mmol, 86%) using **3j** (159 mg, 0.547 mmol, 1.0 equiv.). ^1H NMR (500 MHz, $CDCl_3$) δ 7.26 (t, *J* = 8.0 Hz, 1H), 6.96 (d, *J* = 7.5 Hz, 1H), 6.94-6.93 (m, 1H), 6.86 (d, *J* = 1.5 Hz, 1H), 6.70 (dd, *J* = 8.0 Hz and *J* = 2.5 Hz, 1H), 5.93 (d, *J* = 2.0 Hz, 1H), 3.38 (br s, 1H), 3.01 (s, 6H), 2.85 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 150.9, 150.1, 144.6, 135.4, 129.5, 115.9, 114.4, 112.0, 109.9, 94.6, 40.7, 32.7; HRMS (EI): *m/z* calcd for $C_{13}H_{16}N_2S$ $[M]^+$ 232.1034, found 232.1032.

5-(2-(Dimethylamino)phenyl)-N-methylthiophen-3-amine (***5k***). Compound **5k** was obtained as a yellow liquid (110 mg, 0.473 mmol, 81%) starting from **3k** (170 mg, 0.585 mmol, 1.0 equiv.). ^1H NMR (600 MHz, $CDCl_3$) δ 7.48 (d, *J* = 7.8 Hz, 1H), 7.23 (t, *J* = 7.2 Hz, 1H), 7.11 (d, *J* = 8.4 Hz, 1H), 7.03 (t, *J* = 7.5 Hz, 1H), 7.00 (s, 1H), 5.99 (s, 1H), 3.56 (br s, 1H), 2.86 (s, 3H), 2.67 (s, 6H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 151.3, 149.1, 141.4, 129.5, 128.9, 128.1, 122.8, 119.5, 117.9, 96.4, 44.2, 32.8; HRMS (EI): *m/z* calcd for $C_{13}H_{16}N_2S$ $[M]^+$ 232.1034, found 232.1035.

5-(4-(Diethylamino)phenyl)-N-methylthiophen-3-amine (***5l***). Compound **5l** was obtained as a red-brown solid (41.5 mg, 0.159 mmol, 63%) starting from **3l** (80.8 mg, 0.254 mmol, 1.0 equiv.). m.p: 88-90 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 7.44 (dd, *J* = 6.5 Hz and *J* = 2.3 Hz, 2H), 6.70-6.67 (m, 3H), 5.81 (d, *J* = 1.5 Hz, 1H), 3.62 (br s, 1H), 3.39 (q, *J* = 7.0 Hz, 4H), 2.84 (s, 3H), 1.20 (t, *J* = 7.3 Hz, 6H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 150.2, 147.3, 144.6, 126.8, 122.1, 113.7, 111.7, 92.6, 44.5, 32.7, 12.8; HRMS (EI): *m/z* calcd for $C_{15}H_{20}N_2S$ $[M]^+$ 260.1347, found 260.1346.

N-Methyl-5-(4-(4-methylpiperazin-1-yl)phenyl)thiophen-3-amine (***5m***). Compound **5m** was obtained as a brown solid (123 mg, 0.428 mmol, 82%) starting from **3m** (180 mg, 0.521 mmol, 1.0 equiv.). m.p: 149-150 °C; ^1H NMR (600 MHz, $CDCl_3$) δ 7.45 (d, *J* = 9.0 Hz, 2H), 6.89 (d, *J* = 9.0 Hz, 2H), 6.73 (s, 1H), 5.84 (s, 1H), 3.60 (br s, 1H), 3.24 (t, *J* = 4.8 Hz, 4H), 2.83 (s, 3H), 2.57 (t, *J* = 5.1 Hz, 4H), 2.35 (s, 3H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 150.7, 150.3, 143.9, 126.5, 126.1, 115.9, 114.6, 93.6, 55.2, 48.9, 46.3, 32.7; HRMS (EI): *m/z* calcd for $C_{16}H_{21}N_3S$ $[M]^+$ 287.1456, found 287.1459.

N-Methyl-5-(2,3,6,7-tetrahydro-1H,5H-pyrido[3,2,1-ij]quinolin-9-yl)thiophen-3-amine (***5n***). Compound **5n** was obtained as a dark-brown solid (74.3 mg, 0.261 mmol, 89%) starting from **3n** (100 mg, 0.292 mmol, 1.0 equiv.). m.p: 66-68 °C; ^1H NMR (600 MHz, $CDCl_3$) δ 7.00 (s, 2H), 6.65 (s, 1H), 5.78 (s, 1H), 3.63 (br s, 1H), 3.16 (t, *J* = 6.0 Hz, 4H), 2.83 (s, 3H), 2.77 (t, *J* = 6.6 Hz, 4H), 2.00-1.96 (m, 4H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 150.1, 145.0, 142.7, 124.5, 122.3, 121.6, 113.6, 92.8, 50.1, 32.8, 27.8, 22.1; HRMS (EI): *m/z* calcd for $C_{17}H_{20}N_2S$ $[M]^+$ 284.1347, found 284.1346.

5-(4-(Diphenylamino)phenyl)-N-methylthiophen-3-amine (***5o***). Compound **5o** was obtained as a red-brown solid (150 mg, 0.421 mmol, 43%) starting from **3o** (406 mg, 0.979 mmol, 1.0 equiv.). m.p: 125-126 °C; ^1H NMR (600 MHz, $CDCl_3$) δ 7.41 (d, *J* = 8.4 Hz, 2H), 7.29-7.25 (m, 4H), 7.11 (d, *J* = 7.8 Hz, 4H), 7.05-7.02 (m, 4H), 6.77 (s, 1H), 5.88 (s, 1H), 2.84 (s, 3H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) 150.3, 147.7, 147.3, 143.5, 129.4, 128.9, 126.4, 124.6, 123.8, 123.1, 115.2, 94.3, 32.8; HRMS (EI): *m/z* calcd for $C_{23}H_{20}N_2S$ $[M]^+$ 356.1347, found 356.1349.

N-Methyl-5-(4-(trifluoromethoxy)phenyl)thiophen-3-amine (***5p***). Compound **5p** was obtained as a green solid (224 mg, 0.820 mmol, 80%) starting from **3p** (339 mg, 1.02 mmol, 1.0 equiv.). m.p: 121-123 °C; ^1H NMR (600 MHz, $CDCl_3$) δ 7.56 (dd, *J* = 6.6 Hz and *J* = 1.8 Hz, 2H), 7.21 (d, *J* = 9.0 Hz and *J* = 0.6 Hz, 2H), 6.82 (d, *J* = 1.8 Hz, 1H), 5.95 (d, *J* = 1.2 Hz, 1H), 2.85 (s, 3H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 150.4, 148.6, 141.9, 133.5, 126.9, 121.4, 119.8 (q, $J_{C\text{-}F}$ = 255.6 Hz), 116.5, 95.5, 32.7; $^{19}F\{^1H\}$ NMR (600 MHz, $CDCl_3$) δ -57.9; HRMS (EI): *m/z* calcd for $C_{12}H_{10}F_3NOS$ $[M]^+$ 273.0435, found 273.0437.

N-Methyl-5-(4-(trifluoromethyl)phenyl)thiophen-3-amine (***5q***). Compound **5q** was obtained as a yellow-green solid (112 mg, 0.435 mmol, 80%) starting from **3q** (172 mg, 0.545 mmol, 1.0 equiv.). m.p: 116-118 °C; ^1H NMR (600 MHz, $CDCl_3$) δ 7.64 (d, *J* = 8.4 Hz, 2H), 7.59 (d, *J* = 8.4 Hz, 2H), 6.92 (d, *J* = 1.8 Hz, 1H), 6.00 (d, *J* = 1.8 Hz,1H), 2.86 (s, 3H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 150.6, 141.7, 138.1, 129.3 (q, $J_{C\text{-}F}$ = 32.4 Hz), 125.9 (q, $J_{C\text{-}F}$ = 3.8 Hz), 125.6, 124.3 (q, $J_{C\text{-}F}$ = 270.1 Hz), 117.0, 96.3, 32.7; $^{19}F\{^1H\}$ NMR (600 MHz, $CDCl_3$) δ -62.5; HRMS (EI): *m/z* calcd for $C_{12}H_{10}F_3NS$ $[M]^+$ 257.0486, found 257.0483.

