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S_NAr and Palladium-Catalyzed Reactions of Deactivated Thiophene: Application to the Synthesis of Protein Farnesyltransferase Inhibitors

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To investigate the influence of the 5-thioether moiety of our previously identified hit thiophene compound upon protein farnesyltransferase inhibition, we synthesized a new library of 3-(4-chlorophenyl)-4-cyanothiophene-2-carboxylic derivatives through the application of aromatic nucleophilic substitutions benefiting from a sulfone-based leaving group and by direct palladium-catalyzed reactions on a thioalkylthiophene. This small library of ester derivatives and their corresponding acids was then evaluated for protein farnesyltransferase inhibitory activity; some library members exhibited promising submicromolar activities.

Introduction

Protein farnesyltransferase (FTase) has received considerable attention since its discovery two decades ago. FTase is a key posttranslational enzyme responsible for catalyzing farnesylation of numerous proteins, thereby allowing their correct binding to the intracellular membrane.[1] First studied as a potential anticancer target,[2] FTase has recently turned out to be an effective antiparasitic target for treating tropical pathologies such as malaria, African sleeping sickness and Chagas disease where resistance to established therapeutics has become commonplace or where there is simply a lack of effective treatments available.[3]

In the course of our search for new active FTase inhibitors (FTIs), we previously reported the discovery of a new class of inhibitors in the arylthiophene series.[4] Using the scaffold from our highly potent hit compound **1** (Figure 1), we evaluated the importance of selected functionalities by substituting the carboxylic acid moiety in position 2 as well as the nature of the central aromatic ring. We also designed an original synthesis of a new thiophene library, where the 3-aryl moiety was varied, which will be reported elsewhere.[5]

This article details structure-activity relationship studies focused on understanding the effect of position 5 of the thiophene ring and we report herein the aromatic nucleophilic substitution of the thio-isopropyl group of compound **1** to afford a new library of 3-(4-chlorophenyl)-4-cyano-2-carboxylic derivatives. The impact of alterations to **1** on FTase inhibition by new library members is also presented.

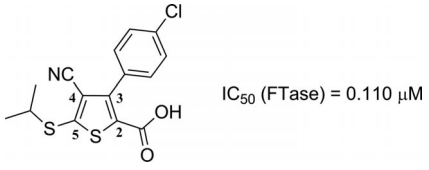

Figure 1. Structure of hit thiophene **1**.

Results and Discussion

Chemistry

Direct substitution of thioethers on electron-deficient thiophene rings has only been achieved either by palladium-catalyzed coupling with alkyl or aryl thiols[6] or by aromatic nucleophilic substitutions with morpholine.[6–7] However, we wished to find a common precursor allowing for facile modification of this part of compound **1** by various groups, especially through the application of S_NAr reactions. Therefore, we decided to activate thioether **1** by oxidation since oxidized thioethers are better leaving groups than are thioethers themselves. Additionally, successful substitutions of thienyl sulfoxides or sulfones by amines or alcohols have been previously described.[6,8–11] Because we thought that the presence of a free carboxylic acid could be troublesome during the course of our synthesis, we used ethyl 3-(4-chlorophenyl)-4-cyano-5-(isopropylthio)thiophene-2-carboxylate **2** as the starting point for the construction of new esters which would ultimately be saponified to afford the desired acids. In order to oxidize thiophene **2**, we used 1 or 2.5 equiv. of a mild oxidant such as *m*CPBA which afforded corresponding sulfoxide **3** and sulfone **4** in excellent yields, respectively (Scheme 1).

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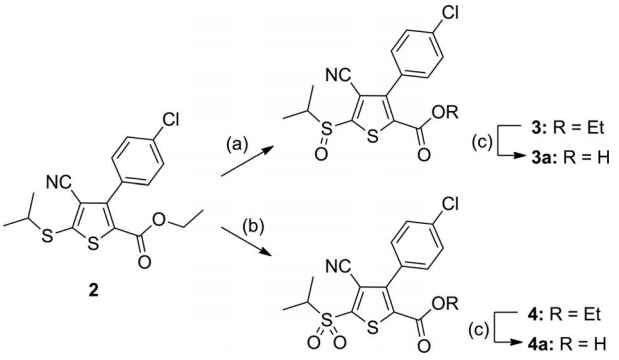


Scheme 1. Oxidation of thioether derivative **2**. Reagents and conditions: (a) *m*CPBA (1 equiv.), CH_2Cl_2, 18 h, 81%; (b) *m*CPBA (2.5 equiv.), CH_2Cl_2, 4 h, 93%; (c) NaOH 2 M, THF/EtOH, 2:1, 16 h, **3a** 91%, **4a** quant.

Sulfone **4** was obtained in a yield superior to that of **3** and was also easier to purify than **3**. Consequently, we used **4** as the precursor for our S_NAr reactions.

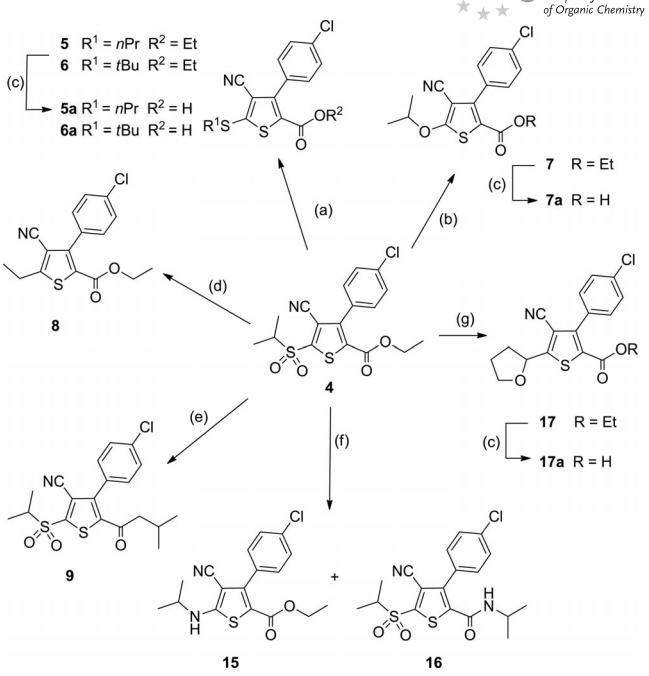
In our initial SAR studies,[4] various commercially available 5-(thioether)thiophenes were evaluated for their ability to inhibit FTase. However, the series in which the thioalkyl side chain contained four carbon atoms or less were devoid of the *tert*-butylthio and the *n*-propylthio ethers. These derivatives constituted the starting point of our methodology. Using the corresponding thiols in the presence of *t*BuOK as a base, desired 5-thioalkylthiophenes **5** and **6** were obtained in very good yields when 18-crown-6 ether was added to the reaction mixture, likely due to a better ion-pair dissociation (Scheme 2).

To further determine the influence of the 5-thioether moiety on FTase inhibition by library members, we substituted it with analogous oxygen, carbon and nitrogen atoms.

Substitution of the isopropyl thioether with its oxygenated isostere was difficult because of the lower nucleophilicity of the hydroxy group relative to thiols. After several attempts, we found that this reaction required relatively harsh conditions (130 °C in a sealed tube) to provide desired compound **7** in a moderate but sufficient yield for our SAR studies (Scheme 2). It is notable that, under these conditions, a transesterification was observed although ultimately this had no effect on subsequent saponification efforts.

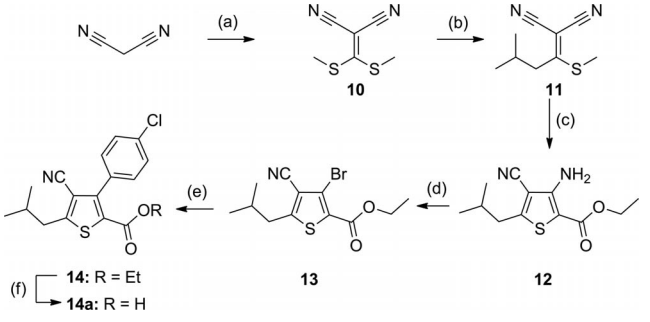
The replacement of the 5-thioether by an analogous all carbon moiety was first carried out under previously reported conditions[6] with commercially available diethylzinc which provided 5-ethylthiophene **8** in a reasonable yield (Scheme 2). Based on this encouraging result, we performed the same reaction in which di-isobutylzinc was generated in situ by mixing zinc dichloride and isobutylmagnesium chloride. Unfortunately, the desired compound was never obtained. Instead, the only product observed was ketone **9**; no alteration of the sulfone was obtained.

To get the desired isobutyl product, we found it necessary to substitute a thiomethyl group earlier in the synthetic pathway. Specifically, thiomethyl installation was achieved after the formation of the ketene dithioacetal (Scheme 3).



Scheme 2. Substitution of sulfone **4**. Reagents and conditions: (a) *n*PrSH or *t*BuSH, *t*BuOK, 18-crown-6, THF, 16–19 h, 75–94%; (b) K_2CO_3, *i*PrOH, 130 °C, 17 h, sealed tube, 55%; (c) NaOH 2 M, THF/EtOH, 2:1, 16 h, **5a** 95%, **6a** 93%, **7a** 99%, **17a** 72%; (d) $ZnEt_2$, CH_2Cl_2, 7 d, 44%; (e) $ZnCl_2$, *i*BuMgCl, CH_2Cl_2, 6 d, 19%; (f) *i*PrNH$_2$, THF, room temp., 16 h, **15** 51%, **16** 34%; (g) THF, reflux, 3 d, 67%.

To avoid the formation of regioisomers, we took advantage of a synthetic pathway devised for solid phase synthesis in which the 3-aryl moiety is introduced after thiophene ring closure[12] and Sandmeyer bromation.[5] Following this pathway, desired 5-isobutyl-modified thiophene **14** was obtained in a good overall yield allowing us to determine the influence of a carbon for sulfur exchange at the 5 position.



Scheme 3. Synthesis of the carbon analogue **14**. Reagents and conditions: (a) K_2CO_3, DMF, room temp., 30 min, then CS_2, 10 min, then MeI, TBAB, 60 °C, 64 h, 66%; (b) *i*BuMgBr, THF, room temp., 48 h, 41%; (c) ethyl thioglycolate, K_2CO_3, EtOH, reflux, 3 h, 62%; (d) $CuBr_2$, *t*BuONO, CH_3CN, room temp., 10 min, 56%; (e) *p*-ClPhB(OH)$_2$, Pd(PPh$_3$)$_4$, K_2CO_3, toluene/EtOH, 9:1, reflux, 4 h, 68%; (f) NaOH 2 M, THF/EtOH, 2:1, room temp., 16 h, quantitative.

To complete the series of C-5 dethio FTI candidates, we substituted the sulfone of **4** with isopropylamine. In this case, our S_NAr strategy proved problematic due to the pres-

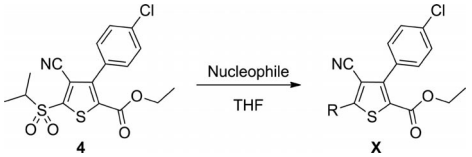
ence of the ester which constitutes a competitive electrophile. Stirring sulfone **4** with isopropylamine at room temperature afforded a mixture of expected 5-*N*-isopropylamine **15** and 2-isopropylamide **16** in a 60:40 ratio (Scheme 2). A rapid survey showed that the use of other solvents such as 1,4-dioxane, dichloromethane, acetonitrile or DMF increased the ratio in favour of amide byproduct **16** which was found to be preferentially formed in a strong polar solvents such as ethanol. The same effect was observed upon addition of salts like LiCl or $MgCl_2$, leading to 10:90 and 25:75 ratios, respectively.

These reactions were also carried out under refluxing conditions to see if product ratios could be improved in favour of desired amine **15**. Surprisingly, the major product of this reaction, when using THF as solvent, was compound **17** where the sulfone of **4** was replaced by THF. To understand the influence of isopropylamine in this reaction, sulfone **4** was refluxed in THF alone for 3 d to afford the same 2-THF adduct **17** in good yield (Scheme 2). We suspected that a radical reaction, rather than the desired S_NAr reaction, might explain this unexpected substitution. We envisioned a spontaneous homolytic cleavage of the C-SO_2 bond and trapping of the radical thus formed by a molecule of THF. To support this hypothesis, we showed that addition of the spin trap TEMPO to sulfone **4** in boiling THF abolished formation of compound **17**. It is notable that such adducts were not observed when using tetrahydrothiophene, methyltetrahydrofuran or tetrahydropyrane.

Nevertheless, we used this methodology to substitute the sulfone of **4** with other amine nucleophiles (Table 1). However, the latter side reaction clearly indicated that S_NAr reactions with **4** were not compatible with refluxing conditions. It turned out that substitutions were found to occur with primary and secondary amines in moderate to good yield (Table 1, Entries 2–5 and 8). However, the formation of amides as non-desired products was always observed and the reaction was not amenable to sterically hindered amines (Table 1, Entries 6 and 7). In addition, sodium amide was too poor a nucleophile to substitute the sulfone (Table 1, Entry 1). Finally, substitution of the sulfone by sodium azide gave us desired 5-azidothiophene **26** in quantitative yield (Table 1, Entry 9). This was a very interesting result, opening the way for new 5-nitrogenated substituents from this easily modifiable azido group.

