Synthesis J. M. Rodrigues, M.-J. R. P. Queiroz Paper

Efficient One-Pot Synthesis of Alkyl 3-[4-(Aryl or Heteroaryl)-1*H*-1,2,3-triazol-1-yl]thieno[3,2-*b*]pyridine-2-carboxylates by 'Click' Cu(I)-Catalyzed Azide–Alkyne Cycloaddition

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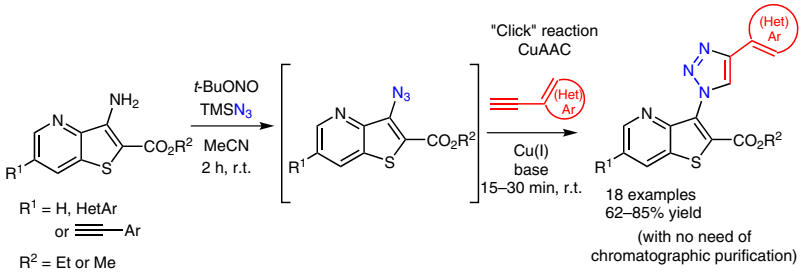

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Abstract An efficient one-pot synthesis of several new alkyl 3-[4-(aryl or heteroaryl)-1*H*-1,2,3-triazol-1-yl]thieno[3,2-*b*]pyridine-2-carboxylates has been performed by in situ azidation of alkyl 3-aminothieno[3,2-*b*]pyridine-2-carboxylates followed by Cu(I)-catalyzed azide-alkyne cycloaddition (CuAAC). Both reactions were carried out at room temperature, the first using *tert*-butyl nitrite and $TMSN_3$ in MeCN for 2 hours and the latter using several (hetero)arylalkynes, CuI, and Et_3N in MeCN for very short reaction times (15–30 min). The active Cu(I) species was used directly, instead of the commonly employed Cu(II) species ($CuSO_4$) with a reducing agent (sodium ascorbate) to generate Cu(I) in situ, which did not work in our case. This one-pot process showed wide scope and the products, which may have biological activity, were obtained in good to high yields with no need for chromatographic purification, thus fulfilling the criteria of 'click' chemistry. To our knowledge it is the first time that this methodology, using these conditions, has been applied to a heterocyclic moiety.

Key words thieno[3,2-*b*]pyridines, azides, CuAAC, click chemistry, 1,2,3-triazoles

Several functionalized thieno[3,2-*b*]pyridines have recently shown interesting biological activities. Diheteroarylamines[1] and N^3-arylmalonamides,[2] as well as substituted thieno[3,2-*b*]pyridine ureas[3] were shown to be inhibitors of the vascular endothelial growth factor receptor (VEGFR-2) involved in angiogenesis. Other thieno[3,2-*b*]pyridine derivatives were described as inhibitors of the nonreceptor Src tyrosine kinases[4] that are over-expressed and/or activated in several types of cancer and also play a key role in tumor progression and metastases.

For some years now our research group has prepared several functionalized thieno[3,2-*b*]pyridines by Pd and/or Cu-catalyzed C–C couplings (Sonogashira[5] and Suzuki–Miyaura[6]), C–N (Buchwald–Hartwig),[7] or C–O (Ullmann)[8] couplings either on the pyridine or on the thiophene[7b] ring. Some of the coupling products obtained showed promising activities as antitumorals[5–8] and antioxidants.[9]

The copper(I)-catalyzed azide-alkyne cycloaddition (CuAAC) to give 1,4-disubstituted 1,2,3-triazoles under mild conditions in high yields, described for the first time by Fokin, Sharpless, and co-workers[10a] and Meldal and co-workers[10b] in 2002, fulfill the criteria of 'click' chemistry, which were earlier defined by Sharpless and co-workers in 2001. These criteria include that the reaction must be modular, using simple reaction conditions and readily available starting materials and reagents, wide in scope, giving only one product in very high yields using non-chromatographic methods for purification.[11]

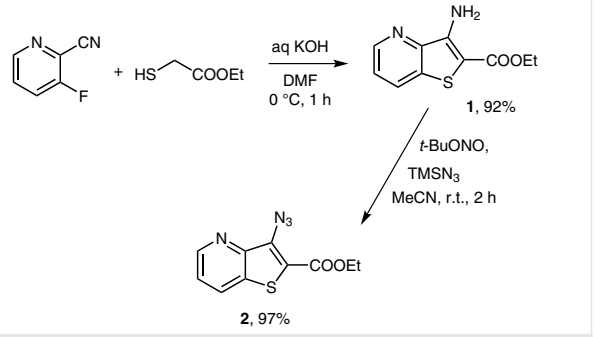
Recently, the mechanism of CuAAC has been studied more deeply and instead of mononuclear copper intermediates that had earlier been postulated to be involved in the catalytic cycle,[10a] dinuclear copper intermediates were fished out and characterized by ESI(+)-MS/MS and a new catalytic cycle was proposed.[12] These experiments corroborated the studies performed by Fokin in 2013 using calorimetry and metal isotope crossover methods that have allowed the deduction of the involvement of unstable and non-isolable dinuclear copper intermediates.[13]