N-Benzyl-5-(4-methoxyphenyl)thiophen-3-amine (***5r***). Compound **5r** was obtained as a yellow solid (278 mg, 0.941 mmol, 99%) starting from **3r** (336 mg, 0.951 mmol, 1.0 equiv.). m.p: 92-93 °C; ^1H NMR (600 MHz, $CDCl_3$) δ 7.48 (d, *J* = 9.0 Hz, 2H), 7.42-7.41 (m, 2H), 7.38-7.35 (m, 2H), 7.30 (tt, *J* = 7.2 Hz and *J* = 1.7 Hz, 1H), 6.91 (d, *J* = 9.0 Hz, 2H), 6.78 (d, *J* = 1.2 Hz, 1H), 5.89 (d, *J* = 1.2 Hz, 1H), 4.29 (s, 2H), 3.83 (s, 3H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 159.3, 148.8, 143.5, 139.4, 128.7, 127.8, 127.5, 127.4, 126.9, 115.2, 114.3, 94.9, 55.5, 50.5; HRMS (EI): *m/z* calcd for $C_{18}H_{17}NOS$ $[M]^+$ 295.1031, found 295.1033.

N-Benzyl-5-(4-(dimethylamino)phenyl)thiophen-3-amine (***5s***). Compound **5s** was obtained as a red-brown solid (230 mg, 0.746 mmol, 78%) starting from **3s** (350 mg, 0.955 mmol, 1.0 equiv.). m.p: 125-126 °C; ^1H NMR (600 MHz, $CDCl_3$) δ 7.45-7.41 (m, 4H), 7.37 (t, *J* = 7.5 Hz, 2H), 7.30 (t, *J* = 7.2 Hz, 1H), 6.74-6.740 (m, 1H), 6.71 (d, *J* = 8.4 Hz, 2H), 5.84 (d, *J* = 1.8 Hz, 1H), 4.29 (s, 2H), 3.95 (br s, 1H), 2.98 (s, 6H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 150.1, 148.7, 144.4, 139.5, 128.7, 127.8, 127.4, 126.6, 123.2, 114.1, 112.6, 93.9, 50.5, 40.6; HRMS (EI): *m/z* calcd for $C_{19}H_{20}N_2S$ $[M]^+$ 308.1347, found 308.1351.

General Procedure for the Synthesis of 6a-6q

To a solution of **5a** (29.4 mg, 0.155 mmol, 1.0 equiv.) in DMF (1.5 mL, 0.1 M), mono-methyl fumarate (25.0 mg, 0.186 mmol, 1.2 equiv.), BOP (83.0 mg, 0.186 mmol, 1.2 equiv.) and *N*,*N*-diisopropylethylamine (67.0 µL, 0.388 mmol, 1.2 equiv.) were added. The reaction was stirred for 5 min at room temperature. After completion of the reaction, water (2 mL) was added. The crude was extracted with EtOAc (3 mL) at three times. The organic layer was dried over Na_2SO_4, filtered and evaporated *in vacuo*. The residue was purified by flash column chromatography (Hexane/EtOAc = 1/1, v/v) on silica to afford the product **6a**.

*Methyl 4-methyl-5-oxo-2-phenyl-4,5,6,7-tetrahydrothieno [3,2-b]pyridine-7-carboxylate (**6a**)*. Compound **6a** was obtained as a pale yellow liquid (21.2 mg, 0.0703 mmol, 45%) starting from **5a** (29.4 mg, 0.155 mmol, 1.0 equiv.). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.56 (d, *J* = 7.8 Hz, 2H), 7.39 (t, *J* = 12.5 Hz, 2H), 7.31 (t, *J* = 6.9 Hz, 1H), 6.99 (s, 1H), 4.03 (t, *J* = 7.2 Hz, 1H), 3.79 (s, 3H), 3.36 (s, 3H), 3.03 (ddd, *J* = 7.7 Hz, *J* = 16.2 Hz and *J* = 31.5 Hz, 2H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 171.3, 167.2, 143.9, 140.4, 133.8, 129.2, 128.2, 125.6, 113.3, 112.5, 52.9, 38.4, 34.4, 30.6; HRMS (EI): *m/z* calcd for $C_{16}H_{15}NO_3S$ [M]$^+$ 301.0773, found 301.0770.

*Methyl 2-(4-methoxyphenyl)-4-methyl-5-oxo-4,5,6,7-tetrahydrothieno[3,2-b]pyridine-7-carboxylate (**6b**)*. Compound **6b** was obtained as a pale yellow solid (36.3 mg, 0.109 mmol, 48%) starting from **5b** (50.0 mg, 0.228 mmol, 1.0 equiv.). m.p: 164-165 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.48 (dd, *J* = 6.9 Hz and *J* = 1.8 Hz, 2H), 6.92 (dd, *J* = 6.6 Hz and *J* = 1.8 Hz, 2H), 6.88 (s, 1H), 4.01 (t, *J* = 7.5 Hz, 1H), 3.84 (s, 3H), 3.79 (s, 3H), 3.35 (s, 3H), 3.02 (ddd, *J* = 48.9 Hz, *J* = 16.2 Hz and *J* = 7.5 Hz, 2H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 171.4, 167.2, 159.8, 143.9, 140.3, 126.9, 126.7, 114.5, 112.4, 111.3, 55.5, 52.9, 38.4, 34.5, 30.6; HRMS (EI): *m/z* calcd for $C_{17}H_{17}NO_4S$ [M]$^+$ 331.0878, found 331.0876.

*Methyl 2-(3-methoxyphenyl)-4-methyl-5-oxo-4,5,6,7-tetrahydrothieno[3,2-b]pyridine-7-carboxylate (**6c**)*. Compound **6c** was obtained as a brown liquid (106 mg, 0.320 mmol, 58%) starting from **5c** (121 mg, 0.552 mmol, 1.0 equiv.). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28 (t, *J* = 8.0 Hz, 1H), 7.13 (d, *J* = 8.5 Hz, 1H), 7.05-7.06 (m, 1H), 6.96 (s, 1H), 6.84 (dd, *J* = 2.3 Hz and *J* = 8.3 Hz, 1H), 4.01 (t, *J* = 7.5 Hz, 1H), 3.83 (s, 3H), 3.77 (s, 3H), 3.33 (s, 3H), 3.00 (ddd, *J* = 46.8 Hz, *J* = 19.2 Hz and *J* = 8.9 Hz, 2H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 171.2, 167.0, 160.1, 143.5, 140.3, 135.0, 130.1, 118.0, 113.5, 113.4, 112.5, 111.2, 55.4, 52.8, 38.3, 34.3, 30.5; HRMS (EI): *m/z* calcd for $C_{17}H_{17}NO_4S$ [M]$^+$ 331.0878, found 331.0876.

*Methyl 2-(2-methoxyphenyl)-4-methyl-5-oxo-4,5,6,7-tetrahydrothieno[3,2-b]pyridine-7-carboxylate (**6d**)*. Compound **6d** was obtained as a pale brown solid (134 mg, 0.404 mmol, 65%) starting from **5d** (136 mg, 0.620 mmol, 1.0 equiv.). m.p: 160-161 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.59 (d, *J* = 7.5 Hz, 1H), 7.28 (t, *J* = 7.8 Hz, 1H), 7.17 (s, 1H), 7.01-6.98 (m, 2H), 4.02 (t, *J* = 7.3 Hz, 1H), 3.94 (s, 3H), 3.77 (s, 3H), 3.36 (s, 3H), 3.02 (ddd, *J* = 57.8 Hz, *J* = 19.4 Hz and *J* = 8.6 Hz, 2H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 171.5, 167.2, 155.8, 139.6, 139.0, 129.0, 128.0, 122.6, 121.1, 115.3, 113.1, 111.7, 55.7, 52.8, 38.4, 34.5, 30.5; HRMS (EI): *m/z* calcd for $C_{17}H_{17}NO_4S$ [M]$^+$ 331.0878, found 331.0881.

*Methyl 4-benzyl-2-(4-methoxyphenyl)-5-oxo-4,5,6,7-tetrahydrothieno[3,2-b]pyridine-7-carboxylate (**6e**)*. Compound **6e** was obtained as a yellow solid (73.3 mg, 0.180 mmol, 77%) starting from **5r** (69.4 mg, 0.235 mmol, 1.0 equiv.). m.p: 99-100 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.36 (dd, *J* = 4.2 Hz and *J* = 2.4 Hz, 2H), 7.31 (t, *J* = 7.5 Hz, 2H), 7.28-7.24 (m, 3H), 6.86 (dd, *J* = 6.6 Hz and *J* = 1.8 Hz, 2H), 6.73 (s, 1H), 5.19 (d, *J* = 16.2 Hz, 1H), 4.99 (d, *J* = 16.2 Hz, 1H), 4.04 (t, *J* = 6.9 Hz, 1H), 3.81 (s, 3H), 3.77 (s, 3H), 3.13 (ddd, *J* = 47.7 Hz, *J* = 16.2 Hz and *J* = 6.9 Hz, 2H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 171.4, 167.4, 159.7, 143.7, 139.6, 137.0, 128.9, 127.5, 126.94, 126.92, 126.6, 114.5, 112.9, 111.8, 55.5, 52.9, 47.0, 38.5, 34.7; HRMS (EI): *m/z* calcd for $C_{23}H_{21}NO_4S$ [M]$^+$ 407.1191, found 407.1188.