As shown below by the biological results for compound **20a**, placement of pyrrolidine at the thiophene 5-position induced significant FTase inhibition. Thus, we explored sulfone substitution by five-atom nitrogenated aromatic heterocycles. Reaction of starting material **4** with 1,2,4-triazole was used as the model for S_NAr chemistry with aryl derivatives. After several attempts, *t*BuOK, in the presence of 18-crown-6, was found to be the best system and provided desired azole derivative **27** in very good yield (80%). These reaction conditions were transposed to other heterocycles of the azole family such as tetrazole, pyrazole, imidazole, and pyrrole (Table 1). For all these compounds, the substitution worked more sluggishly than had been the case with 1,2,4-triazole and the expected products were not obtained with either pyrrole or tetrazole. Except for tetrazole, there was found to be a strong inverse correlation between heterocycle pK_a and yield; the lower the pK_a of the nucleophile, the higher the coupling yield (Figure 2).

Table 1. S_NAr reactions with sulfone **4** and various aliphatic nitrogenated nucleophiles.[a]



Entry	Nucleophile	Solvent	Time [h]	X	Yield [%][b]
1	sodium amide	THF	24	**18**	0
2	cyclopentylamine	THF	21	**19**	52
3	pyrrolidine	/	3	**20**	73
4	piperidine	THF	4	**21**	58
5	*N*-methylpiperazine	/	16	**22**	38
6	diethylamine	THF	20	**23**	0
7	diisopropylamine	THF	26[c]	**24**	0
8	tMEDA[e]	THF	92[d]	**25**	30
9	sodium azide	DMF	5	**26**	100
10	1,2,4-triazole[f]	THF	20	**27**	80
11	pyrrole[g]	THF	48	**28**	0
12	imidazole[f]	THF	20	**29**	43
13	pyrazole[g]	THF	7	**30**	48
14	tetrazole[g]	THF	8	**31**	0

[a] Typical reaction was performed on 0.1 to 0.3 mmol of sulfone at room temp. with 1.5–6 equiv. of solid or 50–100 equiv. of liquid nucleophile. [b] Isolated yield after flash column chromatography. [c] 26 h at room temp. and 64 h at 50 °C. [d] At 40 °C. [e] tMEDA, *N*,*N*,*N*′-trimethylethylenediamine. [f] Using 2 equiv. of nucleophile, *t*BuOK and 18-crown-6. [g] Using 3 equiv. of nucleophile, *t*BuOK and 18-crown-6.

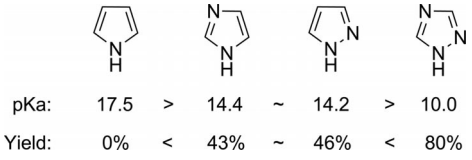
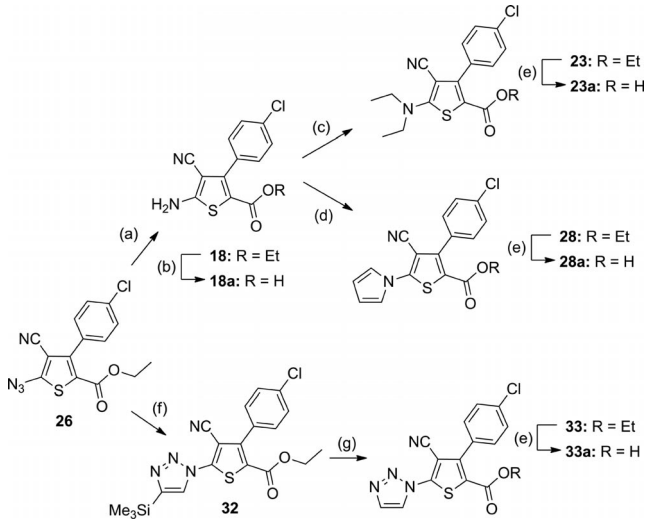


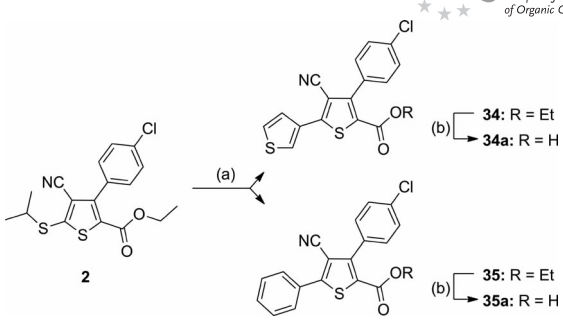
Figure 2. Relationship of S_NAr reaction yields and nucleophile pK_a.

To synthesize compounds **18**, **23**, **24** and **28**, we took advantage of the facile synthesis of aryl azide **26**. Reduction of **26** by fast catalytic hydrogenation afforded primary amine **18** in good yield contrary to direct substitution. However, it should be noted that amine **18** could be more rapidly obtained using Gewald's procedure.[13,14] Amine **18** was then alkylated with iodoethane to provide 5-diethylamine **23** or reacted with 2,5-dimethoxytetrahydrofuran to give pyrrole **28** in excellent yield (Scheme 4).[15]

Azide **26** was also converted to 1,2,3-triazole analogue **32** by a [2+3] Huisgen cycloaddition with (trimethylsilyl)-acetylene.[16] Without solvent or catalyst, this reaction proceeded in a very efficient way and gave, after removal of the trimethylsilyl group with HF·Et_3N, free 1,2,3-triazole derivative **33**. [2+3] Cycloadditions of organic nitriles with metallic azides are also frequently used to synthesize tetrazoles. However, it is more difficult to carry out these cyclo-



Scheme 4. Derivatives synthesized from azide **26**. Reagents and conditions: (a) H_2, Pd/C, EtOH, 5 min, 80%; (b) LiOH 2 M, THF/EtOH, 2:1, 16 h, 75%; (c) EtI, K_2CO_3, DMF, 16 h, 68%; (d) 2,5-dimethoxytetrahydrofuran, glacial AcOH, 90 °C, 1 h, 87%; (e) NaOH 2 M, THF/EtOH, 2:1, 16 h, **23a** 56%, **28a** quantitative, **33a** 93%; (f) (trimethylsilyl)acetylene, 7 h, 83%; (g) HF·Et_3N, THF, 6 h, 83%.



Scheme 5. Liebeskind-Srogl coupling with thiophene **2**. Reagents and conditions: (a) 3-thienylboronic acid or phenylboronic acid, $Pd(PPh_3)_4$, copper(I) thiophenecarboxylate, THF, 50 °C, 48 h, **34** 61%, **35** 52%; (b) NaOH 2 M, THF/EtOH, 2:1, 16 h, **34a** quantitative, **35a** 36%.

additions with organic azides and, to the best of our knowledge, very few methodologies have been described. In our hands, the conditions reported by Sharpless and co-workers with organic azides and *p*-toluenesulfonylnitrile[17] in the presence of a catalyst such as $Cu_2(OTf)_2{\cdot}C_6H_6$ did not afford the expected tetrazole. Previous reports that aromatic azides afforded only the 1,5-substituted tetrazole in low yields and did not give any product when the azide is sterically hindered support our results with **26**.

In 2000, Liebeskind and Srogl described an unprecedented copper–palladium-catalyzed procedure to create C–C bonds from thioesters and boronic acids.[18] Rapidly extended to aromatic thioethers, this coupling was found to be more powerful with π-deficient heterocycles.[19] Given the strong electron-withdrawing nature of groups located on our thiophene, we applied this efficient methodology to our starting thiophene **2**. Using this approach with **2**, we successfully obtained, in moderate but unoptimized yields, two new products **34** and **35** bearing a 3-thienyl or a phenyl moiety in the 5-position of the thiophene ring, respectively (Scheme 5).

To the best of our knowledge, this is only the second example described using a thiophene. Moreover, we found that application of this methodology to obtain other tricyclic compounds is a very good alternative to the long sequence of: oxidation of **2** – substitution of **4** by NaN_3 – reduction of **26** – Sandmeyer reaction on **18** which ultimately affords the substrate for Suzuki–Miyaura couplings.

Finally, esters **5**–**7**, **17**, **18** (Scheme 2), **14** (Scheme 3), **34**–**35** (Scheme 5), **15**, **19**–**23**, **27**–**30** and **33** were submitted to hydrolysis under basic conditions to afford the corresponding acids in fair to excellent yields except for compounds **15** and **19** bearing secondary amines (Table 2). Variation of base (LiOH, KOH, *t*BuOK, TMSOK) and of the solvent (THF, EtOH, DMSO, CH_3CN) used in saponification attempts with **15** and **19** revealed that both compounds were surprisingly resistant to hydrolysis; each was recovered either unchanged or completely degraded when more drastic conditions were applied.

Table 2. Saponification of esters.[a]

Entry	Ester	Acid	Yield [%][b]
1	**15**	**15a**	0
2	**17**	**17a**	72
3	**19**	**19a**	0
4	**20**	**20a**	70
5	**21**	**21a**	91
6	**22**	**22a**	85
7	**23**	**23a**	56
8	**27**	**27a**	85
9	**28**	**28a**	100
10	**29**	**29a**	55
11	**30**	**30a**	66
12	**33**	**33a**	93

[a] Hydrolysis carried out with NaOH 2 M (5 equiv.) in THF/EtOH, 2:1 (10 mL/mmol). [b] Isolated yield.

Biological Evaluation

All acids were evaluated for their ability to inhibit recombinant FTase using a fluorescence-based assay adapted to 96-well plate format.[20] Results are reported in Table 3.

FTase inhibition by compounds **5a** and **6a**, bearing *n*-propyl and *tert*-butyl groups, respectively (Table 3, Entries 4 and 5), revealed the isopropyl group as the best substituent to have on the C-5 sulfur atom. The bulky *t*Bu group was more detrimental to activity than the less hindered *n*-propyl relative to lead thiophene **1**. Additionally, replacement of the sulfur atom by an oxygen or a carbon resulted in weaker FTase inhibition (Table 3, Entries 6 and 7). It is notable that all these derivatives retained submicromolar activity. In the case of the 5-isopropylamine derivative we could only evaluate the activity of ester **15** which was found to be inactive; corresponding ester **2** inhibited FTase with an IC_{50} = 3.8 μM.[4] This comparison revealed that a secondary amine does not favorably replace the thioisopropyl group. Among

Table 3. Inhibitory activity of library members against recombinant FTase.

Entry	X	R	IC_{50} [μM]
1	**1**	*i*PrS	0.110 ± 0.008
2	**3a**	*i*PrSO	21.5 ± 1
3	**4a**	*i*PrSO$_2$	21.4 ± 2.8
4	**5a**	*n*PrS	0.17 ± 0.03
5	**6a**	*t*BuS	1.2 ± 0.4
6	**7a**	*i*PrO	0.41 ± 0.008
7	**14a**	*i*Bu	0.26 ± 0.03
8	**17a**	2-THF	3.0 ± 1
9	**18a**	NH_2	5.0 ± 0.9
10	**20a**	pyrrolidinyl	0.080 ± 0.006
11	**21a**	piperidinyl	1.25 ± 0.1
12	**22a**	*N*-methylpiperazinyl	> 100
13	**23a**	NEt_2	10.1 ± 0.2
14	**27a**	1,2,4-triazolyl	1.3 ± 0.1
15	**28a**	pyrrolyl	0.33 ± 0.06
16	**29a**	imidazolyl	6.5 ± 0.1
17	**30a**	pyrazolyl	0.25 ± 0.02
18	**33a**	1,2,3-triazolyl	2.10 ± 0.15
19	**34a**	3-thienyl	0.27 ± 0.05
20	**35a**	Ph	1.2 ± 0.1

all our new derivatives, only pyrrolidine **20a** exhibited activity superior to our lead compound; **20a** inhibited FTase with an IC_{50} of 80 nM (Table 3, Entry 10). As previously noticed, increasing the steric bulk of such compounds resulted in partial to complete loss of activity (Table 3, Entries 10–13). Thus, FTase inhibitory activity decreased as the size of the cycle or the nitrogen substitution increased. This was apparent for diethylamine compound **23a** although amine substitution seemed important as shown by the low activity of primary amine-modified thiophene **18a** (Table 3, Entry 9). In the 5-arylthiophene series, pyrrole **28a**, pyrazole **30a** and 5-(3-thienyl)thiophene derivative **34a** all retained submicromolar activity (Table 3, Entries 15, 17 and 19) but were less active than aliphatic pyrrolidine analog **20a**. Triazoles **27a** and **33a**, imidazole **29a** and phenyl derivative **35a** exhibited 10-fold lower FTase inhibitory activity relative to our hit compound **1** (Table 3, Entries 14, 16, 18 and 20).