Many heterocycles with incorporated triazole cores have been shown to possess a wide range of biological activity.[14]

Herein we present the formation of 1,4-di[(hetero)aryl]-1,2,3-triazole derivatives in a one-pot procedure from alkyl 3-aminothieno[3,2-*b*]pyridine-2-carboxylates via the corresponding azides, and several (hetero)arylalkynes using CuAAC. The compounds obtained may possess interesting biological activity.

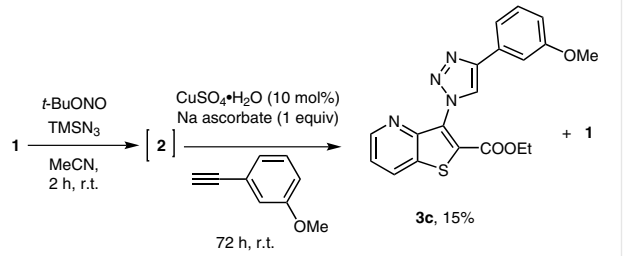
The ethyl 3-aminothieno[3,2-*b*]pyridine-2-carboxylate (**1**) was prepared by reaction of 3-fluoropicolinonitrile with ethyl thioglycolate in 92% yield following a procedure devel-

oped earlier by us with methyl thioglycolate.[15] Compound **1** was then treated with *tert*-butyl nitrite (*t*-BuONO) and azidotrimethylsilane ($TMSN_3$) in MeCN at room temperature for 2 hours, as reported by Moses et al. in 2007 for anilines,[16] to give the corresponding azide **2** in almost quantitative yield (Scheme 1).



Scheme 1 Synthesis of amine **1** and azide **2**

In order to obtain 1,4-disubstituted 1,2,3-triazoles by CuAAC in a one-pot procedure from amine **1**, after the complete formation of azide **2** (observed by TLC), the commonly used system to generate Cu(I) active species *in situ*, $CuSO_4{\cdot}5H_2O$ (10 mol%) and sodium ascorbate (0.2 equiv + 0.8 equiv after 48 h) as the reducing agent, was added[10a] followed by the addition of 1-ethynyl-3-methoxybenzene. After 3 days at room temperature, and with no formation of product in the first 48 hours, these conditions gave rise only to the reduction of azide **2** to amine **1** and formation of the corresponding triazole **3c** in 15% yield after chromatographic purification (Scheme 2). Lesser quantities of the reducing agent were used, and using only 0.5 equivalents for 20 hours after the formation of azide **2**, amine **1** was observed together with a small amount of triazole **3c**.



Scheme 2 One-pot synthesis of **3c** from amine **1** and reduction of azide intermediate **2** to amine **1**

As the yield for compound **3c** was very low, other conditions were tried. Thus CuI was used directly with Et_3N since it was reported that organic bases could help the formation of the active Cu(I) acetylide and promote the 'click' reaction.[10a] The use of CuI and Et_3N in MeCN was previously described by Liang et al. in 2009 for the reaction of aliphatic and aromatic azides with acetylene.[17] The 1,4-di[(hetero)aryl]-1,2,3-triazoles **3a**–**o** were obtained in good to high yields (62–85%) in a one-pot procedure from amine **1**, generating *in situ* the intermediate azide **2** which reacts with (hetero)arylalkynes (Table 1). The CuAAC occurred in very short reaction times, without side products and with no need for chromatographic purification, thus fulfilling the criteria of 'click' chemistry.[11]

The reaction is wide in application regarding to different (hetero)arylalkynes, but the derivatives of phenylacetylene and *ortho*-substituted arylalkynes were obtained in the lowest yields, 62–71% (Table 1, entries 1, 2, and 5). Arylalkynes with electron-donating groups in the *meta* position and with a bromine in the *para* position gave the corresponding products in 73–80% yields (Table 1, entries 3, 8, 9, and 12). The reaction is successful with alkynes bearing electron-deficient or electron-rich heteroaromatic rings (Table 1, entries 13–15).