*2-(4-Methoxyphenyl)-4-methyl-6,7-dihydrothieno[3,2-b] pyridin-5(4H)-one (**6f**)*. Compound **6f** was obtained as a white solid (38.2 mg, 0.140 mmol, 77%) starting from **5b** (40.0 mg, 0.182 mmol, 1.0 equiv.) and acrylic acid (15.0 µL, 0.218 mmol, 1.2 equiv.). m.p: 152-153 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.46 (dd, *J* = 9.5 Hz and *J* = 2.4 Hz, 2H), 6.91 (dd, *J* = 9.5 Hz and *J* = 2.4 Hz, 2H), 6.87 (s, 1H), 3.83 (s, 3H), 3.34 (s, 3H), 2.94 (t, *J* = 7.8 Hz, 2H), 2.78 (t, *J* = 7.8 Hz, 2H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 168.7, 159.5, 141.6, 139.8, 127.0, 126.8, 115.3, 114.5, 112.5, 55.5, 32.3, 30.5, 20.8; HRMS (EI): *m/z* calcd for $C_{15}H_{15}NO_2S$ [M]$^+$ 273.0824, found 273.0825.

*Methyl 4-methyl-5-oxo-2-(4-phenoxyphenyl)-4,5,6,7-tetrahydrothieno[3,2-b]pyridine-7-carboxylate (**6g**)*. Compound **6g** was obtained as a yellow solid (25.0 mg, 0.0635 mmol, 54%) starting from **5e** (33.0 mg, 0.117 mmol, 1.0 equiv.). m.p: 56-58 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.51 (dd, *J* = 6.6 Hz and *J* = 2.4 Hz, 2H), 7.38-7.35 (m, 2H), 7.14 (tt, *J* = 7.8 Hz and *J* = 2.4 Hz, 1H), 7.05-7.04 (m, 2H), 7.02 (dd, *J* = 2.4 Hz and *J* = 6.6 Hz, 2H), 6.91 (s, 1H), 4.02 (t, *J* = 7.2 Hz, 1H), 3.79 (s, 3H), 3.35 (s, 3H), 3.03 (ddd, *J* = 47.1 Hz, *J* = 16.5 Hz and *J* = 7.2 Hz, 2H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 171.3, 167.1, 157.6, 156.8, 143.3, 140.4, 130.0, 128.9, 127.1, 123.8, 119.3, 119.2, 112.9, 111.9, 52.9, 38.4, 34.4, 30.6; HRMS (EI): *m/z* calcd for $C_{22}H_{19}NO_4S$ [M]$^+$ 393.1035, found 393.1039.

*Methyl 2-(benzo[d][1,3]dioxol-5-yl)-4-methyl-5-oxo-4,5,6,7-tetrahydrothieno[3,2-b]pyridine-7-carboxylate (**6h**)*. Compound **6h** was obtained as a yellow solid (32.8 mg, 0.0950 mmol, 55%) starting from **5f** (40.5 mg, 0.174 mmol, 1.0 equiv.). m.p: 150-151 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.03 (dd, *J* = 8.0 Hz and *J* = 2.0 Hz, 1H), 7.00 (d, *J* = 2.0 Hz, 1H), 6.83 (s, 1H), 6.79 (d, *J* = 8.0 Hz, 1H), 5.97 (s, 2H), 3.99 (t, *J* = 7.3 Hz, 1H), 3.77 (s, 3H), 3.32 (s, 3H), 3.00 (ddd, *J* = 49.4 Hz, *J* = 19.7 Hz and *J* = 8.9 Hz, 2H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 171.3, 167.1, 148.3, 147.8, 143.7, 140.2, 128.1, 119.4, 112.7, 111.5, 108.8, 106.2, 101.5, 52.8, 38.3, 34.4, 30.5; HRMS (EI): *m/z* calcd for $C_{17}H_{15}NO_5S$ [M]$^+$ 345.0671, found 345.0668.

*Methyl 2-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-4-methyl-5-oxo-4,5,6,7-tetrahydrothieno[3,2-b]pyridine-7-carboxlate (**6i**)*. Compound **6i** was obtained as a yellow solid (130 mg, 0.362 mmol, 62%) starting from **5g** (145 mg, 0.586 mmol, 1.0 equiv.). m.p: 126-128 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.02 (d, *J* = 2.0 Hz, 1H), 6.99 (dd, *J* = 2.3 Hz and *J* = 9.0 Hz, 1H), 6.82-6.80 (m, 2H), 4.23 (s, 4H), 3.95 (t, *J* = 7.3 Hz, 1H), 3.74 (s, 3H), 3.28 (s, 3H), 2.96 (ddd, *J* = 51.9 Hz, *J* = 19.8 Hz and *J* = 8.7 Hz, 2H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 171.2, 167.0, 143.8, 143.7, 143.3, 140.1, 127.3, 118.7, 117.7, 114.3, 112.5, 111.4, 64.44, 64.39, 52.7, 38.2, 34.3, 30.4; HRMS (EI): *m/z* calcd for $C_{18}H_{17}NO_5S$ [M]$^+$ 359.0827, found 359.0825.

*Methyl 4-methyl-5-oxo-2-(3,4,5-trimethoxyphenyl)-4,5,6,7-tetrahydrothieno[3,2-b]pyridine-7-carboxylate (**6j**)*. Compound **6j** was obtained as a yellow solid (60.4 mg, 0.154 mmol, 54%) starting from **5h** (80.0 mg, 0.286 mmol, 1.0 equiv.). m.p: 133-134 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.89 (s, 1H), 6.73 (s, 2H), 4.02 (t, *J* = 7.5 Hz, 1H), 3.91 (s, 6H), 3.86 (s, 3H), 3.79 (s, 3H), 3.36 (s, 3H), 3.02 (ddd, *J* = 38.4 Hz, *J* = 16.2 Hz and *J* = 7.2 Hz, 2H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 171.3, 167.2, 153.7, 144.0, 140.2, 138.4, 129.6, 113.2, 112.2, 103.2, 61.1, 56.4, 52.9, 38.3, 34.4, 30.7; HRMS

(EI): *m/z* calcd for $C_{19}H_{21}NO_6S$ $[M]^+$ 391.1090, found 391.1088.

Methyl 2-(4-(dimethylamino)phenyl)-4-methyl-5-oxo-4,5,6,7-tetrahydrothieno[3,2-b]pyridine-7-carboxylate ***(6k)***. Compound **6k** was obtained as an orange-brown solid (83.1 mg, 0.241 mmol, 61%) starting from **5i** (91.6 mg, 0.394 mmol, 1.0 equiv.). m.p: 121-123 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.43 (d, *J* = 9.0 Hz, 2H), 6.82 (s, 1H), 6.72 (d, *J* = 7.8 Hz, 2H), 3.99 (t, *J* = 7.2 Hz, 1H), 3.78 (s, 3H), 3.34 (s, 3H), 3.02 (m, 8H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 171.6, 167.3, 150.4, 144.8, 140.2, 126.6, 122.1, 112.6, 111.1, 110.0, 52.8, 40.6, 38.4, 34.5, 30.6; HRMS (EI): *m/z* calcd for $C_{18}H_{20}N_2O_3S$ $[M]^+$ 344.1195, found 344.1193.

Methyl 2-(3-(dimethylamino)phenyl)-4-methyl-5-oxo-4,5,6,7-tetrahydrothieno[3,2-b]pyridine-7-carboxylate ***(6l)***. Compound **6l** was obtained as a brown solid (102 mg, 0.296 mmol, 61%) starting from **5j** (114 mg, 0.491 mmol, 1.0 equiv.). m.p: 99-100 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.24 (t, *J* = 8.1 Hz, 1H), 6.96 (s, 1H), 6.92 (d, *J* = 7.8 Hz, 1H), 6.86 (s, 1H), 6.70 (dd, *J* = 8.4 Hz and *J* = 2.4 Hz, 1H), 4.02 (t, *J* = 7.2 Hz, 1H), 3.78 (s, 3H), 3.35 (s, 3H), 3.08-2.96 (m, 8H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 171.4, 167.2, 151.0, 144.9, 140.2, 134.5, 129.8, 114.2, 113.1, 112.5, 112.0, 109.5, 52.9, 40.7, 38.4, 34.4, 30.6; HRMS (EI): *m/z* calcd for $C_{18}H_{20}N_2O_3S$ $[M]^+$ 344.1195, found 344.1193.