Conclusions

In conclusion, we have shown that modifications to the thioether group of our hit thiophene **1** can be easily realized using either S_NAr reactions after activation of the thioether as the sulfone or by a direct palladium-catalyzed reaction. These methods allowed us to create a new small library of about 20 new esters and their corresponding acids, which were evaluated for their ability to inhibit recombinant FTase. This study showed that, when it comes to substitution at the 5-position of this 3-arylthiophene-2-carboxylic acid: (i) bulky or small substituents are detrimental to activity, (ii), five-membered heterocycles are good substituents, and (iii) the aliphatic heterocycle pyrrolidine is preferred to aromatic pyrrole or pyrazole substituents.

Experimental Section

General Considerations: All reactions were carried out in oven-dried glassware under argon. Commercial compounds were purchased from suppliers and used without further purification. Solvents were dried by standards methods. Analytical TLC was carried out on a pre-coated silica gel aluminium-backed plates (SDS TLC plates, silica gel $60F_{254}$). Column chromatography was performed with silica gel SDS 60 A CC (40–63 μm) or with prepacked Redisep columns.

^{1}H NMR and ^{13}C NMR were acquired with Bruker Avance 300 (300 MHz) and Avance 500 (500 MHz) NMR spectrometers. Chemical shifts (δ) are given relative to $CDCl_3$ (δ = 7.26 ppm; 77.2 ppm) or CD_3OD (δ = 3.34 ppm; 49.9 ppm). Splitting patterns are designed as: s singlet, d doublet, t triplet, q quartet, qi quintuplet, hx hexuplet, h heptuplet, oct octuplet, n nonuplet, m multiplet, br. broad. Coupling constants *J* are reported in Hertz (Hz). IR spectra were obtained with a Perkin–Elmer Spectrum BX. Mass spectra were recorded with a Thermoquest AQA Navigator with a TOF detector (ESI-HRMS). Elemental analyses were obtained by the ICSN-CNRS Microanalytical Laboratory of Gif-sur-Yvette. Melting points were measured with a Büchi b-450 apparatus. Ultra-high pressure liquid-chromatography (UHPLC) analyses were performed with a Waters Acquity UPLC system. Purities of evaluated compounds were measured using reversed-phase UHPLC (HSS C-18, 2.1 × 50 mm s-1.8 μm) with two diverse solvent systems: compounds were eluted with 95:5 A/B for 0.5 min then with a gradient of 5–100% B/A for 3.5 min followed by 100% B for 1 min at a flow rate of 0.6 mL/min, where solvent A was 0.1% formic acid in H_2O and solvent B was 0.1% formic acid in MeCN (system 1) or 0.1% formic acid in MeOH (system 2). Purity was determined with TAC (total absorbance current from 200 to 400 nm).

Ethyl 3-(4-Chlorophenyl)-4-cyano-5-(isopropylsulfinyl)thiophene-2-carboxylate (3): To a solution of ester **2** (140.7 mg, 0.385 mmol) in CH_2Cl_2 (3 mL) was added *m*CPBA (70% pure, 94.9 mg, 0.385 mmol). After stirring at room temperature for 18 h, the reaction mixture was quenched with a saturated aqueous $NaHCO_3$ solution (3 mL) and extracted with CH_2Cl_2 (3 × 4 mL). The combined organic layers were dried with $MgSO_4$, filtered and concentrated under reduced pressure. Chromatography on silica gel [heptane/EtOAc, 10:0 to 6:4 (v/v) in 20 min] afforded sulfoxide **3** (119.0 mg, 81%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.46 (d, *J* = 8.5 Hz, 2 H, *H*ar), 7.36 (d, *J* = 8.5 Hz, 2 H, *H*ar), 4.26 (q, *J* = 7.1 Hz, 2 H, OCH_2), 3.33 (h, *J* = 6.9 Hz, 1 H, C*H*), 1.46 (d, *J* = 6.9 Hz, 3 H, CHCH_3), 1.34 (d, *J* = 6.9 Hz, 3 H, CHCH_3), 1.25 (t, *J* = 7.1 Hz, 3 H, CH_2CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.4, 159.8, 148.5, 136.1, 133.2, 130.9, 129.7, 128.8, 112.2, 111.7, 62.6, 57.0, 16.2, 14.1, 14.0 ppm. IR (film): $\tilde{\nu}$ = 2984, 2237, 1728, 1314, 1251 cm^{-1}. MS (ESI$^+$, CH_2Cl_2/MeOH) *m*/*z* 404.0 [M + Na]$^+$. HRMS (ESI$^+$, CH_2Cl_2/MeOH) calcd. for $C_{17}H_{16}{}^{35}ClNO_3S_2Na^+$ [M + Na]$^+$ 404.0158; found 404.0163. $C_{17}H_{16}ClNO_3S_2$ (381.89): calcd. C 53.47, H 4.22, N 3.67, O 12.57, S 16.79, Cl 9.28; found C 52.92, H 4.16, N 3.76, S 16.39.

Ethyl 3-(4-Chlorophenyl)-4-cyano-5-(isopropylsulfonyl)thiophene-2-carboxylate (4): To a solution of ester **2** (4.0 g, 10.9 mmol) in CH_2Cl_2 (80 mL) was added *m*CPBA (70% pure, 6.74 g, 27.3 mmol). After stirring at room temperature for 4 h, the reaction mixture was quenched with a saturated aqueous $NaHCO_3$ solution (120 mL) and extracted with CH_2Cl_2 (3 × 150 mL). The combined organic layers were dried with $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was washed with ethanol and dried under vacuum to provide sulfone **4** (4.05 g, 93%) as a white powder; m.p. 150 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ =

7.48 (d, J = 8.5 Hz, 2 H, *H*ar), 7.36 (d, J = 8.5 Hz, 2 H, *H*ar), 4.28 (q, J = 7.1 Hz, 2 H, OCH_2), 3.59 (h, J = 6.9 Hz, 1 H, C*H*), 1.49 (d, J = 6.9 Hz, 6 H, CHCH_3), 1.26 (t, J = 7.1 Hz, 3 H, CH_2CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.5, 150.1, 149.2, 136.4, 135.7, 131.0, 129.4, 128.9, 116.5, 111.6, 63.0, 57.4, 15.9, 14.1 ppm. IR (film): $\tilde{\nu}$ = 2986, 2238, 1728, 1313, 1251, 1123 cm^{-1}. MS (ESI$^+$, CH_2Cl_2/MeOH) m/z 420.0 [M + Na]$^+$. HRMS (ESI$^+$, CH_2Cl_2/MeOH) calcd. for $C_{17}H_{16}{}^{35}ClNO_4S_2Na^+$ [M + Na]$^+$ 420.0107; found 420.0112 and calcd. for $C_{17}H_{16}{}^{37}ClNO_4S_2Na^+$ [M + Na]$^+$ 422.0077; found 422.0097. $C_{17}H_{16}ClNO_4S_2$ (397.90): calcd. C 51.32, H 4.05, N 3.52, O 16.08, S 16.12, Cl 8.91; found C 51.23, H 3.94, N 3.42, O 15.84, S 16.13.

Ethyl 3-(4-Chlorophenyl)-4-cyano-5-(propylthio)thiophene-2-carboxylate (5): To a solution of sulfone **4** (80.0 mg, 0.201 mmol) in THF (2 mL) were added *n*-propanethiol (27 μL, 0.302 mmol), *t*BuOK (33.8 mg, 0.302 mmol) and 18-crown-6 (79.2 mg, 0.302 mmol). After stirring at room temperature for 16 h, the reaction mixture was diluted with water (3 mL) and extracted with EtOAc (3 × 5 mL). The combined organic layers were dried with $MgSO_4$, filtered and concentrated under reduced pressure. Chromatography on silica gel [heptane/EtOAc, 10:0 to 7:3 (v/v) in 20 min] afforded thioether **5** (69.0 mg, 94%) as a white solid; m.p. 67 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.43 (d, J = 8.5 Hz, 2 H, *H*ar), 7.34 (d, J = 8.5 Hz, 2 H, *H*ar), 4.21 (q, J = 7.0 Hz, 2 H, OCH_2), 3.13 (t, J = 7.2 Hz, 2 H, SCH_2), 1.84 (hx, J = 7.2 Hz, 2 H, SCH_2CH_2), 1.21 (t, J = 7.0 Hz, 3 H, OCH_2CH_3), 1.10 (t, J = 7.2 Hz, 3 H, SCH_2CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.2, 156.3, 148.2, 135.6, 130.9, 130.8, 128.6, 127.8, 113.6, 112.9, 61.9, 38.7, 22.7, 14.2, 13.4 ppm. IR (film): $\tilde{\nu}$ = 2963, 2925, 2222, 1721, 1694, 1486, 1264, 1182, 1083 cm^{-1}. MS (ESI$^+$, CH_2Cl_2/MeOH) m/z 388.0 [M + Na]$^+$. HRMS (ESI$^+$, CH_2Cl_2/MeOH) calcd. for $C_{17}H_{16}{}^{35}ClNO_2S_2Na^+$ [M + Na]$^+$ 388.0209; found 388.0212.

Ethyl 5-(*tert*-Butylthio)-3-(4-chlorophenyl)-4-cyanothiophene-2-carboxylate (6): To a solution of sulfone **4** (100.0 mg, 0.251 mmol) in THF (2 mL) were added *tert*-butanethiol (42.5 μL, 0.377 mmol), *t*BuOK (42.3 mg, 0.377 mmol) and 18-crown-6 (99.6 mg, 0.302 mmol). After stirring at room temperature for 19 h, the reaction mixture was diluted with water (3 mL) and extracted with EtOAc (3 × 5 mL). The combined organic layers were dried with $MgSO_4$, filtered and concentrated under reduced pressure. Chromatography on silica gel [heptane/EtOAc, 10:0 to 7:3 (v/v) in 20 min] afforded thioether **6** (71.2 mg, 75%) as a yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.44 (d, J = 8.5 Hz, 2 H, *H*ar), 7.36 (d, J = 8.5 Hz, 2 H, *H*ar), 4.23 (q, J = 7.1 Hz, 2 H, OCH_2), 1.48 (s, 9 H, *t*Bu), 1.23 (t, J = 7.1 Hz, 3 H, CH_2CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.1, 148.8, 147.8, 135.6, 133.0, 130.9, 130.8, 128.6, 121.8, 114.0, 62.1, 51.7, 31.1, 14.2 ppm. IR (film): $\tilde{\nu}$ = 2964, 2230, 1724, 1702, 1485, 1367, 1256, 1183, 1156, 1083, 1014, 826, 764 cm^{-1}. MS (ESI$^+$, CH_2Cl_2/MeOH) m/z 402.0 [M + Na]$^+$. HRMS (ESI$^+$, CH_2Cl_2/MeOH) calcd. for $C_{18}H_{18}{}^{35}ClNO_2S_2Na^+$ [M + Na]$^+$ 402.0365; found 402.0362.

Isopropyl 3-(4-Chlorophenyl)-4-cyano-5-isopropoxythiophene-2-carboxylate (7): A solution of sulfone **4** (100 mg, 0.251 mmol) and potassium carbonate (174 mg, 1.26 mmol) in isopropanol (2 mL) was stirred in a sealed tube at 130 °C for 5 h. After cooling to room temperature, the reaction mixture was diluted with water (4 mL) and extracted with EtOAc (3 × 5 mL). The combined organic layers were dried with $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by chromatography on silica gel [heptane/EtOAc, 10:0 to 8:2 (v/v) in 15 min] to give ester **7** (50.1 g, 55%) as a white powder; m.p. 125 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.41 (d, J = 8.5 Hz, 2 H, *H*ar), 7.34 (d, J = 8.5 Hz, 2 H, *H*ar), 5.03 (h, J = 6.2 Hz, 1 H, C*H*), 4.65 (h, J = 6.1 Hz, 1 H, CO_2CH), 1.53 (d, J = 6.1 Hz, 6 H, CHCH_3), 1.17 (d, J = 6.2 Hz, 6 H, CO_2CHCH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 175.2, 160.6, 146.0, 135.3, 131.3, 130.9, 128.4, 115.0, 113.3, 96.4, 81.6, 69.6, 22.1, 21.9 ppm. IR (film): $\tilde{\nu}$ = 2977, 2223, 1683, 1350, 1257, 1099, 1088 cm^{-1}. MS (ESI$^+$, CH_2Cl_2/MeOH) m/z 386.1 [M + Na]$^+$. HRMS (ESI$^+$, CH_2Cl_2/MeOH) calcd. for $C_{18}H_{18}{}^{35}ClNO_3SNa^+$ [M + Na]$^+$ 386.0594; found 386.0604. $C_{18}H_{18}ClNO_3S$ (363.86): calcd. C 59.42, H 4.99, N 3.85, O 13.19, S 8.81, Cl 9.74; found C 58.74, H 4.89, N 3.77, O 13.22, S 8.70.