In order to increase the scope of the reaction, 1,4-disubstituted 1,2,3-triazoles **4a**,**b** and **5** were prepared in good to high yields (71–88%) using the same one-pot reaction from the 6-substituted corresponding 3-amino precursors, previously prepared in our research group,[5,6] and 1-ethynyl-3-methoxybenzene (Figure 1).

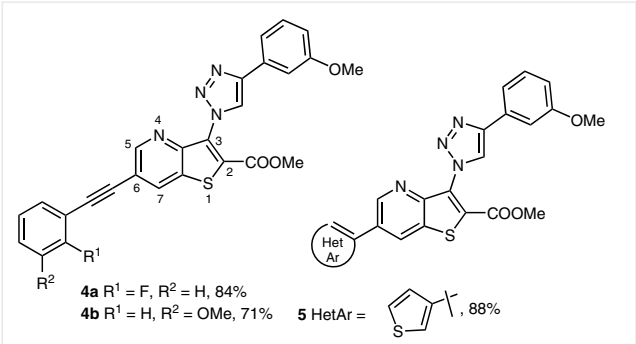
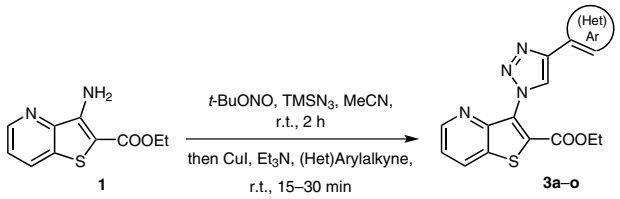


Figure 1 Compounds **4a**,**b** and **5** prepared by one-pot azidation and CuAAC from the corresponding 3-amino precursors and 1-ethynyl-3-methoxybenzene

In this work we were able to prepare several 1,4-di[(hetero)aryl]-1,2,3-triazoles in good to high yields with no need for chromatographic purification, in a one-pot procedure from alkyl 3-aminothieno[3,2-*b*]pyridine-2-carboxylates *via* the corresponding azides and (hetero)arylalkynes. The efficient conditions for the CuAAC were found using directly the active Cu(I) species and Et_3N in MeCN at room temperature in very short reaction times, thus constituting a 'click' reaction. The wide scope of the reaction was shown not only regarding different (hetero)arylalkynes but also Sonogashira and Suzuki–Miyaura coupling products obtained earlier by us at the 6-position of the methyl 3-aminothieno[3,2-*b*]pyridine-2-carboxylate. To our knowledge, it is the first time that this one-pot reaction, under these mild conditions, was applied to a heterocyclic moiety.

Table 1 One-Pot Synthesis of 1,4-Di[(hetero)aryl]triazoles **3a–o** from Amine **1** and (Hetero)arylalkynes[a]



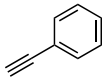
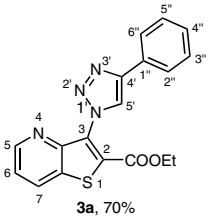
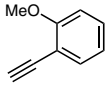
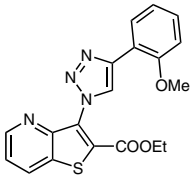
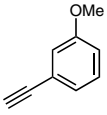
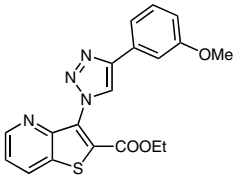
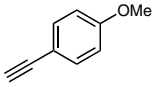
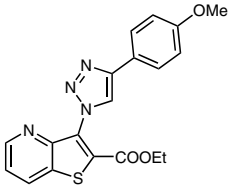
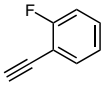
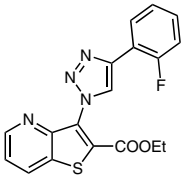
Entry	(Hetero)arylalkynes	Product
1		 **3a**, 70%
2		 **3b**, 71%
3		 **3c**, 80%
4		 **3d**, 83%
5		 **3e**, 62%

Table 1 (continued)