Methyl 2-(2-(dimethylamino)phenyl)-4-methyl-5-oxo-4,5,6,7-tetrahydrothieno[3,2-b]pyridine-7-carboxylate ***(6m)***. Compound **6m** was obtained as a yellow liquid (118 mg, 0.342 mmol, 76%) starting from **5k** (105 mg, 0.452 mmol, 1.0 equiv.). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.52 (d, *J* = 7.8 Hz, 1H), 7.24 (t, *J* = 7.5 Hz, 1H), 7.16 (d, *J* = 8.4 Hz, 1H), 7.12 (s, 1H), 7.06 (t, *J* = 7.2 Hz, 1H), 4.03 (t, *J* = 6.9 Hz, 1H), 3.79 (s, 3H), 3.38 (s, 3H), 3.04 (ddd, *J* = 7.1 Hz, *J* = 16.4 Hz and *J* = 60.2 Hz, 2H), 2.65 (s, 6H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 171.6, 167.2, 151.0, 140.9, 139.0, 128.6, 128.5, 128.4, 123.6, 120.5, 114.5, 113.9, 52.7, 44.4, 38.4, 34.5, 30.4; HRMS (EI): *m/z* calcd for $C_{18}H_{20}N_2O_3S$ $[M]^+$ 344.1195, found 344.1197.

Methyl 4-benzyl-2-(4-(dimethylamino)phenyl)-5-oxo-4,5,6,7-tetrahydrothieno[3,2-b]pyridine-7-carboxylate ***(6n)***. Compound **6n** was obtained as an orange liquid (66.3 mg, 0.158 mmol, 81%) starting from **5s** (60.0 mg, 0.194 mmol, 1.0 equiv.). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.33-7.27 (m, 6H), 7.25-7.22 (m, 1H), 6.69 (s, 1H), 6.67 (d, *J* = 8.4 Hz, 2H), 5.19 (d, *J* = 15.6 Hz, 1H), 4.99 (d, *J* = 15.6 Hz, 1H), 4.02 (t, *J* = 6.6 Hz, 1H), 3.77 (s, 3H), 3.12 (ddd, *J* = 49.8 Hz, *J* = 16.2 Hz and *J* = 6.6 Hz, 2H), 2.96 (s, 6H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 171.4, 167.4, 150.3, 144.6, 139.4, 137.0, 128.7, 127.3, 126.9, 126.5, 121.9, 112.4, 111.6, 110.3, 52.7, 46.8, 40.4, 38.4, 34.6; HRMS (EI): *m/z* calcd for $C_{24}H_{24}N_2O_3S$ $[M]^+$ 420.1508, found 420.1505.

Methyl 2-(4-(diethylamino)phenyl)-4-methyl-5-oxo-4,5,6,7-tetrahydrothieno[3,2-b]pyridine-7-carboxylate ***(6o)***. Compound **6o** was obtained as a sticky orange solid (166 mg, 0.446 mmol, 73%) starting from **5l** (160 mg, 0.614 mmol, 1.0 equiv.). m.p: 62-64 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 (d, *J* = 8.5 Hz, 2H), 6.79 (s, 1H), 6.64 (d, *J* = 8.5 Hz, 2H), 3.97 (t, *J* = 7.0 Hz, 1H), 3.77 (s, 3H), 3.38 (q, *J* = 7.2 Hz, 4H), 3.33 (s, 3H), 3.00 (ddd, *J* = 46.6 Hz, *J* = 16.3 Hz and *J* = 7.1 Hz, 2H), 1.18 (t, *J* = 7.3 Hz, 6H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 171.5, 167.2, 147.7, 145.0, 140.1, 126.7, 120.9, 111.7, 110.7, 109.5, 52.7, 44.4, 38.3, 34.5, 30.5, 12.7; HRMS (EI): *m/z* calcd for $C_{20}H_{24}N_2O_3S$ $[M]^+$ 372.1508, found 372.1505.

Methyl 4-methyl-2-(4-(4-methylpiperazin-1-yl)phenyl)-5-oxo-4,5,6,7-tetrahydrothieno[3,2-b]pyridine-7-carboxylate ***(6p)***. Compound **6p** was obtained as a pale orange solid (26.1 mg, 0.0653 mmol, 38%) starting from **5m** (50.0 mg, 0.174 mmol, 1.0 equiv.) The mixture was purified by flash column chromatography (DCM/MeOH = 15/1, v/v) on silica. m.p: 112-114 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.45 (d, *J* = 8.4 Hz, 2H), 6.91 (d, *J* = 9.0 Hz, 2H), 6.86 (s, 1H), 4.00 (t, *J* = 7.2 Hz, 1H), 3.78 (s, 3H), 3.34 (s, 3H), 3.30-3.28 (m, 4H), 3.02 (ddd, *J* = 49.8 Hz, *J* = 16.2 Hz and *J* = 7.2 Hz, 2H), 2.34-2.62 (m, 4H), 2.39 (s, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 171.5, 167.2, 151.0, 144.2, 140.3, 126.6, 125.2, 116.0, 111.9, 110.8, 55.0, 52.9, 48.5, 46.1, 38.4, 34.5, 30.6; HRMS (EI): *m/z* calcd for $C_{21}H_{25}N_3O_3S$ $[M]^+$ 399.1617, found 399.1615.

Methyl 4-methyl-5-oxo-2-(2,3,6,7-tetrahydro-1H,5H-pyrido[3,2,1-ij]quinolin-9-yl)-4,5,6,7-tetrahydrothieno[3,2-b]pyridine-7-carboxylate ***(6q)***. Compound **6q** was obtained as an orange solid (63.6 mg, 0.160 mmol, 65%) starting from **5n** (70.0 mg, 0.246 mmol, 1.0 equiv.). m.p: 135-137 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.00 (s, 2H), 6.77 (s, 1H), 3.98 (t, *J* = 7.3 Hz, 1H), 3.78 (s, 3H), 3.34 (s, 3H), 3.19 (m, 4H), 3.01 (ddd, *J* = 44.0 Hz, *J* = 16.3 Hz and *J* = 7.8 Hz, 2H), 2.78 (t, *J* = 6.5 Hz, 4H), 2.00 (m, 4H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 171.6, 167.3, 145.3, 143.1, 140.1, 125.0, 124.4, 121.7, 121.6, 121.1, 110.6, 109.4, 52.8, 50.1, 38.4, 34.6, 30.6, 27.8, 22.0; HRMS (EI): *m/z* calcd for $C_{22}H_{24}N_2O_3S$ $[M]^+$ 396.1508, found 396.1504.

General Procedure for the Synthesis of KF-1 ~ KF-5, KF-12 ~ KF-19, KF-22 ~ KF-24 (Route B)

To a solution of **6a** (20.2 mg, 0.0670 mmol, 1.0 equiv.) in DMF (0.7 mL, 0.25 M), potassium carbonate (14.0 mg, 0.100 mmol, 1.5 equiv.) was added. And then, the reaction was heated to 70 °C and stirred for 1 h. After completion of the reaction, water (1 mL) was added. The crude was extracted with EtOAc (1 mL) at three times. The organic layer was dried over Na_2SO_4, filtered and evaporated *in vacuo*. The residue was purified by flash column chromatography (Hexane/EtOAc = 1/1, v/v) on silica to afford the product **KF-1**.

Methyl 4-methyl-5-oxo-2-phenyl-4,5-dihydrothieno[3,2-b]pyridine-7-carboxylate ***(KF-1)***. Compound **KF-1** was obtained as a yellow solid (9.60 mg, 0.0320 mmol, 48%) starting from **6a** (20.2 mg, 0.0670 mmol, 1.0 equiv.). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.72 (d, *J* = 7.2 Hz, 2H), 7.46 (t, *J* = 7.5 Hz, 2H), 7.41 (t, *J* = 7.2 Hz, 1H), 7.27 (s, 1H), 7.23 (s, 1H), 4.02 (s, 3H), 3.79 (s, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 165.1, 162.4, 151.3, 145.8, 134.1, 133.4, 129.5, 129.4, 126.4, 119.0, 115.7, 111.3, 53.3, 32.4; Data are consistent with those reported in the literature.[7a]

Methyl 2-(4-methoxyphenyl)-4-methyl-5-oxo-4,5-dihydrothieno[3,2-b]pyridine-7-carboxylate ***(KF-2)***. Compound **KF-2** was obtained as a yellow solid (29.5 mg, 0.0896 mmol, 50%) starting from **6b** (60.0 mg, 0.181 mmol, 1.0 equiv.). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.65 (d, *J* = 9.0 Hz, 2H), 7.22 (s, 1H), 7.17 (s, 1H), 6.97 (d, *J* = 9.0 Hz, 2H), 4.01 (s, 3H), 3.87 (s, 3H), 3.79 (s, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 165.2, 162.5, 160.8, 151.6, 146.0, 134.1, 127.7, 126.0, 118.1, 114.8, 110.1, 55.6, 53.3, 32.4; Data are consistent with those reported in the literature.[7a]

*Methyl 2-(3-methoxyphenyl)-4-methyl-5-oxo-4,5-dihydro thieno[3,2-b]pyridine-7-carboxylate (**KF-3**)*. Compound **KF-3** was obtained as a yellow solid (54.8 mg, 0.166 mmol, 65%) starting from **6c** (85.1 mg, 0.257 mmol, 1.0 equiv.). m.p: 155-156 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.40 (t, *J* = 8.1 Hz, 1H), 7.34 (d, *J* = 7.2 Hz, 1H), 7.29 (d, *J* = 4.2 Hz, 2H), 7.26-7.25 (m, 1H), 6.98 (dd, *J* = 8.1 Hz and *J* = 2.7 Hz, 1H), 4.05 (s, 3H), 3.92(s, 3H), 3.82 (s, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 165.1, 162.3, 160.3, 151.0, 145.7, 134.6, 134.0, 130.4, 119.0, 118.8, 115.6, 115.0, 111.8, 111.4, 55.6, 53.3, 32.3; HRMS (EI): *m/z* calcd for $C_{17}H_{15}NO_4S$ [M]$^+$ 329.0722, found 329.0719.