2-[Bis(methylthio)methylene]malononitrile (10): To a solution of malononitrile (2.0 g, 30.3 mmol) in DMF (70 mL) was added potassium carbonate (4.6 g, 33.3 mmol). After stirring for 30 min at room temperature, carbon disulfide (1.83 mL, 30.3 mmol) was added dropwise and the reaction mixture was stirred at room temperature for another 10 min before methyl iodide (3.96 mL, 63.6 mmol) and tetrabutylammonium bromide (1.95 g, 6.06 mmol) were added. After being stirred for 64 h at 60 °C, the reaction mixture was cooled to room temperature, diluted with water (150 mL) and extracted with Et_2O (4 × 200 mL). The combined organic layers were dried with $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by recrystallization from hot Et_2O, filtered and dried under vacuum to provide ketene dithioacetal **10** (3.40 g, 66%) as a yellow solid; m.p. 78 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.74 (s, 6 H, SCH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 184.3, 112.9, 76.0, 19.3 ppm. IR (film): $\tilde{\nu}$ = 2214, 1450, 1423, 1316, 1210, 932, 868 cm^{-1}. MS (ESI$^+$, CH_2Cl_2/MeOH) m/z 170.0 [M + Na]$^+$.

2-[3-Methyl-1-(methylthio)butylidene]malononitrile (11): To a solution of compound **10** (1.5 g, 8.71 mmol) in THF (40 mL) at –40 °C was added isobutylmagnesium bromide (2 M in Et_2O, 4.44 mL, 8.80 mmol). After stirring for 30 min at –40 °C, the mixture was warmed to room temperature and stirred for 48 h. The reaction mixture was then quenched with a saturated aqueous NH_4Cl solution (30 mL) and extracted with EtOAc (3 × 50 mL). The combined organic layers were dried with $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by chromatography on silica gel [heptane/EtOAc, 10:0 to 5:5 (v/v) in 25 min] to afford compound **11** (644.0 mg, 41%) as a yellow liquid. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.67 (d, J = 7.0 Hz, 2 H, CH_2), 2.62 (s, 3 H, SCH_3), 2.00 (n, J = 6.8 Hz, 1 H, C*H*), 1.06 (d, J = 6.8 Hz, 6 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 184.9, 113.0, 112.2, 78.4, 44.1, 30.0, 22.1, 15.8 ppm. IR (film): $\tilde{\nu}$ = 2962, 2872, 2220, 1510, 1466, 1427, 1134, 924, 812 cm^{-1}. MS (ESI$^+$, CH_2Cl_2/MeOH) m/z 180.0 [M + Na]$^+$.

Ethyl 3-Amino-4-cyano-5-isobutylthiophene-2-carboxylate (12): To a solution of compound **11** (82.4 mg, 0.457 mmol) in ethanol (2 mL) were successively added potassium carbonate (82.4 mg, 0.594 mmol) and ethyl thioglycolate (60 μL, 0.548 mmol). After stirring at reflux for 3 h, the reaction mixture was quenched with water (3 mL). The precipitated crude product was filtered and purified by chromatography on silica gel [heptane/EtOAc, 10:0 to 7:3 (v/v) in 15 min] to provide thiophene **12** (71 mg, 62%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.77 (br. s, 2 H, NH_2), 4.27 (q, J = 7.1 Hz, 2 H, OCH_2), 2.74 (d, J = 7.1 Hz, 2 H, CH_2), 1.99 (n, J = 7.1 Hz, 1 H, C*H*), 1.32 (t, J = 7.1 Hz, 3 H, OCH_2CH_3), 0.97 (d, J = 6.8 Hz, 6 H, CHCH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.6, 160.5, 152.9, 113.4, 101.7, 99.4, 60.7, 39.4, 30.7, 22.3, 14.6 ppm. IR (film): $\tilde{\nu}$ = 3427, 3334, 3221, 2956, 2870, 2222, 1672, 1626, 1549, 1300, 1214, 1129, 764 cm^{-1}. MS (ESI$^+$, CH_2Cl_2/MeOH) m/z 253.1 [M + H]$^+$. HRMS (ESI$^+$, CH_2Cl_2/MeOH) calcd. for $C_{12}H_{17}N_2O_2S^+$ [M + H]$^+$ 253.1011; found 253.1016.

Ethyl 3-Bromo-4-cyano-5-isobutylthiophene-2-carboxylate (13): To a solution of amine **12** (67.2 mg, 0.266 mmol) and $CuBr_2$ (77.3 mg, 0.346 mmol) in acetonitrile (1.5 mL) was added *tert*-butylnitrite (46.3 μL, 0.40 mmol). The reaction mixture was stirred at room temperature for 10 min (until complete stop of gas release), poured onto a 20% HCl solution (2 mL) and extracted by Et_2O (3 × 5 mL). The combined organic layers were dried with $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by chromatography on silica gel [heptane/EtOAc, 10:0 to 5:5 (v/v) in 15 min] to give bromo compound **13** (47.0 mg, 56%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.37 (q, J = 7.1 Hz, 2 H, OCH_2), 2.89 (d, J = 7.0 Hz, 2 H, CH_2), 2.04 (n, J = 6.8 Hz, 1 H, CH), 1.39 (t, J = 7.1 Hz, 3 H, OCH$_2$CH_3), 1.00 (d, J = 6.8 Hz, 6 H, CHCH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.7, 159.7, 127.2, 117.5, 115.4, 113.3, 62.3, 39.5, 31.0, 22.3, 14.4 ppm. IR (film): $\tilde{\nu}$ = 2965, 2937, 2874, 2224, 1722, 1519, 1455, 1225, 1065, 754 cm^{-1}. MS (ESI$^+$, CH_2Cl_2/MeOH) m/z 370.0 [M + Na + MeOH]$^+$. HRMS (ESI$^+$, CH_2Cl_2/MeOH) calcd. for $C_{13}H_{18}{}^{79}BrNO_3SNa^+$ [M + Na + MeOH]$^+$ 370.0088; found 370.0098 and calcd. for $C_{13}H_{18}{}^{81}BrNO_3SNa^+$ [M + Na + MeOH]$^+$ 372.0068; found 372.0083.

Ethyl 3-(4-Chlorophenyl)-4-cyano-5-isobutylthiophene-2-carboxylate (14): A solution of compound **13** (37.0 mg, 0.117 mmol), potassium carbonate (2 M in H_2O, 0.147 mL, 0.293 mmol), $Pd(PPh_3)_4$ (13.5 mg, 11.7 μmol) and *p*-chlorophenylboronic acid (36.6 mg, 0.234 mmol) in a mixture toluene/EtOH, 9:1 (1 mL) was stirred at reflux for 4 h before dilution by water (3 mL). The reaction mixture was then extracted by EtOAc (3 × 5 mL) and the combined organic layers were dried with $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by chromatography on silica gel [heptane/EtOAc, 10:0 to 8:2 (v/v) in 15 min] to provide product **14** (27.6 mg, 68%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.43 (d, J = 8.5 Hz, 2 H, *H*ar), 7.35 (d, J = 8.5 Hz, 2 H, *H*ar), 4.21 (q, J = 7.1 Hz, 2 H, OCH_2), 2.92 (d, J = 7.0 Hz, 2 H, CH_2), 2.08 (n, J = 7.0 Hz, 1 H, CH), 1.22 (t, J = 7.1 Hz, 3 H, OCH$_2$CH_3), 1.04 (d, J = 6.8 Hz, 6 H, CHCH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.7, 160.4, 147.3, 135.4, 131.2, 130.9, 128.5, 127.5, 114.2, 112.9, 61.8, 39.2, 31.0, 22.4, 14.2 ppm. IR (film): $\tilde{\nu}$ = 2958, 2871, 2225, 1717, 1493, 1272, 1197, 1088, 1070, 1016, 764 cm^{-1}. MS (ESI$^+$, CH_2Cl_2/MeOH) m/z 370.1 [M + Na]$^+$. HRMS (ESI$^+$, CH_2Cl_2/MeOH) calcd. for $C_{18}H_{18}{}^{35}ClNO_2SNa^+$ [M + Na]$^+$ 370.0644; found 370.0651.

Ethyl 3-(4-Chlorophenyl)-4-cyano-5-(isopropylamino)thiophene-2-carboxylate (15): To a solution of sulfone **4** (180.0 mg, 0.452 mmol) in THF (2 mL) was added isopropylamine (2 mL) and the reaction mixture was stirred at room temperature for 18 h before dilution by water (3 mL). The reaction mixture was then extracted by EtOAc (3 × 5 mL) and the combined organic layers were dried with $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by chromatography on silica gel [heptane/EtOAc, 10:0 to 5:5 (v/v) in 20 min] to provide amine **15** (80.4 mg, 51%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.40 (d, J = 8.5 Hz, 2 H, *H*ar), 7.35 (d, J = 8.5 Hz, 2 H, *H*ar), 5.24 (d, J = 7.4 Hz, 1 H, N*H*), 4.15 (q, J = 7.1 Hz, 2 H, OCH_2), 3.63 (oct, J = 6.7 Hz, 1 H, CH), 1.37 (d, J = 6.7 Hz, 6 H, CHCH_3), 1.18 (t, J = 7.1 Hz, 3 H, CH$_2$CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.7, 161.2, 147.3, 135.0, 131.4, 130.6, 128.2, 115.0, 110.2, 88.8, 60.9, 50.2, 22.3, 14.1 ppm. IR (film): $\tilde{\nu}$ = 3256, 2967, 2929, 2211, 1702 cm^{-1}. MS (ESI$^+$, CH_2Cl_2/MeOH) m/z 371.0 [M + Na]$^+$. HRMS (ESI$^+$, CH_2Cl_2/MeOH) calcd. for $C_{17}H_{17}{}^{35}ClN_2O_2SNa^+$ [M + Na]$^+$ 371.0597; found 371.0594 and calcd. for $C_{17}H_{17}{}^{37}ClN_2O_2SNa^+$ [M + Na]$^+$ 373.0567; found 373.0588. $C_{17}H_{17}ClN_2O_2S$ (348.85): calcd. C 58.53, H 4.91, N 8.03, O 9.17, S 9.19, Cl 10.16; found C 58.30, H 4.99, N 7.92, O 9.23, S 8.98.

Ethyl 3-(4-Chlorophenyl)-4-cyano-5-(tetrahydrofuran-2-yl)thiophene-2-carboxylate (17): A solution of sulfone **4** (90.0 mg, 0.226 mmol) in THF (5 mL) was refluxed for 3 d before concentration under reduced pressure. The crude product was purified by chromatography on silica gel [heptane/EtOAc, 10:0 to 7:3 (v/v) in 15 min] to provide compound **17** (54.4 mg, 67%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.42 (d, J = 8.5 Hz, 2 H, *H*ar), 7.35 (d, J = 8.5 Hz, 2 H, *H*ar), 5.36 (t, J = 7.4 Hz, 1 H, C*H* THF), 4.21 (q, J = 7.1 Hz, 2 H, OCH_2), 4.16 (q, J = 7.2 Hz, 1 H, OCH_2 THF), 3.97 (q, J = 7.4 Hz, 1 H, CH_2), 2.61 (m, 1 H, CH_2 THF), 2.09 (m, 2 H, CH_2 THF), 1.99 (m, 1 H, CH_2 THF), 1.22 (t, J = 7.1 Hz, 3 H, CH$_2$CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.0, 160.8, 147.9, 135.5, 130.9, 128.6, 127.5, 113.6, 108.9, 76.6, 69.7, 61.9, 34.7, 26.3, 14.2 ppm. IR (film): $\tilde{\nu}$ = 2981, 2876, 2227, 1720, 1697, 1492, 1275, 1176, 1085, 1015, 826, 765 cm^{-1}. MS (ESI$^+$, CH_2Cl_2/MeOH) m/z 384.0 [M + Na]$^+$. HRMS (ESI$^+$, CH_2Cl_2/MeOH) calcd. for $C_{18}H_{16}{}^{35}ClNO_3SNa^+$ [M + Na]$^+$ 384.0437; found 384.0436 and calcd. for $C_{18}H_{16}{}^{37}ClNO_3SNa^+$ [M + Na]$^+$ 386.0408; found 386.0439.

Ethyl 5-Amino-3-(4-chlorophenyl)-4-cyanothiophene-2-carboxylate (18): To a solution of azide **26** (50.0 mg, 0.150 mmol) in ethanol (2 mL) was added palladium on charcoal (50 mg, 0.015 mmol). Hydrogen in a baloon was bubbled in the stirred reaction mixture for 1 min and the mixture was stirred another 4 min under hydrogen atmosphere before filtration through a Celite pad. Filtrate was concentrated under reduced pressure and the resulting crude product was purified by chromatography on silica gel [heptane/EtOAc, 10:0 to 5:5 (v/v) in 20 min] to give amine **18** (37.0 mg, 80%) as a grey solid; m.p. 182 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.43 (d, J = 8.5 Hz, 2 H, *H*ar), 7.38 (d, J = 8.5 Hz, 2 H, *H*ar), 5.37 (br. s, 2 H, NH_2), 4.18 (q, J = 7.1 Hz, 2 H, OCH_2), 1.20 (t, J = 7.1 Hz, 3 H, CH$_2$CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.9, 161.2, 146.9, 135.3, 131.5, 130.8, 128.5, 114.5, 112.3, 92.4, 61.4, 14.3 ppm. IR (film): $\tilde{\nu}$ = 3364, 3320, 3212, 2988, 2212, 1679, 1649, 1501, 1478, 1318, 1269, 1173, 1088, 1070 cm^{-1}. MS (ESI$^-$, CH_2Cl_2/MeOH) m/z 305.0 [M – H]$^-$. HRMS (ESI$^-$, CH_2Cl_2/MeOH) calcd. for $C_{14}H_{10}{}^{35}ClN_2O_2S^-$ [M – H]$^-$ 305.0152; found 305.0155.