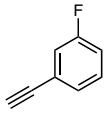
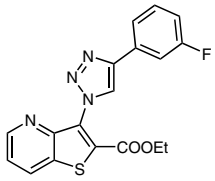
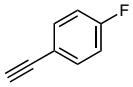
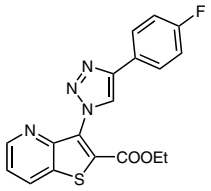
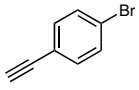
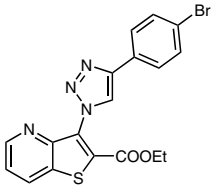
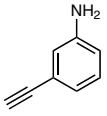
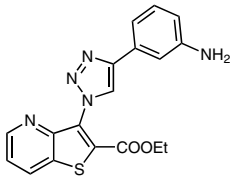
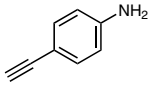
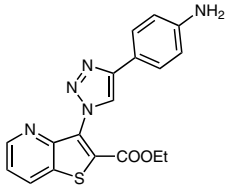
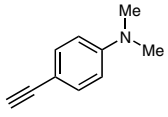
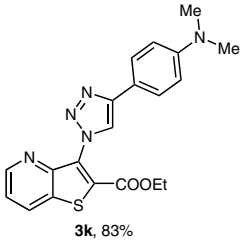
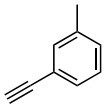
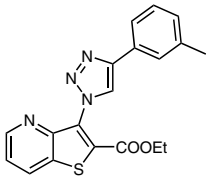
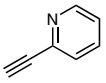
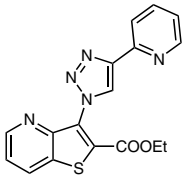
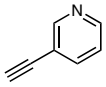
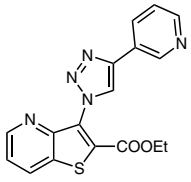
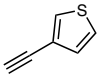
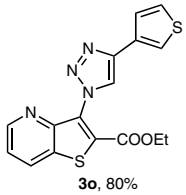
Entry	(Hetero)arylalkynes	Product
6		 **3f**, 81%
7		 **3g**, 82%
8		 **3h**, 76%
9		 **3i**, 73%
10		 **3j**, 82%
11		 **3k**, 83%

Table 1 (continued)

Entry	(Hetero)arylalkynes	Product
12		 **3l**, 75%
13		 **3m**, 79%
14		 **3n**, 85%
15		 **3o**, 80%

[a] 1. *t*-BuONO (1.5 equiv), $TMSN_3$ (1.2 equiv), MeCN, r.t., 2 h; 2. [(het)aryl]alkyne (1 equiv), CuI (20 mol%), Et_3N (40 mol%), r.t., 15–30 min.

Melting points were determined in a Stuart SMP3 and are uncorrected. ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance III at 400 and 100.6 MHz, respectively. Heteronuclear correlations ^1H-^{13}C, HSQC, and HMBC were performed to attribute some signals. HRMS (EI or ESI) on the M^+ or on the $[M + H]^+$ data were recorded by the mass spectrometry services of the University of Vigo (CACTI), Spain or of the University of Orleans (ICOA), France.

Ethyl 3-Aminothieno[3,2-*b*]pyridine-2-carboxylate (1)

To a round-bottomed flask containing DMF (5 mL), 3-fluoropicolinonitrile (300 mg, 250 mmol), ethyl thioglycolate (1.5 equiv), and 30% aq KOH (3 equiv) were added at 0 °C. The mixture was stirred for 1 h, then it was poured into ice and the resultant precipitate was filtered and dried at 50 °C overnight to give the product as a yellow solid; yield: 505 mg (92%); mp 137.0–139.0 °C.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.41 (t, *J* = 7.2 Hz, 3 H, CH_3), 4.39 (q, *J* = 7.2 Hz, 2 H, CH_2), 6.28 (br s, 2 H, NH_2), 7.39 (dd, *J* = 8.0, 4.6 Hz, 1 H, 6-H), 8.08 (dd, *J* = 8.0, 1.6 Hz, 1 H, 7-H), 8.63 (dd, *J* = 4.6, 1.6 Hz, 1 H, 5-H).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 14.5 (CH_3), 60.7 (CH_2), 100.4 (C), 122.3 (6-CH), 131.6 (7-CH), 134.5 (C), 146.0 (5-CH), 146.3 (C), 147.2 (C), 164.4 (C=O).

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{10}H_{11}N_2O_2S$: 233.0536; found: 233.0536.

Ethyl 3-Azidothieno[3,2-*b*]pyridine-2-carboxylate (2)

To a round-bottomed flask containing MeCN (5 mL), **1** (100 mg, 4.50 mmol), *t*-BuONO (1.5 equiv), and $TMSN_3$ (1.2 equiv) were added and the mixture was stirred at r.t. for 2 h. Water (15 mL) and EtOAc (15 mL) were then added and the phases were separated. The aqueous phase was extracted with EtOAc (3 × 15 mL), the combined organic phases were dried ($MgSO_4$), and the solvent was removed to give the product as a white solid; yield: 108 mg (97%); mp 112.0–114.5 °C.