*Methyl 2-(2-methoxyphenyl)-4-methyl-5-oxo-4,5-dihydrothieno[3,2-b]pyridine-7-carboxylate (**KF-4**)*. Compound **KF-4** was obtained as a yellow solid (47.8 mg, 0.145 mmol, 49%) starting from **6d** (98.6 mg, 0.297 mmol, 1.0 equiv.). m.p: 164-168 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.70 (dd, *J* = 8.0 Hz and *J* = 1.8 Hz, 1H), 7.45 (s, 1H), 7.35 (td, *J* = 8.0 Hz and *J* = 1.5 Hz, 1H), 7.17 (s, 1H), 7.05-7.01 (m, 2H), 3.98 (s, 3H), 3.97 (s, 3H), 3.75 (s, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 165.3, 162.5, 156.5, 147.2, 145.2, 134.1, 130.5, 128.9, 122.1, 121.3, 118.6, 116.4, 113.6, 112.0, 55.8, 53.2, 32.3; HRMS (EI): *m/z* calcd for $C_{17}H_{15}NO_4S$ [M]$^+$ 329.0722, found 329.0722.

*Methyl 4-benzyl-2-(4-methoxyphenyl)-5-oxo-4,5-dihydrothieno[3,2-b]pyridine-7-carboxylate (**KF-5**)*. Compound **KF-5** was obtained as a yellow solid (17.8 mg, 0.0439 mmol, 42%) starting from **6e** (42.3 mg, 0.104 mmol, 1.0 equiv.). m.p: 143-145 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.54 (dd, *J* = 6.9 Hz and *J* = 2.1 Hz, 2H), 7.32-7.26 (m, 6H), 7.06 (s, 1H), 6.93 (dd, *J* = 6.6 Hz and *J* = 1.8 Hz, 2H), 5.52 (s, 2H), 4.02 (s, 3H), 3.84 (s, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 165.2, 162.4, 160.8, 151.4, 145.6, 135.9, 134.4, 129.1, 127.9, 127.7, 127.2, 126.0, 118.4, 115.4, 114.7, 110.7, 55.6, 53.3, 48.7; HRMS (EI): *m/z* calcd for $C_{23}H_{19}NO_4S$ [M]$^+$ 405.1035, found 405.1032.

*Methyl 4-methyl-5-oxo-2-(4-phenoxyphenyl)-4,5-dihydrothieno[3,2-b]pyridine-7-carboxylate (**KF-12**)*. Compound **KF-12** was obtained as a yellow solid (15.0 mg, 0.0383 mmol, 63%) starting from **6g** (24.2 mg, 0.0615 mmol, 1.0 equiv.). m.p: 178-180 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.67 (dd, *J* = 8.4 Hz and *J* = 3.0 Hz, 2H), 7.38 (t, *J* = 8.1 Hz, 2H), 7.20-7.16 (m, 3H), 7.08-7.05 (m, 4H), 4.01 (s, 3H), 3.78 (s, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 165.1, 162.4, 158.9, 156.4, 150.9, 145.9, 134.1, 130.1, 128.2, 127.9, 124.2, 119.7, 119.0, 118.6, 115.4, 110.7, 53.3, 32.4; HRMS (EI): *m/z* calcd for $C_{22}H_{17}NO_4S$ [M]$^+$ 391.0878, found 391.0875.

*Methyl 2-(benzo[d][1,3]dioxol-5-yl)-4-methyl-5-oxo-4,5-dihydrothieno[3,2-b]pyridine-7-carboxylate (**KF-13**)*. Compound **KF-13** was obtained as a yellow solid (13.0 mg, 0.0379 mmol, 40%) starting from **6h** (32.8 mg, 0.0950 mmol, 1.0 equiv.). m.p: 183-184 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.22 (dd, *J* = 7.8 Hz and *J* = 1.8 Hz, 1H), 7.20 (s, 1H), 7.16 (d, *J* = 1.8 Hz, 1H), 7.13 (s, 1H), 6.87 (d, *J* = 7.8 Hz, 1H), 6.04 (s, 2H), 4.01 (s, 3H), 3.77 (s, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 165.1, 162.4, 151.3, 148.9, 148.6, 145.8, 134.0, 127.6, 120.6, 118.5, 115.1, 110.6, 109.1, 106.7, 101.8, 53.3, 32.3; HRMS (EI): *m/z* calcd for $C_{17}H_{13}NO_5S$ [M]$^+$ 343.0514, found 343.0513.

*Methyl 2-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-4-methyl-5-oxo-4,5-dihydrothieno[3,2-b]pyridine-7-carboxylate (**KF-14**)*. Compound **KF-14** was obtained as a yellow solid (58.4 mg, 0.163 mmol, 50%) starting from **6i** (116 mg, 0.323 mmol, 1.0 equiv.). m.p: 222-224 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.17-7.13 (m, 2H), 7.22 (s, 1H), 7.07 (s, 1H), 6.68 (d, *J* = 8.4 Hz, 1H), 4.29 (s, 4H), 3.98 (s, 3H), 3.72 (s, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 165.0, 162.3, 151.0, 145.8, 144.9, 144.0, 133.8, 126.8, 119.6, 118.3, 118.1, 115.1, 114.9, 110.3, 64.6, 64.5, 53.2, 32.2; HRMS (EI): *m/z* calcd for $C_{18}H_{15}NO_5S$ [M]$^+$ 357.0671, found 357.0669.

*Methyl 4-methyl-5-oxo-2-(3,4,5-trimethoxyphenyl)-4,5-dihydrothieno[3,2-b]pyridine-7-carboxylate (**KF-15**)*. Compound **KF-15** was obtained as a yellow solid (13.3 mg, 0.0342 mmol, 26%) starting from **6j** (52.0 mg, 0.133 mmol, 1.0 equiv.). m.p: 205-208 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.21 (s, 1H), 7.18 (s, 1H), 6.89 (s, 2H), 4.01 (s, 3H), 3.95 (s, 6H), 3.90 (s, 3H), 3.80 (s, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 165.2, 162.4, 153.9, 151.4, 145.7, 139.5, 133.9, 129.0, 118.8, 115.4, 111.1, 103.8, 61.2, 56.5, 53.3, 32.4; HRMS (EI): *m/z* calcd for $C_{19}H_{19}NO_6S$ [M]$^+$ 389.0933, found 389.0930.

*Methyl 2-(4-(dimethylamino)phenyl)-4-methyl-5-oxo-4,5-dihydrothieno[3,2-b]pyridine-7-carboxylate (**KF-16**)*. Compound **KF-16** was obtained as an orange-red solid (19.6 mg, 0.0572 mmol, 33%) starting from **6k** (60.0 mg, 0.174 mmol, 1.0 equiv.). m.p: 178-180 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.60 (d, *J* = 8.4 Hz, 2H), 7.14 (s, 1H), 7.10 (s, 1H), 6.73 (d, *J* = 8.4 Hz, 2H), 4.00 (s, 3H), 3.77 (s, 3H), 3.04 (s, 6H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 165.4, 162.5, 152.6, 151.2, 146.4, 133.9, 127.3, 121.1, 117.2, 114.2, 112.3, 108.5, 53.2, 40.4, 32.3; HRMS (EI): *m/z* calcd for $C_{18}H_{18}N_2O_3S$ [M]$^+$ 342.1038, found 342.1037.