Ethyl 3-(4-Chlorophenyl)-4-cyano-5-(cyclopentylamino)thiophene-2-carboxylate (19): To a solution of sulfone **4** (130.0 mg, 0.327 mmol) in THF (2 mL) was added the cyclopentylamine (1 mL). The reaction mixture was stirred at room temperature for 21 h and concentrated under reduced pressure. The crude product was purified by chromatography on silica gel [heptane/EtOAc, 10:0 to 6:4 (v/v) in 30 min] to provide amine **19** (64.0 mg, 52%) as an off-white solid; m.p. 182 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.40 (d, J = 8.5 Hz, 2 H, *H*ar), 7.35 (d, J = 8.5 Hz, 2 H, *H*ar), 5.39 (d, J = 5.39 Hz, 1 H, N*H*), 4.15 (q, J = 7.1 Hz, 2 H, OCH_2), 3.80 (hx, J = 6.4 Hz, 1 H, C*H*), 2.15 (m, 2 H, CHCH_2), 1.79 (m, 2 H, CH$_2$CH_2), 1.70 (m, 2 H, CH$_2$CH_2), 1.63 (m, 2 H, CHCH_2), 1.18 (t, J = 7.1 Hz, 3 H, CH$_2$CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.4, 161.4, 147.6, 135.2, 131.7, 130.8, 128.4, 115.3, 110.6, 89.0, 61.1, 59.5, 33.1, 24.1, 14.3 ppm. IR (film): $\tilde{\nu}$ = 3270, 2959, 2206, 1705 cm^{-1}. MS (ESI$^+$, CH_2Cl_2/MeOH) m/z 397.1 [M + Na]$^+$. HRMS (ESI$^+$, CH_2Cl_2/MeOH) calcd. for $C_{19}H_{19}{}^{35}ClN_2O_2SNa^+$ [M + Na]$^+$ 397.0753; found 397.0737.

Ethyl 3-(4-Chlorophenyl)-4-cyano-5-(pyrrolidin-1-yl)thiophene-2-carboxylate (20): A solution of sulfone **4** (96.0 mg, 0.241 mmol) in pyrrolidine (1.5 mL) was stirred at room temperature for 3 h and concentrated under reduced pressure. The crude product was purified by chromatography on silica gel [heptane/EtOAc, 10:0 to 5:5

(v/v) in 15 min] to provide amine **20** (63.9 mg, 73%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.39 (d, J = 8.5 Hz, 2 H, *H*ar), 7.32 (d, J = 8.5 Hz, 2 H, *H*ar), 4.12 (q, J = 7.1 Hz, 2 H, OCH_2), 3.69 (m, 4 H, NCH_2), 2.10 (m, 4 H, CH_2CH_2), 1.15 (t, J = 7.1 Hz, 3 H, CH_2CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.4, 161.2, 149.5, 134.7, 132.1, 130.6, 128.1, 117.2, 110.0, 87.1, 60.8, 51.8, 25.9, 14.1 ppm. IR (film): $\tilde{\nu}$ = 2953, 2206, 1699, 1520, 1257 cm^{-1}. MS (ESI$^+$, CH_2Cl_2/MeOH) m/z 383.0 [M + Na]$^+$. HRMS (ESI$^+$, CH_2Cl_2/MeOH) calcd. for $C_{18}H_{17}{}^{35}ClN_2O_2SNa^+$ [M + Na]$^+$ 383.0597; found 383.0581 and calcd. for $C_{18}H_{17}{}^{37}ClN_2O_2SNa^+$ [M + Na]$^+$ 385.0567; found 385.0570. $C_{18}H_{17}ClN_2O_2S$ (360.86): calcd. C 59.91, H 4.75, N 7.76, O 8.87, S 8.89, Cl 9.82; found C 59.90, H 4.77, N 7.85, O 9.01, S 8.75.

Ethyl 3-(4-Chlorophenyl)-4-cyano-5-(piperidin-1-yl)thiophene-2-carboxylate (21): To a solution of sulfone **4** (81.7 mg, 0.206 mmol) in THF (1 mL) was added the piperidine (0.25 mL). The reaction mixture was stirred at room temperature for 4 h and concentrated under reduced pressure. The crude product was purified by chromatography on silica gel [heptane/EtOAc, 10:0 to 5:5 (v/v) in 15 min] to provide amine **21** (44.7 mg, 58%) as a yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.39 (d, J = 8.5 Hz, 2 H, *H*ar), 7.31 (d, J = 8.5 Hz, 2 H, *H*ar), 4.12 (q, J = 7.1 Hz, 2 H, OCH_2), 3.65 (m, 4 H, NCH_2), 1.75 (m, 4 H, CH_2CH_2), 1.69 (m, 2 H, CH_2CH_2), 1.15 (t, J = 7.1 Hz, 3 H, CH_2CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.7, 161.1, 149.5, 134.9, 132.2, 130.8, 128.3, 116.7, 111.2, 89.9, 61.0, 52.4, 25.4, 23.7, 14.2 ppm. IR (film): $\tilde{\nu}$ = 2936, 2198, 1672, 1508, 1485, 1444, 1368, 1320, 1299, 1244, 1222, 1077, 917, 822 cm^{-1}. MS (ESI$^+$, CH_2Cl_2/MeOH) m/z 397.1 [M + Na]$^+$. HRMS (ESI$^+$, CH_2Cl_2/MeOH) calcd. for $C_{19}H_{19}{}^{35}ClN_2O_2SNa^+$ [M + Na]$^+$ 397.0753; found 397.0735.

Ethyl 3-(4-Chlorophenyl)-4-cyano-5-(4-methylpiperazin-1-yl)thiophene-2-carboxylate (22): A solution of sulfone **4** (260.0 mg, 0.655 mmol) in *N*-methylpiperazine (4 mL) was stirred at room temperature for 16 h and diluted with water. The reaction mixture was extracted with Et_2O (3 × 10 mL) and the combined organic layers were dried with $MgSO_4$, fiiltrated and concentrated under reduced pressure. The crude product was purified by chromatography on silica gel [CH_2Cl_2/MeOH, 100:0 to 95:5 (v/v) in 40 min] to provide compound **22** (96.5 mg, 38%) as a yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.39 (d, J = 8.5 Hz, 2 H, *H*ar), 7.30 (d, J = 8.5 Hz, 2 H, *H*ar), 4.13 (q, J = 7.1 Hz, 2 H, OCH_2), 3.69 (m, 4 H, NCH_2), 2.58 (m, 4 H, NCH_2), 2.35 (s, 3 H, NCH_3), 1.26 (t, J = 7.1 Hz, 3 H, CH_2CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.7, 161.0, 149.3, 135.1, 131.9, 130.8, 128.4, 116.4, 112.3, 91.0, 61.2, 54.1, 50.8, 46.1, 14.2 ppm. IR (film): $\tilde{\nu}$ = 2986, 2941, 2807, 2210, 1704, 1493, 1222 cm^{-1}. MS (ESI$^+$, CH_2Cl_2/MeOH) m/z 390.1 [M + H]$^+$. HRMS (ESI$^+$, CH_2Cl_2/MeOH) calcd. for $C_{19}H_{21}{}^{35}ClN_3O_2S^+$ [M + H]$^+$ 390.1043; found 390.1039. $C_{19}H_{21}ClN_3O_2S$ (389.90): calcd. C 58.53, H 5.17, N 10.78, O 8.21, S 8.22, Cl 9.09; found C 58.45, H 5.27, N 10.69, O 7.72, S 7.90.

Ethyl 3-(4-Chlorophenyl)-4-cyano-5-(diethylamino)thiophene-2-carboxylate (23): A solution of amine **18** (50.0 mg, 0.163 mmol), potassium carbonate (56.3 mg, 0.407 mmol) and ethyl iodide (32.6 μL, 0.407 mmol) in DMF (1 mL) was stirred at room temperature for 55 h. The reaction mixture was diluted by water (5 mL) and extracted by CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried with $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by chromatography on silica gel [Heptane + 0.5% Et_3N/EtOAc + 0.5% Et_3N, 10:0 to 3:7 (v/v) in 20 min] to furnish product **23** (40.0 mg, 68%) as an orange solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.39 (d, J = 8.5 Hz, 2 H, *H*ar), 7.31 (d, J = 8.5 Hz, 2 H, *H*ar), 4.12 (q, J = 7.1 Hz, 2 H, OCH_2), 3.65 (q, J = 7.1 Hz, 4 H, NCH_2), 1.35 (t, J = 7.1 Hz, 6 H, NCH_2CH_3), 1.14 (t, J = 7.1 Hz, 3 H, OCH_2CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.0, 161.3, 150.0, 134.9, 132.4, 130.8, 128.3, 117.1, 109.9, 87.2, 61.0, 48.6, 14.3, 13.1 ppm. IR (film): $\tilde{\nu}$ = 2977, 2935, 2199, 1710, 1530, 1488, 1448, 1242, 1177, 1072, 1016, 820, 758 cm^{-1}. MS (ESI$^+$, CH_2Cl_2/MeOH) m/z 385.1 [M + Na]$^+$. HRMS (ESI$^+$, CH_2Cl_2/MeOH) calcd. for $C_{18}H_{19}{}^{35}ClN_2O_2SNa^+$ [M + Na]$^+$ 385.0753; found 385.0758 and calcd. for $C_{18}H_{19}{}^{37}ClN_2O_2SNa^+$ [M + Na]$^+$ 387.0724; found 387.0749.

Ethyl 3-(4-Chlorophenyl)-4-cyano-5-{[2-(dimethylamino)ethyl]methylamino}thiophene-2-carboxylate (25): To a solution of sulfone **4** (80.0 mg, 0.201 mmol) in THF (1 mL) was added the *N*,*N*,*N*′-trimethylethylenediamine (0.5 mL). The reaction mixture was stirred at 40 °C for 92 h, diluted with water (3 mL) and extracted with EtOAc (3 × 5 mL). The combined organic layers were dried with $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by chromatography on silica gel [heptane/EtOAc, 10:0 to 5:5 (v/v) in 15 min] to provide amine **25** (23.4 mg, 30%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.39 (d, J = 8.5 Hz, 2 H, *H*ar), 7.30 (d, J = 8.5 Hz, 2 H, *H*ar), 4.12 (q, J = 7.1 Hz, 2 H, OCH_2), 3.85 (t, J = 7.0 Hz, 2 H, NCH_2), 3.31 (s, 3 H, NCH_3), 2.64 (t, J = 7.0 Hz, 2 H, NCH_2), 2.30 (s, 6 H, NCH_3), 1.14 (t, J = 7.1 Hz, 3 H, OCH_2CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.6, 161.1, 149.7, 135.0, 132.1, 130.8, 128.3, 117.2, 111.0, 87.9, 61.1, 56.4, 53.2, 45.5, 42.5, 14.3 ppm. MS (ESI$^+$, CH_2Cl_2/MeOH) m/z 392.1 [M + H]$^+$. HRMS (ESI$^+$, CH_2Cl_2/MeOH) calcd. for $C_{19}H_{23}{}^{35}ClN_3O_2S^+$ [M + H]$^+$ 392.1200; found 392.1201.

Ethyl 5-Azido-3-(4-chlorophenyl)-4-cyanothiophene-2-carboxylate (26): To a solution of sulfone **4** (500.0 mg, 1.26 mmol) in DMF (15 mL) was added sodium azide (246.0 mg, 3.78 mmol). The reaction mixture was stirred at room temperature for 5 h, diluted with water (3 mL) and extracted with EtOAc (3 × 25 mL). The combined organic layers were dried with $MgSO_4$, filtered and concentrated under reduced pressure to provide pure azide **26** (418.0 mg, quantitative) as a red solid without further purification. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.43 (d, J = 8.5 Hz, 2 H, *H*ar), 7.35 (d, J = 8.5 Hz, 2 H, *H*ar), 4.22 (q, J = 7.1 Hz, 2 H, OCH_2), 1.22 (t, J = 7.1 Hz, 3 H, OCH_2CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.0, 155.4, 147.0, 135.9, 130.8, 130.2, 128.6, 121.5, 111.9, 103.0, 62.2, 14.1 ppm. IR (film): $\tilde{\nu}$ = 2119, 1724, 1494 cm^{-1}.