^1H NMR (400 MHz, DMSO-d_6): δ = 1.31 (t, *J* = 7.2 Hz, 3 H, CH_3), 4.32 (q, *J* = 7.2 Hz, 2 H, CH_2), 7.60 (dd, *J* = 8.4, 4.4 Hz, 1 H, 6-H), 8.53 (dd, *J* = 8.4, 1.2 Hz, 1 H, 7-H), 8.76 (dd, *J* = 4.4, 1.2 Hz, 1 H, 5-H).

^{13}C NMR (100.6 MHz, DMSO-d_6): δ = 14.1 (CH_3), 61.5 (CH_2), 118.6 (C), 122.7 (6-CH), 132.4 (7-CH), 132.8 (C), 134.1 (C), 147.9 (5-CH), 148.3 (C), 160.5 (C=O).

HRMS (EI): *m*/*z* $[M^+]$ calcd for $C_{10}H_8N_4O_2S$: 248.0368; found: 248.0360.

One-Pot Synthesis of Thieno[3,2-*b*]pyridine Containing 1,4-Disubstituted 1,2,3-Triazoles 3a–o, 4a,b, and 5; General Procedure

To a round-bottomed flask containing MeCN (5 mL), **1** (100 mg, 4.50 mmol), *t*-BuONO (1.5 equiv), and $TMSN_3$ (1.2 equiv) were added and the mixture was stirred at r.t. for 2 h (TLC monitoring). Then, CuI (20 mol%), Et_3N (40 mol%), and (hetero)arylalkyne (1 equiv) were added and the mixture were stirred at r.t. for 15–30 min (TLC monitoring). EtOAc (10 mL) and H_2O (10 mL) were added and the phases were separated. The aqueous phase was extracted with EtOAc and then the organic phase was washed with H_2O (2 × 10 mL) and brine (10 mL). The organic phase was dried and filtered, and the removal of the solvent gave solids that were washed with Et_2O.

Ethyl 3-(4-Phenyl-1*H*-1,2,3-triazol-1-yl)thieno[3,2-*b*]pyridine-2-carboxylate (3a)

Beige solid; yield: 110 mg (70%); mp 128.5–130.0 °C.

^1H NMR (400 MHz, DMSO-d_6): δ = 1.10 (t, *J* = 7.2 Hz, 3 H, CH_3), 4.23 (q, *J* = 7.2 Hz, 2 H, CH_2), 7.37–7.41 (m, 1 H, 4″-H), 7.49–7.52 (m, 2 H, 3″-H, 5″-H), 7.71 (dd, *J* = 8.4, 4.4 Hz, 1 H, 6-H), 7.94–7.96 (m, 2 H, 2″-H, 6″-H), 8.76 (dd, *J* = 8.4, 1.6 Hz, 1 H, 7-H), 8.83 (dd, *J* = 4.4, 1.6 Hz, 1 H, 5-H), 9.05 (s, 1 H, 5′-H).

^{13}C NMR (100.6 MHz, DMSO-d_6): δ = 13.6 (CH_3), 62.2 (CH_2), 122.9 (6-CH), 124.3 (5′-CH), 125.3 (2″-CH, 6″-CH), 128.1 (4″-CH), 129.1 (3″-CH, 5″-CH), 130.3 (C), 131.9 (C), 132.1 (C), 132.6 (7-CH), 132.7 (C), 145.9 (C), 148.4 (C), 150.0 (5-CH), 159.9 (C=O).

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{18}H_{15}N_4O_2S$: 351.0910; found: 351.0912.

Ethyl 3-[4-(2-Methoxyphenyl)-1*H*-1,2,3-triazol-1-yl]thieno[3,2-*b*]pyridine-2-carboxylate (3b)

Beige solid; yield: 120 mg, (71%); mp 148.0–150.0 °C.

^1H NMR (400 MHz, DMSO-d_6): δ = 1.09 (t, *J* = 7.2 Hz, 3 H, CH_3), 3.90 (s, 3 H, OCH_3), 4.22 (q, *J* = 7.2 Hz, 2 H, CH_2), 7.09–7.17 (m, 2 H, 3″-H, 5″-H), 7.36–7.40 (m, 1 H, 4″-H), 7.69 (dd, *J* = 8.4, 4.4 Hz, 1 H, 6-H), 8.27 (dd, *J* = 7.6, 1.6 Hz, 1 H, 6″-H), 8.74 (dd, *J* = 8.4, 1.6 Hz, 1 H, 7-H), 8.82 (br s, 2 H, 5-H, 5′-H).