*Methyl 2-(3-(dimethylamino)phenyl)-4-methyl-5-oxo-4,5-dihydrothieno[3,2-b]pyridine-7-carboxylate (**KF-17**)*. Compound **KF-17** was obtained as a yellow solid (22.0 mg, 0.0642 mmol, 27%) starting from **6l** (81.2 mg, 0.236 mmol, 1.0 equiv.). m.p: 170-172 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.29-7.26 (m, 1H), 7.19 (s, 1H), 7.16 (s, 1H), 7.02 (d, *J* = 7.2 Hz, 1H), 6.94 (s, 1H), 6.74 (d, *J* = 8.4 Hz, 1H), 3.99 (s, 3H), 3.75 (s, 3H), 3.01 (s, 6H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 165.1, 162.3, 152.4, 151.0, 145.7, 134.0, 133.9, 129.9, 118.5, 115.3, 114.5, 113.5, 111.0, 109.8, 53.2, 40.6, 32.3; HRMS (EI): *m/z* calcd for $C_{18}H_{18}N_2O_3S$ [M]$^+$ 342.1038 found 342.1039.

*Methyl 2-(2-(dimethylamino)phenyl)-4-methyl-5-oxo-4,5-dihydrothieno[3,2-b]pyridine-7-carboxylate (**KF-18**)*. Compound **KF-18** was obtained as a yellow solid (28.3 mg, 0.0826 mmol, 32%) starting from **6m** (88.0 mg, 0.255 mmol, 1.0 equiv.). m.p: 120-122 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.60 (d, *J* = 7.8 Hz, 1H), 7.41 (s, 1H), 7.32 (t, *J* = 7.8 Hz, 1H), 7.21-7.20 (m, 2H), 7.11 (t, *J* = 7.8 Hz, 1H), 4.00 (s, 3H), 3.78 (s, 3H), 2.69 (s, 6H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 165.3, 162.4, 151.9, 149.6, 145.0, 134.3, 129.9, 129.6, 127.9, 123.5, 120.4, 118.6, 117.2, 112.8, 53.1, 44.4, 32.2; HRMS (EI): *m/z* calcd for $C_{18}H_{18}N_2O_3S$ [M]$^+$ 342.1038, found 342.1041.

*Methyl 4-benzyl-2-(4-(dimethylamino)phenyl)-5-oxo-4,5-dihydrothieno[3,2-b]pyridine-7-carboxylate (**KF-19**)*. Compound **KF-19** was obtained as a red solid (18.4 mg, 0.0440 mmol, 37%) starting from **6n** (50.0 mg, 0.119 mmol, 1.0 equiv.). m.p: 187-189 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.48 (d, *J* = 9.0 Hz, 2H), 7.32-7.28 (m, 4H), 7.26-7.25 (m, 1H), 7.21 (s, 1H), 7.00 (s, 1H), 6.69 (d, *J* = 8.4 Hz, 2H), 5.50 (s, 2H), 4.01 (s, 3H), 3.01 (s, 6H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 165.3, 162.5, 152.5, 151.0, 146.0, 136.0, 134.3,

129.0, 127.8, 127.3, 127.2, 117.3, 114.6, 112.3, 109.1, 53.2, 48.6, 40.4; HRMS (EI): *m/z* calcd for $C_{24}H_{22}N_2O_3S$ $[M]^+$ 418.1351, found 418.1348.

*Methyl 2-(4-(diethylamino)phenyl)-4-methyl-5-oxo-4,5-dihydrothieno[3,2-b]pyridine-7-carboxylate (**KF-22**)*. Compound **KF-22** was obtained as an orange solid (29.4 mg, 0.0794 mmol, 53%) starting from **6o** (55.8 mg, 0.150 mmol, 1.0 equiv.). m.p: 146-148 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.53 (d, *J* = 9.0 Hz, 2H), 7.08 (s, 1H), 7.02 (s, 1H), 6.66 (d, *J* = 8.4 Hz, 2H), 3.97 (s, 3H), 3.72 (s, 3H), 3.40 (q, *J* = 7.2 Hz, 4H), 1.20 (t, *J* = 7.2 Hz, 6H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 165.3, 162.5, 151.7, 148.6, 146.4, 133.8, 127.5, 120.0, 116.8, 114.0, 111.6, 108.0, 53.1, 44.5, 32.2, 12.7; HRMS (EI): *m/z* calcd for $C_{20}H_{22}N_2O_3S$ $[M]^+$ 370.1351, found 370.1354.

*Methyl 4-methyl-2-(4-(4-methylpiperazin-1-yl)phenyl)-5-oxo-4,5-dihydrothieno[3,2-b]pyridine-7-carboxylate (**KF-23**)*. Compound **KF-23** was obtained as a dark red solid (10.0 mg, 0.0252 mmol, 41%) starting from **6p** (24.6 mg, 0.0616 mmol, 1.0 equiv.). m.p: 135-136 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.60 (d, *J* = 10.2 Hz, 2H), 7.15 (s, 1H), 7.12 (s, 1H), 6.93 (d, *J* = 10.8 Hz, 2H), 3.99 (s, 3H), 3.76 (s, 3H), 3.32 (t, *J* = 5.7 Hz, 4H), 2.62 (t, *J* = 5.7 Hz, 4H), 2.38 (s, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 165.3, 162.5, 151.9, 151.8, 146.2, 133.9, 127.3, 124.0, 117.8, 115.6, 114.6, 109.4, 54.9, 53.2, 48.1, 46.2, 32.3; HRMS (EI): *m/z* calcd for $C_{21}H_{23}N_3O_3S$ $[M]^+$ 397.1460 found 397.1459.

*Methyl 4-methyl-5-oxo-2-(2,3,6,7-tetrahydro-1H,5H-pyrido[3,2,1-ij]quinolin-9-yl)-4,5-dihydrothieno[3,2-b]pyridine-7-carboxylate (**KF-24**)*. Compound **KF-24** was obtained as an orange solid (18.0 mg, 0.0456 mmol, 36%) starting from **6q** (50.0 mg, 0.126 mmol, 1.0 equiv.). m.p: 176-177 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.16 (s, 2H), 7.10 (s, 1H), 7.03 (s, 1H), 3.99 (s, 3H), 3.76 (s, 3H), 3.24-3.22 (m, 4H), 2.89 (t, *J* = 6.6 Hz, 4H), 2.10-2.08 (m, 4H);^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 165.4, 162.6, 153.2, 146.5, 144.2, 133.9, 125.0, 121.6, 120.0, 116.6, 114.0, 107.8, 53.1, 50.0, 32.3, 27.9, 21.8; HRMS (EI): *m/z* calcd for $C_{22}H_{22}N_2O_3S$ $[M]^+$ 394.1351, found 394.1347.

Procedures for the Synthesis of KF-6 ~ KF-8 (Route C)

*2-(4-Methoxyphenyl)-4-methylthieno[3,2-b]pyridin-5(4H)-one (**KF-6**)*. To a solution of **KF-6** (37.9 mg, 0.139 mmol, 1.0 equiv.) in DCM (1.5 mL, 0.25 M), *N*-bromosuccinimide (28.0 mg, 0.193 mmol, 1.1 equiv.) was added at 0 °C. The reaction was warmed up to room temperature and stirred for 18 h. After completion of the reaction, water (2 mL) was added. The crude was extracted with DCM (2 mL) at three times. The organic layer was dried over Na_2SO_4, filtered and evaporated *in vacuo*. The residue was purified by flash column chromatography (Hexane/EtOAc = 1/2, v/v) on silica to afford the product **KF-6** as a white solid (16.9 mg, 0.0623 mmol, 45%). m.p: 158-160 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.63 (d, *J* = 9.0 Hz, 1H), 7.58 (d, *J* = 8.4 Hz, 2H), 7.13 (s, 1H), 6.96 (d, *J* = 8.4 Hz, 2H), 6.55 (d, *J* = 9.0 Hz, 1H), 3.86 (s, 3H), 3.74 (s, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 162.4, 160.6, 148.9, 145.0, 133.1, 127.6, 126.0, 117.3, 116.6, 114.7, 110.9, 55.6, 32.0; HRMS (EI): *m/z* calcd for $C_{15}H_{13}NO_2S$ $[M]^+$ 271.0667, found 271.0666.