Ethyl 3-(4-Chlorophenyl)-4-cyano-5-(1*H*-1,2,4-triazol-1-yl)thiophene-2-carboxylate (27): A solution of sulfone **4** (100.0 mg, 0.251 mmol), 1,2,4-triazole (34.8 mg, 0.504 mmol), *t*BuOK (56.5 mg, 0.504 mmol) and 18-crown-6 (133.1 mg, 0.504 mmol) in THF (2 mL) was stirred at room temperature for 20 h and diluted with water (5 mL). The reaction mixture was extracted with EtOAc (3 × 10 mL) and the combined organic layers were dried with $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by chromatography on silica gel [heptane/EtOAc, 10:0 to 8:2 (v/v) in 20 min] to give compound **27** (71.8 mg, 80%) as a white powder; m.p. 135 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.15 (s, 1 H, NC*H5*N triazole), 8.17 (s, 1 H, NC*H3*N triazole), 7.48 (d, J = 8.5 Hz, 2 H, *H*ar), 7.39 (d, J = 8.5 Hz, 2 H, *H*ar), 4.28 (q, J = 7.1 Hz, 2 H, OCH_2), 1.26 (t, J = 7.1 Hz, 3 H, OCH_2CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.1, 153.4, 149.8, 146.8, 142.2, 136.2, 130.9, 129.9, 128.9, 125.0, 113.3, 101.0, 62.5, 14.2 ppm. IR (film): $\tilde{\nu}$ = 3116, 2987, 2226, 1727, 1518, 1181 cm^{-1}. MS (ESI$^+$, acetonitrile) m/z 359.1 [M + H]$^+$. HRMS (ESI$^+$, acetonitrile): calcd. for $C_{16}H_{12}{}^{35}ClN_4O_2S^+$ [M + H]$^+$ 359.0370; found 359.0373.

Ethyl 3-(4-Chlorophenyl)-4-cyano-5-(1*H*-pyrrol-1-yl)thiophene-2-carboxylate (28): To a solution of amine **18** (48.0 mg, 0.157 mmol)

in glacial acetic acid (2 mL) was added 2,5-dimethoxytetrahydrofuran (63.5 μL, 0.469 mmol) and the reaction mixture was stirred for 1 h at 90 °C before concentration under reduced pressure. The crude product was purified by chromatography on silica gel [heptane/EtOAc, 10:0 to 7:3 (v/v) in 15 min] to give compound **28** (48.5 mg, 87%) as a pale orange solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.46 (d, J = 8.5 Hz, 2 H, *H*ar), 7.38 (d, J = 8.5 Hz, 2 H, *H*ar), 7.34 (m, 2 H, N=C*H*), 6.44 (m, 2 H, =C*H*), 4.23 (q, J = 7.1 Hz, 2 H, OCH_2), 1.22 (t, J = 7.1 Hz, 3 H, OCH_2CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.4, 154.9, 147.6, 135.8, 130.9, 130.6, 128.7, 121.3, 121.1, 114.0, 113.8, 100.5, 62.1, 14.2 ppm. IR (film): $\tilde{\nu}$ = 2990, 2222, 1725, 1502, 1487, 1248, 1172, 716 cm^{-1}. MS (ESI$^+$, CH_2Cl_2/MeOH) *m*/*z* 379.0 [M + Na]$^+$. HRMS (ESI$^+$, CH_2Cl_2/MeOH) calcd. for $C_{18}H_{13}{}^{35}ClN_2O_2SNa^+$ [M + Na]$^+$ 379.0284; found 379.0277.

Ethyl 3-(4-Chlorophenyl)-4-cyano-5-(1*H*-imidazol-1-yl)thiophene-2-carboxylate (29): A solution of sulfone **4** (96.1 mg, 0.236 mmol), imidazole (32.2 mg, 0.473 mmol), *t*BuOK (53.1 mg, 0.473 mmol) and 18-crown-6 (125.0 mg, 0.473 mmol) in THF (2 mL) was stirred at room temperature for 20 h and diluted with water (5 mL). The reaction mixture was extracted with EtOAc (3 × 10 mL) and the combined organic layers were dried with $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by chromatography on silica gel [heptane/EtOAc, 10:0 to 5:5 (v/v) in 15 min] to give compound **29** (36.2 mg, 43%) as a white powder; m.p. 172 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.14 (s, 1 H, *H*2-imidazole), 7.53 (s, 1 H, *H*5-imidazole), 7.47 (d, J = 8.5 Hz, 2 H, *H*ar), 7.39 (d, J = 8.5 Hz, 2 H, *H*ar), 7.31 (s, 1 H, *H*4-imidazole), 4.28 (q, J = 7.1 Hz, 2 H, OCH_2), 1.26 (t, J = 7.1 Hz, 3 H, OCH_2CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.0, 149.9, 147.2, 136.7, 136.2, 132.2, 130.9, 130.0, 128.9, 124.2, 119.4, 112.9, 104.5, 62.5, 14.2 ppm. IR (film): $\tilde{\nu}$ = 3140, 3102, 2990, 2228, 1681, 1505, 1290, 1256, 1086 cm^{-1}. MS (ESI$^+$, acetonitrile) *m*/*z* 358.1 [M + H]$^+$. HRMS (ESI$^+$, acetonitrile): calcd. for $C_{17}H_{13}{}^{35}ClN_3O_2S^+$ [M + H]$^+$ 358.0417; found 358.0418.

Ethyl 3-(4-Chlorophenyl)-4-cyano-5-(1*H*-pyrazol-1-yl)thiophene-2-carboxylate (30): A solution of sulfone **4** (100.0 mg, 0.251 mmol), pyrazole (51.3 mg, 0.754 mmol), *t*BuOK (84.6 mg, 0.754 mmol) and 18-crown-6 (199.2 mg, 0.754 mmol) in THF (2 mL) was stirred at room temperature for one week and diluted with water (5 mL). The reaction mixture was extracted with EtOAc (3 × 10 mL) and the combined organic layers were dried with $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by chromatography on silica gel [Heptane + 0.5% Et_3N/EtOAc + 0.5% Et_3N, 10:0 to 6:4 (v/v) in 15 min] to give compound **30** (41.1 mg, 46%) as a white powder. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.58 (d, J = 2.6 Hz, 1 H, *H*5-pyrazole), 7.79 (d, J = 1.7 Hz, 1 H, *H*3-pyrazole), 7.43 (d, J = 8.5 Hz, 2 H, *H*ar), 7.35 (d, J = 8.5 Hz, 2 H, *H*ar), 6.60 (m, 1 H, *H*4-pyrazole), 4.24 (q, J = 7.1 Hz, 2 H, OCH_2), 1.24 (t, J = 7.1 Hz, 3 H, OCH_2CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.5, 154.5, 147.0, 143.6, 135.8, 130.9, 130.6, 128.8, 128.7, 122.5, 114.1, 110.7, 97.7, 62.1, 14.2 ppm. IR (film): $\tilde{\nu}$ = 3154, 3138, 2989, 2909, 2227, 1726, 1531, 1505, 1485 cm^{-1}. MS (ESI$^+$, CH_2Cl_2/MeOH) *m*/*z* 380.0 [M + Na]$^+$. HRMS (ESI$^+$, CH_2Cl_2/MeOH) calcd. for $C_{17}H_{12}{}^{35}ClN_3O_2SNa^+$ [M + Na]$^+$ 380.0236; found 380.0226.

Ethyl 3-(4-Chlorophenyl)-4-cyano-5-[4-(trimethylsilyl)-1*H*-1,2,3-triazol-1-yl]thiophene-2-carboxylate (32): A solution of azide **26** (144.0 mg, 0.433 mmol) in (trimethylsilyl)acetylene (1 mL, 7.08 mmol) was stirred for 7 h at room temperature and concentrated under reduced pressure. The crude product was purified by chromatography on silica gel [heptane/EtOAc, 10:0 to 6:4 (v/v) in 20 min] to give compound **32** (154.4 mg, 83%) as a purple solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.50 (s, 1 H, *H*5-triazole), 7.48 (d, J = 8.5 Hz, 2 H, *H*ar), 7.39 (d, J = 8.5 Hz, 2 H, *H*ar), 4.27 (q, J = 7.1 Hz, 2 H, OCH_2), 1.26 (t, J = 7.1 Hz, 3 H, OCH_2CH_3), 0.40 (s, 9 H, SiCH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.1, 149.7, 148.9, 146.6, 136.1, 130.9, 130.0, 128.9, 127.3, 125.2, 113.1, 101.5, 62.5, 14.2, –1.1 ppm. IR (film): $\tilde{\nu}$ = 2960, 2228, 1727, 1698, 1513, 1251, 1204, 1178, 1088, 1016, 952, 839, 759 cm^{-1}. MS (ESI$^+$, CH_2Cl_2/MeOH) *m*/*z* 453.0 [M + Na]$^+$. HRMS (ESI$^+$, CH_2Cl_2/MeOH) calcd. for $C_{19}H_{19}{}^{35}ClN_4O_2SSiNa^+$ [M + Na]$^+$ 453.0584; found 453.0603 and calcd. for $C_{19}H_{19}{}^{37}ClN_4O_2SSiNa^+$ [M + Na]$^+$ 455.0555; found 455.0574.

Ethyl 3-(4-Chlorophenyl)-4-cyano-5-(1*H*-1,2,3-triazol-1-yl)thiophene-2-carboxylate (33): To a solution of silylated derivative **32** (50.0 mg, 0.116 mmol) in THF (1 mL) was added HF·Et_3N (95.0 μL, 0.58 mmol). The reaction mixture was stirred at room temperature for 6 h, quenched with a saturated aqueous $NaHCO_3$ solution (5 mL) and extracted with EtOAc (3 × 5 mL). The combined organic layers were dried with $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by chromatography on silica gel [heptane/EtOAc, 10:0 to 5:5 (v/v) in 20 min] to give triazole **33** (34.7 mg, 83%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.63 (br. s, 1 H, *H*5-triazole), 7.93 (br. s, 1 H, *H*4-triazole), 7.48 (d, J = 8.5 Hz, 2 H, *H*ar), 7.40 (d, J = 8.5 Hz, 2 H, *H*ar), 4.28 (q, J = 7.1 Hz, 2 H, OCH_2), 1.26 (t, J = 7.1 Hz, 3 H, OCH_2CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.0, 148.6, 146.6, 136.6, 135.7, 130.9, 129.9, 128.9, 125.7, 122.7, 112.9, 102.1, 62.6, 14.2 ppm. IR (film): $\tilde{\nu}$ = 3148, 3126, 2986, 2229, 1729, 1694, 1514, 1486, 1264, 1245, 1185, 1014 cm^{-1}. MS (ESI$^+$, CH_2Cl_2/MeOH) *m*/*z* 381.0 [M + Na]$^+$. HRMS (ESI$^+$, CH_2Cl_2/MeOH) calcd. for $C_{16}H_{11}{}^{35}ClN_4O_2SNa^+$ [M + Na]$^+$ 381.0189; found 381.0180. $C_{16}H_{11}ClN_4O_2S$ (358.80): calcd. C 53.56, H 3.09, N 15.61, O 8.92, S 8.94, Cl 9.88; found C 53.33, H 3.18, N 15.59, O 8.75, S 8.52.

Ethyl 4-(4-Chlorophenyl)-3-cyano-2,3′-bithiophene-5-carboxylate (34): A solution of compound **2** (100.0 mg, 0.273 mmol), 3-thienylboronic acid (45.4 mg, 0.355 mmol), $Pd(PPh_3)_4$ (31.6 mg, 27.3 μmol) and copper(I) thiophene-2-carboxylate (78.2 mg, 0.410 mmol) in THF (1.5 mL) was stirred at 50 °C for 48 h before quenching by 28% ammoniac solution (2 mL). The reaction mixture was then extracted by EtOAc (3 × 5 mL) and the combined organic layers were dried with $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by chromatography on silica gel [heptane/EtOAc, 10:0 to 5:5 (v/v) in 15 min] and the solid obtained was washed with cold EtOH to provide product **34** (62.0 mg, 61%) as a white solid; m.p. 120 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.07 (br. s, 1 H, *H* thiophene), 7.57 (br. s, 1 H, *H* thiophene), 7.48 (br. s, 1 H, *H* thiophene), 7.46 (d, J = 8.5 Hz, 2 H, *H*ar), 7.39 (d, J = 8.5 Hz, 2 H, *H*ar), 4.24 (q, J = 7.1 Hz, 2 H, OCH_2), 1.23 (t, J = 7.1 Hz, 3 H, OCH_2CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.7, 151.6, 148.8, 135.6, 131.5, 131.0, 130.9, 128.7, 127.8, 127.0, 126.6, 126.2, 115.3, 108.8, 62.0, 14.2 ppm. IR (film): $\tilde{\nu}$ = 3107, 2981, 2901, 2223, 1719, 1696, 1089, 784 cm^{-1}. MS (ESI$^+$, CH_2Cl_2/MeOH) *m*/*z* 396.0 [M + Na]$^+$. HRMS (ESI$^+$, CH_2Cl_2/MeOH) calcd. for $C_{18}H_{12}ClNO_2S_2Na^+$ [M + Na]$^+$ 395.9896; found 395.9913.