^{13}C NMR (100.6 MHz, DMSO-d_6): δ = 13.5 (CH_3), 55.4 (OCH_3), 62.1 (CH_2), 111.5 (3″-CH), 118.6 (C), 120.7 (5″-CH), 122.8 (6-CH), 126.6 (2 CH, 6″-CH, 5′-CH), 129.1 (4″-CH), 132.1 (C), 132.13 (C), 132.5 (7-CH), 132.7 (C), 141.3 (C), 148.6 (C), 149.9 (5-CH), 155.4 (*C*OCH$_3$), 159.9 (C=O).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{17}N_4O_3S$: 381.1016; found: 381.1015.

Ethyl 3-[4-(3-Methoxyphenyl)-1*H*-1,2,3-triazol-1-yl]thieno[3,2-*b*]pyridine-2-carboxylate (3c)

Beige solid; yield: 138 mg (80%); mp 131.0–132.6 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.10 (t, *J* = 7.2 Hz, 3 H, CH_3), 3.83 (s, 3 H, OCH_3), 4.23 (q, *J* = 7.2 Hz, 2 H, CH_2), 6.94–6.97 (m, 1 H, 4″-H), 7.41 (apparent t, *J* = 8.4 Hz, 1 H, 5″-H), 7.52–7.54 (m, 2 H, 2″-H, 6″-H), 7.70 (dd, *J* = 8.4, 4.4 Hz, 1 H, 6-H), 8.76 (dd, *J* = 8.4, 1.2 Hz, 1 H, 7-H), 8.83 (br s, 1 H, 5-H), 9.06 (s, 1 H, 5′-H).

^{13}C NMR (100.6 MHz, DMSO-d_6): δ = 13.6 (CH_3), 55.1 (OCH_3), 62.2 (CH_2), 110.5 (CH), 113.8 (4″-CH), 117.6 (CH), 122.9 (6-CH), 124.5 (5′-CH), 130.2 (5″-CH), 131.6 (C), 131.8 (C), 132.1 (C), 132.6 (7-CH), 132.8 (C), 145.8 (C), 148.3 (C), 150.0 (5-CH), 159.8 (*C*OCH$_3$), 159.9 (C=O).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{17}N_4O_3S$: 381.1016; found: 381.1019.

Ethyl 3-[4-(4-Methoxyphenyl)-1*H*-1,2,3-triazol-1-yl]thieno[3,2-*b*]pyridine-2-carboxylate (3d)

Beige solid; yield: 143 mg (83%); mp 162–164.4 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.10 (t, *J* = 7.2 Hz, 3 H, CH_3), 3.81 (s, 3 H, OCH_3), 4.23 (q, *J* = 7.2 Hz, 2 H, CH_2), 7.06 (d, *J* = 8.8 Hz, 2 H, 3″-H, 5″-H), 7.69 (dd, *J* = 8.4, 4.4 Hz, 1 H, 6-H), 7.87 (d, *J* = 8.8 Hz, 2 H, 2″-H, 6″-H), 8.75 (dd, *J* = 8.4, 2 Hz, 1 H, 7-H), 8.83 (d, *J* = 4.4 Hz, 1 H, 5-H), 8.91 (s, 1 H, 5′-H).

^{13}C NMR (100.6 MHz, DMSO-d_6): δ = 13.6 (CH_3), 55.1 (OCH_3), 62.2 (CH_2), 114.4 (2 CH, 3″-CH, 5″-CH), 122.8 (2 C, 6-CH, C), 123.2 (5′-CH), 126.6 (2 CH, 2″-CH, 6″-CH), 132.0 (C), 132.5 (7-CH), 132.7 (C), 145.9 (C), 148.4 (C), 149.9 (5-CH), 159.2 (*C*OCH$_3$), 159.9 (C=O).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{17}N_4O_3S$: 381.1016; found: 381.1019.

Ethyl 3-[4-(2-Fluorophenyl)-1*H*-1,2,3-triazol-1-yl]thieno[3,2-*b*]pyridine-2-carboxylate (3e)

Brown solid; yield: 107 mg (62%); mp 114.0–114.8 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.09 (t, *J* = 7.2 Hz, 3 H, CH_3), 4.23 (q, *J* = 7.2 Hz, 2 H, CH_2), 7.37–7.50 (m, 3 H, 3 ArH), 7.70 (dd, *J* = 8.4, 4.4 Hz, 1 H, 6-H), 8.24 (apparent dt, *J* = 8.0, 2.0 Hz, 1 H, ArH), 8.75 (dd, *J* = 8.4, 1.6 Hz, 1 H, 7-H), 8.82 (dd, *J* = 4.4, 1.6 Hz, 1 H, 5-H), 8.90 (d, *J* = 3.6 Hz, 1 H, 5′-H).