*2-(4-Methoxyphenyl)-4,7-dimethylthieno[3,2-b]pyridin-5(4 H)-one (**KF-7**)*. To a solution of **5b** (60 mg, 0.2736 mmol, 1.0 equiv.) in DMF (2.0 mL, 0.14 M), crotonic acid (26.6 mg, 0.3283 mmol, 1.2 equiv.), BOP (145 mg, 0.3283 mmol, 1.2 equiv.) and DIPEA (119 μL, 0.684 mmol, 2.5 equiv.) were added. The reaction was stirred at room temperature for 1 h. For quenching the reaction, water was added. The mixture was extracted with EtOAc at three times (4 mL). The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The crude was used without further purification. To a solution of crude (56.4 mg, 0.1963 mmol, 1.0 equiv.) in DCM (1.5 mL, 0.13 M), *N*-bromosuccinimide (42 mg, 0.2355 mmol, 1.2 equiv.) and *p*-toluenesulfonic acid (3.7 mg, 0.0196 mmol, 0.1 equiv.) were added. The reaction mixture was stirred at room temperature for 5 h. After completion of the reaction, water was added. The mixture was extracted with DCM at three times (5 mL). The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The crude was purified by flash column chromatography to obtain the product **KF-7** as a white solid (15.9 mg, 0.0557 mmol, 22%, two steps). m.p: 180-182 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.58 (dd, *J* = 6.6 Hz and *J* = 2.4 Hz, 2H), 7.12 (s, 1H), 6.95 (dd, *J* = 6.6 Hz and *J* = 1.8 Hz, 2H), 6.37 (d, *J* = 1.2 Hz, 1H), 3.85 (s, 3H), 3.69 (s, 3H), 2.35 (d, *J* = 1.2 Hz, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 162.8, 160.5, 147.5, 144.0, 127.5, 126.2, 119.3, 115.6, 114.7, 111.2, 55.6, 31.8, 19.8; HRMS (EI): *m/z* calcd for $C_{16}H_{15}NO_2S$ $[M]^+$ 285.0824, found 285.0826.

*2-(4-Methoxyphenyl)-4-methyl-7-phenylthieno[3,2-b]pyridin-5(4H)-one (**KF-8**)*. To a solution of **5b** (40 mg, 0.1824 mmol, 1.0 equiv.) in DMF (1.8 mL, 0.1 M), *trans*-cinnamic acid (32.4 mg, 0.2189 mmol, 1.2 equiv.), BOP (97 mg, 0.2189 mmol, 1.2 equiv.) and DIPEA (79 μL, 0.456 mmol, 2.5 equiv.) were added. The reaction was stirred at room temperature for 1 h. For quenching the reaction, water was added. The mixture was extracted with EtOAc at three times (4 mL). The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The crude was used without further purification. To a solution of crude (68.8 mg, 0.1969 mmol, 1.0 equiv.) in DCM (2 mL, 0.1 M), *N*-bromosuccinimide (42 mg, 0.2363 mmol, 1.2 equiv.) and *p*-toluenesulfonic acid (3.7 mg, 0.0197 mmol, 0.1 equiv.) were added. The reaction mixture was stirred at room temperature for 5 h. After completion of the reaction, water was added. The mixture was extracted with DCM at three times (5 mL). The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The crude was purified by flash column chromatography to obtain the product **KF-8** as a white solid (16.4 mg, 0.0472 mmol, 15%, two steps). m.p: 165-167 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.68-7.67 (m, 2H), 7.58 (d, *J* = 8.4 Hz, 2H), 7.52-7.49 (m, 3H), 7.19 (s, 1H), 6.93 (d, *J* = 8.4 Hz, 2H), 6.60 (s, 1H), 3.85 (s, 3H), 3.77 (s, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 162.8, 160.6, 148.8, 147.1, 145.0, 137.5, 129.7, 129.1, 127.8, 127.5, 126.0, 117.4, 114.9, 114.7, 111.2, 55.6, 31.9; HRMS (EI): *m/z* calcd for $C_{21}H_{17}NO_2S$ $[M]^+$ 347.0980, found 347.0977.

General Procedure for the Synthesis of KF-9 ~ KF-11, KF-20 ~ KF-21, KF-25 ~ KF-27 (Route A)

To a solution of **5b** (30.0 mg, 0.137 mmol, 1.0 equiv.) in DMF (1.4 ml), 2-oxo-4-pentenoic acid (18.7 mg, 0.164 mmol, 1.2 equiv.), BOP (77 mg, 0.164 mmol, 1.2 equiv.) and DIPEA (61 μL, 0.343 mmol, 2.5 equiv.) were added. The reaction was stirred at room temperature for 0.5 h. After completion of the reaction, water (1 mL) was added. The crude was extracted with EtOAc (1 mL) at three times. The organic layer was dried over Na_2SO_4, filtered and evaporated in vacuo. The residue

was purified by flash column chromatography (Hexane/EtOAc = 1/1, v/v) on silica to afford the product **KF-9**.

*7-Acetyl-2-(4-methoxyphenyl)-4-methylthieno[3,2-b]pyridi n-5(4H)-one (**KF-9**)*. Compound **KF-9** was obtained as a yellow solid (9.6 mg, 0.0320 mmol, 48%) starting from **5b** (30.0 mg, 0.137 mmol, 1.0 equiv.) and 2-oxo-4-pentenoic acid (18.7 mg, 0.164 mmol, 1.2 equiv.). m.p: 221-222 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.64 (d, J = 8.4 Hz, 2H), 7.13 (s, 1H), 7.09 (s, 1H), 6.96 (d, J = 9.0 Hz, 2H), 3.86 (s, 3H), 3.78 (s, 3H), 2.65 (s, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 197.9, 163.0, 160.8, 152.8, 146.1, 139.1, 127.7, 126.1, 118.3, 114.7, 113.1, 109.6, 55.6, 32.4, 26.3; HRMS (EI): *m/z* calcd for $C_{17}H_{15}NO_3S$ $[M]^+$ 313.0773, found 313.0772.

*7-Acetyl-4-benzyl-2-(4-methoxyphenyl)thieno[3,2-b]pyridi n-5(4H)-one (**KF-10**)*. Compound **KF-10** was obtained as a green solid (20.4 mg, 0.0524 mmol, 26%) starting from **5r** (60.0 mg, 0.203 mmol, 1.0 equiv.) and (*E*)-4-oxopent-2-enoic acid (27.8 mg, 0.244 mmol, 1.2 equiv.). m.p: 202-204 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.54 (dd, J = 6.6 Hz and J = 1.8 Hz, 2H), 7.33-7.24 (m, 5H), 7.17 (s, 1H), 7.05 (s, 1H), 6.92 (dd, J = 6.9 Hz and J = 2.1 Hz, 2H), 5.52 (s, 2H), 3.83 (s, 3H), 2.67 (s, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 197.9, 163.0, 160.7, 152.8, 145.8, 139.4, 135.8, 129.0, 127.9, 127.7, 127.1, 126.1, 118.5, 114.6, 113.5, 110.1, 55.5, 48.7, 26.4; Data are consistent with those reported in the literature.[7a]

*7-Benzoyl-4-benzyl-2-(4-methoxyphenyl)thieno[3,2-b]pyrid in-5(4H)-one (**KF-11**)*. Compound **KF-11** was obtained as an orange solid (23.2 mg, 0.0514 mmol, 38%) starting from **5r** (40.0 mg, 0.135 mmol, 1.0 equiv.) and 3-benzoylacrylic acid (28.6 mg, 0.163 mmol, 1.2 equiv.). m.p: 148-150 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.89 (dd, J = 8.1 Hz and J = 1.5 Hz, 2H), 7.65 (tt, J = 7.5 Hz and J = 1.2 Hz, 1H), 7.55-7.52 (m, 4H), 7.34 (d, J = 4.8 Hz, 4H), 6.92 (quin, J = 4.2 Hz, 1H), 7.11 (s, 1H), 6.93-6.91 (m, 3H), 5.54 (s, 2H), 3.83 (s, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 194.7, 162.4, 160.7, 151.8, 145.8, 139.9, 135.94, 135.9, 133.6, 130.1, 129.0, 128.8, 127.9, 127.7, 127.2, 126.0, 120.1, 115.0, 114.7, 110.6, 55.5, 48.7; HRMS (EI): *m/z* calcd for $C_{28}H_{21}NO_3S$ $[M]^+$ 451.1242, found 451.1245.

*7-Acetyl-2-(4-(dimethylamino)phenyl)-4-methylthieno[3,2-b]pyridin-5(4H)-one (**KF-20**)*. Compound **KF-20** was obtained as a red solid (15.0 mg, 0.0460 mmol, 35%) starting from **5i** (31.0 mg, 0.133 mmol, 1.0 equiv.) and (*E*)-4-oxopent-2-enoic acid (28.1 mg, 0.160 mmol, 1.2 equiv.). m.p: 196-198 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.60 (d, J = 8.4 Hz, 2H), 7.08 (s, 1H), 7.03 (s, 1H), 6.73 (d, J = 8.4 Hz, 2H), 3.78 (s, 3H), 3.03 (s, 6H), 2.64 (s, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 198.0, 163.1, 154.0, 151.1, 146.5, 139.0, 127.3, 121.3, 117.4, 112.4, 108.0, 40.4, 32.4, 26.4; HRMS (EI): *m/z* calcd for $C_{18}H_{18}N_2O_2S$ $[M]^+$ 326.1089, found 326.1088.