Ethyl 3-(4-Chlorophenyl)-4-cyano-5-phenylthiophene-2-carboxylate (35): Following the exact same procedure as for product **34** and starting from compound **2** (77.0 mg, 0.191 mmol), desired ester **35** (36.5 mg, 52%) was obtained as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.82 (m, 2 H, *H*ar), 7.52 (m, 3 H, *H*ar), 7.46 (d, J = 8.5 Hz, 2 H, *H*ar), 7.40 (d, J = 8.5 Hz, 2 H, *H*ar), 4.25 (q, J =

7.1 Hz, 2 H, OCH_2), 1.24 (t, J = 7.1 Hz, 3 H, OCH$_2$CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.7, 157.5, 148.9, 135.6, 131.2, 131.1, 131.0, 130.8, 129.7, 129.4, 128.7, 128.2, 114.9, 109.9, 62.0, 14.2 ppm. IR (film): $\tilde{\nu}$ = 2982, 2224, 1723, 1698, 1486, 1302, 1234, 1172, 1090 cm^{-1}. MS (ESI$^+$, CH_2Cl_2/MeOH) m/z 390.0 [M + Na]$^+$. HRMS (ESI$^+$, CH_2Cl_2/MeOH) calcd. for $C_{20}H_{14}ClNO_2SNa^+$ [M + Na]$^+$ 390.0331; found 390.0340.

Typical Procedure for Saponification of Esters: To a solution of ester (1 mmol) in a mixture THF/EtOH, 2:1 (10 mL/mmol) was added NaOH 2 M in water (5 mL/mmol). The reaction mixture was stirred overnight at room temperature and then acidified to pH = 4–5 with HCl 1 M in water.

Method A: The precipitated product was filtered, washed with water and dried under vacuum.

Method B: If the desired acid did not precipitate, the reaction mixture was extracted with EtOAc (3 × 15 mL/mmol) and the combined organic layers were washed with water (40 mL/mmol) dried with $MgSO_4$, filtered and concentrated under reduced pressure.

Unless otherwise indicated, the pure desired product was obtained without further purification.

3-(4-Chlorophenyl)-4-cyano-5-(isopropylsulfinyl)thiophene-2-carboxylic Acid (3a): According to method A for saponification of ester **3** (34.6 mg, 0.091 mmol), acid **3a** (29.1 mg, 91%) was obtained as a white solid. ^{1}H NMR ([D$_6$]acetone, 300 MHz): δ = 7.51 (m, 4 H, Har), 3.38 (m, 1 H, CH), 1.31 (m, 6 H, CHCH_3) ppm. ^{13}C NMR ([D$_6$]acetone, 75 MHz): δ = 161.0, 142.3, 133.7, 132.4, 131.8, 129.1, 129.0, 113.1, 112.7, 57.6, 15.9, 14.3 ppm. IR (film): $\tilde{\nu}$ = 2963, 2924, 2852, 2558, 2230, 1704, 1487, 1255, 1015, 730 cm^{-1}. MS (ESI$^-$, CH_2Cl_2/MeOH) m/z 352.0 [M – H]$^-$. HRMS (ESI$^-$, CH_2Cl_2/MeOH) calcd. for $C_{15}H_{11}{}^{35}ClNO_3S_2^-$ [M – H]$^-$ 351.9869; found 351.9879 and calcd. for $C_{15}H_{11}{}^{37}ClNO_3S_2^-$ [M – H]$^-$ 353.9839; found 353.9883. UHPLC: 2.35 min, 89% (System 1); 2.96 min, 90% (System 2).

3-(4-Chlorophenyl)-4-cyano-5-(isopropylsulfonyl)thiophene-2-carboxylic Acid (4a): According to method B for saponification of ester **4** (210.0 mg, 0.528 mmol), acid **4a** (195.0 mg, quantitative) was obtained as an off-white solid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.37 (d, J = 8.7 Hz, 2 H, Har), 7.31 (d, J = 8.7 Hz, 2 H, Har), 3.52 (h, J = 6.8 Hz, 1 H, CH), 1.41 (d, J = 6.8 Hz, 6 H, CHCH_3) ppm. ^{13}C NMR ([D$_6$]acetone, 125 MHz): δ = 161.2, 149.6, 149.3, 138.3, 135.9, 132.5, 131.6, 129.1, 117.9, 112.6, 58.2, 15.9 ppm. IR (film): $\tilde{\nu}$ = 2856, 2535, 2238, 1693, 1677, 1315, 1278, 1125 cm^{-1}. MS (ESI$^-$, CH_2Cl_2/MeOH) m/z 368.0 [M – H]$^-$. HRMS (ESI$^-$, CH_2Cl_2/MeOH) calcd. for $C_{15}H_{11}{}^{35}ClNO_4S_2^-$ [M – H]$^-$ 351.9869; found 351.9879. UHPLC: 2.41 min, 99% (System 1).

3-(4-Chlorophenyl)-4-cyano-5-(propylthio)thiophene-2-carboxylic Acid (5a): According to method B for saponification of ester **5** (21.2 mg, 0.059 mmol), acid **5a** (18.9 mg, 95%) was obtained as a white powder; m.p. 199 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.38 (d, J = 8.2 Hz, 2 H, Har), 7.32 (d, J = 8.2 Hz, 2 H, Har), 3.13 (t, J = 7.2 Hz, 2 H, SCH_2), 1.85 (hx, J = 7.2 Hz, 2 H, CH$_2$CH_2), 1.10 (t, J = 7.2 Hz, 3 H, CH$_2$CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.9, 158.3, 149.5, 135.8, 130.9, 130.4, 128.7, 126.1, 113.4, 112.6, 38.5, 22.6, 13.6 ppm. IR (film): $\tilde{\nu}$ = 2961, 2922, 2851, 2551, 2219, 1644, 1485, 1351, 1297 cm^{-1}. MS (ESI$^-$, CH_2Cl_2/MeOH) m/z 336.0 [M – H]$^-$. HRMS (ESI$^-$, CH_2Cl_2/MeOH) calcd. for $C_{15}H_{11}{}^{35}ClNO_2S_2^-$ [M – H]$^-$ 335.9920; found 335.9927. UHPLC: 2.97 min, 98% (System 1); 3.52 min, 98% (System 2).

5-(*tert*-Butylthio)-3-(4-cholorophenyl)-4-cyanothiophene-2-carboxylic Acid (6a): According to method A for saponification of ester **6** (38.4 mg, 0.101 mmol), acid **6a** (32.9 mg, 93%) was obtained as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.32 (m, 4 H, Har), 1.49 (s, 9 H, tBu) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.8, 150.0, 148.4, 135.7, 131.0, 130.7, 128.7, 121.8, 113.9, 110.4, 51.9, 31.2 ppm. IR (film): $\tilde{\nu}$ = 2963, 2550, 2230, 1694, 1485, 1155, 1087, 826 cm^{-1}. MS (ESI$^+$, CH_2Cl_2/MeOH) m/z 374.0 [M + Na]$^+$. HRMS (ESI$^+$, CH_2Cl_2/MeOH) calcd. for $C_{16}H_{14}{}^{35}ClNO_2S_2Na^+$ [M + Na]$^+$ 374.0052; found 374.0052 and calcd. for $C_{16}H_{14}{}^{37}ClNO_2S_2Na^+$ [M + Na]$^+$ 376.0023; found 376.0049.

3-(4-Chlorophenyl)-4-cyano-5-isopropoxythiophene-2-carboxylic Acid (7a): According to method A for saponification of ester **7** (50.0 mg, 0.137 mmol), acid **7a** (43.8 mg, 99%) was obtained as a white powder. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.41 (d, J = 8.5 Hz, 2 H, Har), 7.33 (d, J = 8.5 Hz, 2 H, Har), 4.65 (h, J = 6.1 Hz, 1 H, OCH), 1.53 (d, J = 6.1 Hz, 6 H, CHCH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 176.1, 165.8, 135.7, 131.8, 130.9, 130.8, 129.1, 128.6, 113.0, 97.0, 82.0, 22.0 ppm. IR (film): $\tilde{\nu}$ = 2982, 2535, 2225, 1676, 1643, 1087 cm^{-1}. MS (ESI$^-$, DMF/MeOH): m/z = 320.0 [M – H]$^-$. HRMS (ESI$^-$, DMF/MeOH): calcd. for $C_{15}H_{11}{}^{35}ClNO_3S^-$ [M – H]$^-$ 320.0148; found 320.0136.

3-(4-Chlorophenyl)-4-cyano-5-isobutylthiophene-2-carboxylic Acid (14a): According to method B for saponification of ester **14** (25.7 mg, 0.074 mmol), acid **14a** (23.5 mg, quantitative) was obtained as a white solid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.43 (d, J = 8.5 Hz, 2 H, Har), 7.34 (d, J = 8.5 Hz, 2 H, Har), 2.93 (d, J = 6.8 Hz, 2 H, CHCH_2), 2.08 (m, 1 H, CH$_2$CH), 1.04 (d, J = 6.8 Hz, 6 H, CHCH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.4, 162.0, 149.1, 135.7, 130.9, 130.7, 128.8, 126.1, 114.0, 113.6, 39.3, 31.0, 22.4 ppm. IR (film): $\tilde{\nu}$ = 3127, 2959, 2928, 2866, 2237, 1721, 1489, 1159, 1135, 1088, 765, 668 cm^{-1}. MS (ESI$^-$, CH_2Cl_2/MeOH): m/z = 318.1 [M – H]$^-$. HRMS (ESI$^-$, CH_2Cl_2/MeOH) calcd. for $C_{16}H_{13}{}^{35}ClNO_2S^-$ [M – H]$^-$ 318.0356; found 318.0351. UHPLC: 3.02 min, 99% (System 1); 3.58 min, 99% (System 2).

3-(4-Chlorophenyl)-4-cyano-5-(tetrahydrofuran-2-yl)thiophene-2-carboxylic Acid (17a): According to method B for saponification of ester **17** (25.7 mg, 0.074 mmol) and after chromatography on silica gel [CH_2Cl_2 + 0.5% HCOOH/EtOAc + HCOOH 0.5% 10:0 to 9:1 (v/v) in 10 min], acid **17a** (20.3 mg, 72%) was obtained as a white solid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.45 (d, J = 8.5 Hz, 2 H, Har), 7.36 (d, J = 8.5 Hz, 2 H, Har), 5.38 (t, J = 6.9 Hz, 1 H, OCH), 4.18 (m, 1 H, OCH_2), 4.00 (m, 1 H, OCH_2), 2.64 (m, 1 H, CHCH_2), 2.20–1.94 (m, 3 H, CHCH_2 and CH$_2$CH_2) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.6, 165.4, 149.6, 135.8, 130.9, 130.5, 128.8, 126.1, 113.4, 109.4, 76.6, 69.7, 34.7, 26.3 ppm. IR (film): $\tilde{\nu}$ = 2969, 2559, 2225, 1717, 1637, 1483, 1400 cm^{-1}. MS (ESI$^-$, CH_2Cl_2/MeOH): m/z = 332.0 [M – H]$^-$. HRMS (ESI$^-$, CH_2Cl_2/MeOH) calcd. for $C_{16}H_{11}{}^{35}ClNO_3S^-$ [M – H]$^-$ 332.0148; found 334.0146.

5-Amino-3-(4-chlorophenyl)-4-cyanothiophene-2-carboxylic Acid (18a): According to method A for saponification of ester **18** (10.5 mg, 0.034 mmol) and substituting NaOH with LiOH, acid **18a** (7.1 mg, 75%) was obtained as a grey solid. ^{1}H NMR ([D$_6$]-acetone, 300 MHz): δ = 7.45 (m, 2 H, Har) ppm. IR (film): $\tilde{\nu}$ = 3303, 3200, 2962, 2548, 2217, 1613, 1498, 1471, 1311, 1300, 1282, 1186, 1090 cm^{-1}. MS (ESI$^-$, CH_2Cl_2/MeOH): m/z = 277.0 [M – H]$^-$. HRMS (ESI$^-$, CH_2Cl_2/MeOH) calcd. for $C_{12}H_6{}^{35}ClN_2O_2S^-$ [M – H]$^-$ 276.9839; found 276.9849. UHPLC: 2.15 min, 93% (System 1); 2.75 min, 94% (System 2).

3-(4-Chlorophenyl)-4-cyano-5-(pyrrolidin-1-yl)thiophene-2-carboxylic Acid (20a): According to method A for saponification of ester **20** (55.4 mg, 0.154 mmol), acid **20a** (35.8 mg, 70%) was obtained as a white solid; m.p. 200 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ =

7.38 (m, 4 H, *H*ar), 3.69 (m, 4 H, NCH_2), 2.14 (m, 4 H, CH_2CH_2) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.3, 162.2, 149.9, 134.8, 134.0, 132.1, 128.7, 117.5, 110.9, 87.8, 52.7, 26.5 ppm. IR (film): $\tilde{\nu}$ = 2958, 2923, 2871, 2534, 2206, 1641, 1510, 1295 cm^{-1}. MS (ESI$^-$, CH_2Cl_2/MeOH): *m*/*z* = 331.0 [M – H]$^-$. HRMS (ESI$^-$, CH_2Cl_2/MeOH) calcd. for $C_{16}H_{12}{}^{35}ClN_2O_2S^-$ [M – H]$^-$ 331.0308; found 331.0306 and calcd. for $C_{16}H_{12}{}^{37}ClN_2O_2S^-$ [M – H]$^-$ 333.0279; found 333.0311. UHPLC: 2.66 min, 99% (System 1); 3.25 min, 99% (System 2).