^{13}C NMR (100.6 MHz, DMSO-d_6): δ = 13.6 (CH_3), 62.2 (CH_2), 116.1 (d, *J* = 21 Hz, 3″-CH), 118.0 (d, *J* = 13 Hz, 1″-C), 122.9 (6-CH), 125.1 (d, *J* = 3 Hz, ArCH), 126.7 (d, *J* = 11.3 Hz, 5′-CH), 127.5 (d, *J* = 3.2 Hz, ArCH), 130.0 (d, *J* = 8.5 Hz, ArCH), 131.7 (C), 132.4 (C), 132.6 (7-CH), 132.7 (C), 139.3 (C), 148.6 (C), 150.0 (5-CH), 158.5 (d, *J* = 247.5 Hz, CF), 159.9 (C=O).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{14}FN_4O_2S$: 369.0816; found: 369.0818.

Ethyl 3-[4-(3-Fluorophenyl)-1*H*-1,2,3-triazol-1-yl]thieno[3,2-*b*]pyridine-2-carboxylate (3f)

Beige solid; yield: 134 mg (81%); mp 120.7–122.4 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.10 (t, *J* = 7.2 Hz, 3 H, CH_3), 4.24 (q, *J* = 7.2 Hz, 2 H, CH_2), 7.22 (apparent dt, *J* = 8.4, 2.4 Hz, 1 H, ArH), 7.52–7.58 (m, 1 H, 5″-H), 7.70 (dd, *J* = 8.4, 4.4 Hz, 1 H, 6-H), 7.75–7.82 (m, 2 H, 2 ArH), 8.76 (dd, *J* = 8.4, 1.2 Hz, 1 H, 7-H), 8.83 (dd, *J* = 4.4, 1.2 Hz, 1 H, 5-H), 9.13 (s, 1 H, 5′-H).

^{13}C NMR (100.6 MHz, DMSO-d_6): δ = 13.6 (CH_3), 62.3 (CH_2), 111.8 (d, *J* = 23 Hz, CH), 114.9 (d, *J* = 23 Hz, CH), 121.3 (d, *J* = 3 Hz, CH), 122.9 (6-CH), 125.0 (5′-CH), 131.2 (d, *J* = 9 Hz, 5″-CH), 131.7 (C), 132.2 (C), 132.6 (d, *J* = 8.4 Hz, 1″-C), 132.62 (7-CH), 132.8 (C), 144.9 (d, *J* = 3 Hz, 4′-C), 148.3 (C), 150.0 (5-CH), 159.9 (C=O), 162.6 (d, *J* = 243.5 Hz, CF).

HRMS (ESI,): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{14}FN_4O_2S$: 369.0816; found: 369.0813.

Ethyl 3-[4-(4-Fluorophenyl)-1*H*-1,2,3-triazol-1-yl]thieno[3,2-*b*]pyridine-2-carboxylate (3g)

Beige solid; yield: 134 mg (82%); mp 175.0–176.4 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.10 (t, *J* = 7.2 Hz, 3 H, CH_3), 4.24 (q, *J* = 7.2 Hz, 2 H, CH_2), 7.33–7.37 (m, 2 H, 3″-H, 5″-H), 7.70 (dd, *J* = 8.4, 4.4 Hz, 1 H, 6-H), 7.97–8.01 (m, 2 H, 2″-H, 6″-H), 8.76 (dd, *J* = 8.4, 1.6 Hz, 1 H, 7-H), 8.83 (dd, *J* = 4.4, 1.6 Hz, 1 H, 5-H), 9.04 (s, 1 H, 5′-H).

^{13}C NMR (100.6 MHz, DMSO-d_6): δ = 13.6 (CH_3), 62.2 (CH_2), 116.0 (d, *J* = 22 Hz, 3″-CH, 5″-CH), 122.9 (6-CH), 124.2 (5′-CH), 126.8 (d, *J* = 3 Hz, 1″-C), 127.3 (d, *J* = 8 Hz, 2″-CH, 6″-CH), 131.8 (C), 132.2 (C), 132.6 (7-CH), 132.8 (C), 145.1 (C), 148.3 (C), 150.0 (5-CH), 159.9 (C=O), 161.9 (d, *J* = 245 Hz, CF).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{14}FN_4O_2S$: 369.0816; found: 369.0823.

Ethyl 3-[4-(4-Bromophenyl)-1*H*-1,2,3-triazol-1-yl]thieno[3,2-*b*]pyridine-2-carboxylate (3h)

Beige solid; yield: 147 mg (76%); mp 137–138.5 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.10 (t, *J* = 7.2 Hz, 3 H, CH_3), 4,.24 (q, *J* = 7.2 Hz, 2 H, CH_2), 7.69–7.72 (m, 3 H, 2 ArH, 6-H), 7.91 (d, *J* = 8.8 Hz, 2 H, 2 ArH), 8.76 (dd, *J* = 8.4, 1.2 Hz, 1 H, 7-H), 8.83 (dd, *J* = 4.4, 1.2 Hz, 1 H, 5-H), 9.10 (s, 1 H, 5′-H).