*7-Benzoyl-4-benzyl-2-(4-(dimethylamino)phenyl)thieno[3,2-b]pyridin-5(4H)-one (**KF-21**)*. Compound **KF-21** was obtained as a red solid (25.0 mg, 0.0538 mmol, 41%) starting from **5s** (40.0 mg, 0.130 mmol, 1.0 equiv.) and 3-benzoylacrylic acid (27.4 mg, 0.156 mmol, 1.2 equiv.). m.p: 216-218 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.91 (dd, J = 8.4 Hz and J = 1.8 Hz, 2H), 7.64 (tt, J = 7.5 Hz and J =1.3 Hz, 1H), 7.54-7.49 (m, 4H), 7.35-7.33 (m, 4H), 7.27-7.26 (m, 1H), 7.05 (s, 1H), 6.85 (s, 1H), 6.69 (d, J = 9.0 Hz, 2H), 5.54 (s, 2H), 3.01 (s, 6H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 194.9, 165.5, 153.0, 151.1, 146.2, 139.9, 136.1, 136.0, 133.6, 130.1, 129.0, 128.8, 127.8, 127.3, 127.2, 121.1, 119.1, 114.3, 112.3, 109.0, 48.7, 40.4; HRMS (EI): *m/z* calcd for $C_{29}H_{24}N_2O_2S$ $[M]^+$ 464.1558, found 464.1562.

*7-Benzoyl-2-(4-(diphenylamino)phenyl)-4-methylthieno[3,2 -b]pyridin-5(4H)-one (**KF-25**)*. Compound **KF-25** was obtained as a red solid (26.9 mg, 0.0525 mmol, 47%) starting from **5o** (40.0 mg, 0.112 mmol, 1.0 equiv.) and 3-benzoylacrylic acid (23.7 mg, 0.134 mmol, 1.2 equiv.). m.p: 125-128 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.86 (dd, J = 8.4 Hz and J = 0.6 Hz, 2H), 7.65-7.27 (m, 1H), 7.56 (dd, J = 6.6 Hz and J = 2.4 Hz, 2H), 7.52 (t, J = 7.8 Hz, 2H), 7.31-7.29 (m, 4H), 7.20 (s, 1H), 7.16-7.14 (m, 4H), 7.11-7.07 (m, 4H), 6.85 (s, 1H), 3.81 (s, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 194.7, 162.4, 152.2, 149.3, 147.1, 146.3, 139.6, 136.0, 133.6, 130.1, 129.6, 129.0, 128.8, 127.2, 126.4, 125.3, 124.0, 122.5, 119.5, 115.1, 109.8, 32.5; HRMS (EI): *m/z* calcd for $C_{33}H_{24}N_2O_2S$ $[M]^+$ 512.1558, found 512.1556.

*7-Benzoyl-4-methyl-2-(4-(trifluoromethoxy)phenyl)thieno [3,2-b]pyridin-5(4H)-one (**KF-26**)*. Compound **KF-26** was obtained as a green solid (22.0 mg, 0.0512 mmol, 35%) starting from **5p** (40.0 mg, 0.146 mmol, 1.0 equiv.) and 3-benzoylacrylic acid (30.9 mg, 0.175 mmol, 1.2 equiv.). m.p: 220-221 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.83 (dd, J = 7.2 Hz and J = 1.2 Hz, 2H), 7.72 (dd, J = 8.7 Hz and J = 0.9 Hz, 2H), 7.63 (td, J = 7.8 Hz and J = 1.2 Hz, 1H), 7.50 (t, J = 7.5 Hz, 2H), 7.27 (d, J = 8.4 Hz, 2H), 7.23 (s, 1H), 6.89 (s, 1H), 3.80 (s, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 194.6, 162.4, 150.0, 149.9, 145.9, 139.4, 135.9, 133.7, 132.1, 130.0, 128.9, 127.8, 121.7, 121.3, 120.5 (d, J_{C-F} = 256.2 Hz), 115.6, 111.7, 32.4; ^{19}F{^{1}H} NMR (600 MHz, $CDCl_3$) δ -57.8; HRMS (EI): *m/z* calcd for $C_{22}H_{14}F_3NO_3S$ $[M]^+$ 429.0646, found 429.0649.

*7-Benzoyl-4-methyl-2-(4-(trifluoromethyl)phenyl)thieno[3, 2-b]pyridin-5(4H)-one (**KF-27**)*. Compound **KF-27** was obtained as a green solid (18.8 mg, 0.0455 mmol, 29%) starting from **5q** (40.0 mg, 0.155 mmol, 1.0 emquiv.) and 3-benzoylacrylic acid (32.8 mg, 0.186 mmol, 1.2 equiv.). m.p: 236-238 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.85 (dd, J = 20.1 Hz and J = 7.5 Hz, 4H), 7.72 (d, J = 8.4 Hz, 2H), 7.67 (t, J = 7.2 Hz, 1H), 7.54 (t, J = 7.8 Hz, 2H), 7.38 (s, 1H), 6.94 (s, 1H), 3.85 (s, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 194.5, 162.3, 149.4, 145.7, 139.2, 136.7, 135.8, 133.7, 131.1 (q, J_{C-F} = 33.2 Hz), 130.0, 128.9, 126.5, 126.34-126.31 (m), 124.0 (q, J_{C-F} = 270.5 Hz), 121.7, 116.0, 112.3, 32.3; ^{19}F{^{1}H} NMR (600 MHz, $CDCl_3$) δ -62.8; HRMS (EI): *m/z* calcd for $C_{22}H_{14}F_3NO_2S$ $[M]^+$ 413.0697, found 413.0695.

*4-Benzyl-2-(4-methoxyphenyl)-5-oxo-4,5-dihydrothieno[3,2 -b]pyridine-7-carboxylic acid (**KF-28**)*. To a solution of **KF-2** (26.2 mg, 0.0646 mmol, 1.0 equiv.) in EtOH (2 mL), 1 N KOH (0.32 mL) was added. The reaction was heated to 70 °C for 1 h. After completion of the reaction, the solvent was evaporated and acidified by 1 N HCl (2 mL). The crude was extracted with EtOAc (3 mL) at 5 times, dried over Na_2SO_4, filtered and evaporated *in vacuo*. The product was obtained as a yellow solid (19.8 mg, 0.0506 mmol, 78%). m.p: 246-248 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.71 (d, J = 9.0 Hz, 2H), 7.68 (s, 1H), 7.33-7.30 (m, 4H), 7.26-7.23 (m, 1H), 7.02 (d, J = 9.0 Hz, 2H), 6.95 (s, 1H), 5.51 (s, 2H), 3.80 (3H); ^{13}C{^{1}H} NMR (150 MHz, DMSO-d_6) δ 165.5, 161.3, 160.2, 149.7, 145.6, 136.7, 135.5, 128.6, 127.34, 127.30, 127.2, 125.3,

117.2, 114.7, 113.9, 111.7, 55.4, 47.4; HRMS (FAB): *m/z* calcd for $C_{22}H_{18}NO_4S$ $[M+H]^+$ 392.0957, found 392.0954.

*2-(4-(Diethylamino)phenyl)-4-methyl-5-oxo-4,5-dihydrothieno[3,2-b]pyridine-7-carboxylic acid (**KF-29**)*. To a solution of **KF-22** (22.4 mg, 0.0605 mmol, 1.0 equiv.) in EtOH (2.0 mL), 1 N KOH (0.3 mL) was added. The reaction was heated to 70 °C for 1 h. After completion of the reaction, the solvent was evaporated and acidified by 1 N HCl (2 mL). The crude was extracted with EtOAc (3 mL) at 5 times, dried over Na_2SO_4, filtered and evaporated *in vacuo*. The product was obtained as an orange solid (13.8 mg, 0.0387 mmol, 64%). m.p: 257-258 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.63 (d, J = 8.5 Hz, 2H), 7.56 (s, 1H), 6.79 (s, 1H), 6.73 (d, J = 9.0 Hz, 2H), 3.67 (s, 3H), 3.42-3.37 (m, 4H), 1.19 (t, J = 7.0 Hz, 6H); ^{13}C{^{1}H} NMR (150 MHz, DMSO-d_6) δ 165.7, 161.3, 151.2, 148.2, 146.5, 127.2, 119.4, 115.5, 112.4, 111.4, 109.4, 43.7, 32.0, 12.5; HRMS (FAB): *m/z* calcd for $C_{19}H_{21}N_2O_3S$ $[M+H]^+$ 357.1273, found 357.1276.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI:xxxxxxxxxx. Photophysical properties of fluorophores, ^{1}H, ^{13}C NMR and HRMS spectral data (PDF).

AUTHOR INFORMATION

Corresponding Author

* jslee@kiost.ac.kr

ORCID

Jong Seok Lee: 0000-0002-3892-3439

Notes

The authors declare financial interests. D.S., B.M., S.P., H.L., J.L, Y.L, H.J.S., and J.S.L. have filed patent applications whose value may be affected by this publication.

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