3-(4-Chlorophenyl)-4-cyano-5-(piperidin-1-yl)thiophene-2-carboxylic Acid (21a): According to method A for saponification of ester **21** (30.0 mg, 0.080 mmol), acid **21a** (25.3 mg, 91%) was obtained as a white solid. ^{1}H NMR ([D$_6$]acetone, 300 MHz): δ = 7.44 (m, 4 H, *H*ar), 3.71 (m, 2 H, NCH_2), 1.82–1.68 (m, 6 H, CH_2CH_2) ppm. ^{13}C NMR ([D$_6$]acetone, 75 MHz): δ = 168.4, 162.1, 149.7, 134.9, 133.8, 132.1, 128.8, 116.9, 112.4, 90.9, 53.0, 26.0, 24.2 ppm. IR (film): $\tilde{\nu}$ = 2946, 2854, 2554, 2204, 1643, 1514, 1478, 1290, 1241, 1175, 1086, 1014, 915, 814 cm^{-1}. MS (ESI$^-$, CH_2Cl_2/MeOH): *m*/*z* = 345.0 [M – H]$^-$. HRMS (ESI$^-$, CH_2Cl_2/MeOH) calcd. for $C_{17}H_{14}{}^{35}ClN_2O_2S^-$ [M – H]$^-$ 345.0465; found 345.0466.

3-(4-Chlorophenyl)-4-cyano-5-(4-methylpiperazin-1-yl)thiophene-2-carboxylic Acid (22a): According to method A for saponification of ester **22** (30.0 mg, 0.154 mmol), acid **22a** (23.6 mg, 85%) was obtained as a white solid; m.p. 211 °C. ^{1}H NMR ([D$_6$]acetone, 300 MHz): δ = 7.26 (m, 4 H, *H*ar), 3.62 (m, 4 H, NCH_2), 2.56 (m, 4 H, NCH_2), 2.33 (s, 3 H, NCH_3) ppm. IR (film): $\tilde{\nu}$ = 3465, 3359, 2962, 2194, 1698 cm^{-1}. MS (ESI$^-$, CH_2Cl_2/MeOH): *m*/*z* = 360.1 [M – H]$^-$. HRMS (ESI$^-$, CH_2Cl_2/MeOH) calcd. for $C_{17}H_{15}{}^{35}ClN_3O_2S^-$ [M – H]$^-$ 360.0574; found 360.0578. UHPLC: 1.69 min, 100% (System 1); 2.19 min, 100% (System 2).

3-(4-Chlorophenyl)-4-cyano-5-(diethylamino)thiophene-2-carboxylic Acid (23a): According to method B for saponification of ester **23** (26.6 mg, 0.073 mmol), acid **23a** (13.7 mg, 56%) was obtained as a white solid; m.p. 158 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.37 (d, *J* = 8.2 Hz, 2 H, *H*ar), 7.29 (d, *J* = 8.2 Hz, 2 H, *H*ar), 3.65 (q, *J* = 7.1 Hz, 4 H, NCH_2), 1.34 (t, *J* = 7.1 Hz, 6 H, NCH$_2$CH_3), 1.14 (t, *J* = 7.1 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.1, 165.7, 152.3, 135.1, 131.9, 130.8, 128.4, 116.9, 108.9, 87.9, 48.7, 13.0 ppm. IR (film): $\tilde{\nu}$ = 2973, 2930, 2540, 2200, 1643, 1520, 1297 cm^{-1}. MS (ESI$^-$, CH_2Cl_2/MeOH): *m*/*z* = 333.1 [M – H]$^-$. HRMS (ESI$^-$, CH_2Cl_2/MeOH) calcd. for $C_{17}H_{15}{}^{35}ClN_3O_2S^-$ [M – H]$^-$ 333.0465; found 333.0466. UHPLC: 2.71 min, 92% (System 1); 3.27 min, 93% (System 2).

3-(4-Chlorophenyl)-4-cyano-5-(1*H*-1,2,4-triazol-1-yl)thiophene-2-carboxylic Acid (27a): According to method B for saponification of ester **27** (17.8 mg, 0.050 mmol), acid **27a** (13.9 mg, 85%) was obtained as a black solid; m.p. 192 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.20 (s, 1 H, *H*5-triazole), 8.20 (s, 1 H, *H*3-triazole), 7.50 (d, *J* = 8.5 Hz, 2 H, *H*ar), 7.42 (d, *J* = 8.5 Hz, 2 H, *H*ar) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 161.5, 153.3, 149.8, 147.0, 142.3, 136.1, 131.0, 129.9, 128.9, 128.6, 113.3, 101.4 ppm. IR (film): $\tilde{\nu}$ = 3128, 2922, 2852, 2507, 2229, 1650, 1514, 1088, 664 cm^{-1}. MS (ESI$^-$, CH_2Cl_2/MeOH): *m*/*z* = 329.0 [M – H]$^-$. HRMS (ESI$^-$, CH_2Cl_2/MeOH) calcd. for $C_{14}H_6{}^{35}ClN_4O_2S^-$ [M – H]$^-$ 328.9900; found 328.9915. UHPLC: 2.21 min, 87% (System 1); 2.86 min, 87% (System 2).

3-(4-Chlorophenyl)-4-cyano-5-(1*H*-pyrrol-1-yl)thiophene-2-carboxylic Acid (28a): According to method B for saponification of ester **28** (5.1 mg, 0.014 mmol), acid **28a** (4.7 mg, quantitative) was obtained as a white solid. ^{1}H NMR ([D$_6$]acetone, 300 MHz): δ = 7.50–7.00 (m, 6 H, *H*ar and N=C*H*), 6.37 (m, 2 H, =C*H*) ppm. IR (film): $\tilde{\nu}$ = 2922, 2852, 2223, 1503, 1369, 719 cm^{-1}. MS (ESI$^-$, CH_2Cl_2/MeOH): *m*/*z* = 327.0 [M – H]$^-$. HRMS (ESI$^-$, CH_2Cl_2/MeOH) calcd. for $C_{16}H_8{}^{35}ClN_2O_2S^-$ [M – H]$^-$ 326.9995; found 326.9991. UHPLC: 2.82 min, 98% (System 1); 3.43 min, 98% (System 2).

3-(4-Chlorophenyl)-4-cyano-5-(1*H*-imidazol-1-yl)thiophene-2-carboxylic Acid (29a): According to method B for saponification of ester **29** (13.6 mg, 0.038 mmol), acid **29a** (6.9 mg, 55%) was obtained as a white solid; m.p. 214 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.10 (s, 1 H, *H*2-imidazole), 7.54 (s, 1 H, *H*5-imidazol), 7.43 (m, 4 H, *H*ar), 7.37 (s, 1 H, *H*4-imidazole) ppm. IR (film): $\tilde{\nu}$ = 3147, 2922, 2422, 2226, 1704, 1501, 1091 cm^{-1}. MS (ESI$^+$, CH_2Cl_2/MeOH): *m*/*z* = 330.0 [M + H]$^+$. HRMS (ESI$^+$, CH_2Cl_2/MeOH) calcd. for $C_{15}H_9{}^{35}ClN_3O_2S^+$ [M + H]$^+$ 330.0104; found 330.0103. UHPLC: 1.98 min, 87% (System 1); 2.68 min, 88% (System 2).

3-(4-Chlorophenyl)-4-cyano-5-(1*H*-pyrazol-1-yl)thiophene-2-carboxylic Acid (30a): According to method B for saponification of ester **30** (10.0 mg, 0.028 mmol), acid **30a** (6.1 mg, 66%) was obtained as a white solid; m.p. 254 °C. ^{1}H NMR ([D$_6$]acetone, 300 MHz): δ = 8.59 (d, *J* = 2.6 Hz, 1 H, *H*5-pyrazole), 7.79 (d, *J* = 1.7 Hz, 2 H, *H*3-pyrazole), 7.55 (m, 4 H, *H*ar), 6.74 (m, 1 H, *H*4-pyrazole) ppm. IR (film): $\tilde{\nu}$ = 2913, 2630, 2223, 1690 cm^{-1}. MS (ESI$^-$, CH_2Cl_2/MeOH): *m*/*z* = 328.0 [M – H]$^-$. HRMS (ESI$^-$, CH_2Cl_2/MeOH) calcd. for $C_{15}H_7{}^{35}ClN_3O_2S^-$ [M – H]$^-$ 327.9948; found 327.9954. UHPLC: 2.61 min, 100% (System 1).

3-(4-Chlorophenyl)-4-cyano-5-(1*H*-1,2,3-triazol-1-yl)thiophene-2-carboxylic Acid (33a): According to method A for saponification of ester **33** (26.6 mg, 0.074 mmol), acid **33a** (22.8 mg, 93%) was obtained as a white solid. ^{1}H NMR ([D$_6$]acetone, 300 MHz): δ = 8.67 (br. s, 1 H, *H*5-triazole), 7.91 (br. s, 1 H, *H*4-triazole), 7.47 (d, *J* = 8.5 Hz, 2 H, *H*ar), 7.43 (d, *J* = 8.5 Hz, 2 H, *H*ar) ppm. ^{13}C NMR ([D$_6$]acetone, 75 MHz): δ = 161.3, 136.1, 135.9, 132.3, 132.0, 129.2, 128.9, 125.3, 113.4, ppm. IR (film): $\tilde{\nu}$ = 3170, 3150, 2921, 2851, 2468, 2229, 1865, 1683, 1469, 1289, 1244, 1090, 1033, 1014, 822, 786, 764 cm^{-1}. MS (ESI$^-$, CH_2Cl_2/MeOH): *m*/*z* = 329.0 [M – H]$^-$. HRMS (ESI$^-$, CH_2Cl_2/MeOH) calcd. for $C_{14}H_6{}^{35}ClN_4O_2S^-$ [M – H]$^-$ 328.9900; found 328.9914. UHPLC: 2.32 min, 92% (System 1); 2.89 min, 92% (System 2).

4-(4-Chlorophenyl)-3-cyano-2,3′-bithiophene-5-carboxylic Acid (34a): According to method B for saponification of ester **34** (15.7 mg, 0.042 mmol), acid **34a** (14.7 mg, quantitative) was obtained as a yellow solid; m.p. 213 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.98 (br. s, 1 H, *H* thiophene), 7.44 (br. s, 1 H, *H* thiophene), 7.40 (br. s, 1 H, *H* thiophene), 7.31 (m, 4 H, *H*ar) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 152.5, 135.7, 131.3, 131.0, 130.8, 128.8, 128.0, 126.5, 115.1, 109.1, 100.2 ppm. IR (film): $\tilde{\nu}$ = 2922, 2571, 2224, 1682, 1089, 781 cm^{-1}. MS (ESI$^-$, CH_2Cl_2/MeOH): *m*/*z* = 344.0 [M – H]$^-$. HRMS (ESI$^-$, CH_2Cl_2/MeOH) calcd. for $C_{16}H_8{}^{35}ClNO_2S_2^-$ [M – H]$^-$ 343.9607; found 343.9610. UHPLC: 2.89 min, 96% (System 1); 3.49 min, 99% (System 2).

3-(4-Chlorophenyl)-4-cyano-5-phenylthiophene-2-carboxylic Acid (35a): According to method A for saponification from ester **35** (19.9 mg, 0.054 mmol), acid **35a** (6.7 mg, 36%) was obtained as a white solid; m.p. 235 °C. ^{1}H NMR ([D$_6$]acetone, 300 MHz): δ = 7.90 (m, 2 H, *H*ar), 7.65–7.50 (m, 7 H, *H*ar) ppm. IR (film): $\tilde{\nu}$ = 2923, 2228, 1737, 1487, 1142, 755 cm^{-1}. MS (ESI$^-$, CH_2Cl_2/MeOH): *m*/*z* = 338.0 [M – H]$^-$. HRMS (ESI$^-$, CH_2Cl_2/MeOH) calcd. for $C_{18}H_9{}^{35}ClNO_2S^-$ [M – H]$^-$ 338.0043; found 338.0045. UHPLC: 2.92 min, 95% (System 1); 3.50 min, 95% (System 2).

FTase Assay: Assays were performed using 96-well plates, prepared with Biomek NKMC and Biomek 3000 from Beckman Coulter and read using a Wallac Victor fluorimeter from Perkin–Elmer. For

each well 20 μL of farnesyl pyrophosphate (10 μM) was added to 180 μL of a solution containing 2 μL of varying concentrations of potential inhibitors (dissolved in DMSO) and 178 μL of a solution composed of 0.2 mL of partially purified recombinant yeast FTase (2.2 mg/mL) and 14.0 mL of Dansyl-GCVLS peptide [2.5 μM in the following buffer: 5.6 mM DTT, 5.6 mM $MgCl_2$, 11.7 μM $ZnCl_2$ and 0.09% (w/v) CHAPS, 52 mM Tris/HCl, pH 7.5]. Fluorescence was recorded for 15 min (0.7 s/well, 20 repeats) at 30 °C with an excitation filter at 340 nm and an emission filter at 486 nm. Each measurement was performed twice as duplicate or triplicate.

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