^{13}C NMR (100.6 MHz, DMSO-d_6): δ = 13.6 (CH_3), 62.3 (CH_2), 121.2 (C), 122.9 (6-CH), 124.6 (5′-CH), 127.2 (2 ArCH), 129.5 (C), 131.7 (C), 132.1 (2 ArCH), 132.2 (C), 132.6 (7-CH), 132.8 (C), 144.9 (C), 148.3 (C), 150.0 (5-CH), 159.9 (C=O).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{14}{}^{79}BrN_4O_2S$: 429.0015; found: 429.0013; *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{14}{}^{81}BrN_4O_2S$: 431.0000; found: 431.0001.

Ethyl 3-[4-(3-Aminophenyl)-1*H*-1,2,3-triazol-1-yl]thieno[3,2-*b*]pyridine-2-carboxylate (3i)

Yellow solid; yield: 119 mg (73%); mp 172.8–174.3 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.10 (t, *J* = 7.2 Hz, 3 H, CH_3), 4.23 (q, *J* = 7.2 Hz, 2 H, CH_2), 5.21 (br s, 2 H, NH_2), 6.57 (br d, 1 H, 4″-H), 7.02 (br s, 1 H, 6″-H), 7.12 (apparent t, *J* = 7.6 Hz, 1 H, 5″-H), 7.21 (br s, 1 H, 2″-H), 7.69 (dd, *J* = 8.4, 4.4 Hz, 1 H, 6-H), 8.75 (dd, *J* = 8.4, 1.2 Hz, 1 H, 7-H), 8.82 (dd, *J* = 4.4, 1.2 Hz, 1 H, 5-H), 8.86 (s, 1 H, 5′-H).

^{13}C NMR (100.6 MHz, DMSO-d_6): δ = 13.6 (CH_3), 62.2 (CH_2), 110.6 (2″-CH), 113.1 (6″-CH), 113.8 (4″-CH), 122.8 (6-H), 123.8 (5′-CH), 129.4 (5″-CH), 130.7 (C), 131.9 (C), 132.0 (C), 132.5 (7-CH), 132.7 (C), 146.6 (C), 148.4 (C), 149.1 (C), 149.9 (5-CH), 160.0 (C=O).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{16}N_5O_2S$: 366.1019; found: 366.1020.

Ethyl 3-[4-(4-Aminophenyl)-1*H*-1,2,3-triazol-1-yl]thieno[3,2-*b*]pyridine-2-carboxylate (3j)

Beige solid; yield: 135 mg (82%); mp 129.5–131.5 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.11 (t, *J* = 7.2 Hz, 3 H, CH_3), 4.24 (q, *J* = 7.2 Hz, 2 H, CH_2), 5.28 (br s, 2 H, NH_2), 6.66 (d, *J* = 8.4 Hz, 2 H, 3″-H, 5″-H), 7.60 (d, *J* = 8.4 Hz, 2 H, 2″-H, 6″-H), 7.68 (dd, *J* = 8.4, 4.4 Hz, 1 H, 6-H), 8.70 (s, 1 H, 5′-H), 8.73 (dd, *J* = 8.4, 1.2 Hz, 1 H, 7-H), 8.82 (dd, *J* = 4.4, 1.2 Hz, 1 H, 5-H).

^{13}C NMR (100.6 MHz, DMSO-d_6): δ = 13.6 (CH_3), 62.2 (CH_2), 114.0 (3″-CH, 5″-CH), 117.8 (C), 121.9 (5′-CH), 122.8 (6-CH), 126.3 (2″-CH, 6″-CH), 131.7 (C), 132.2 (C), 132.5 (7-CH), 132.7 (C), 146.9 (C), 148.4 (C), 148.8 (C), 149.9 (5-CH), 160.0 (C=O).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{16}N_5O_2S$: 366.1019; found: 366.1013.

Ethyl 3-[4-(4-Dimethylaminophenyl)-1*H*-1,2,3-triazol-1-yl]thieno[3,2-*b*]pyridine-2-carboxylate (3k)

Beige solid; yield: 146 mg (83%); mp 167–168.5 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.10 (t, *J* = 7.2 Hz, 3 H, CH_3), 2.95 [s, 6 H, $N(CH_3)_2$], 4.23 (q, *J* = 7.2 Hz, 2 H, CH_2), 6.82 (d, *J* = 9.2 Hz, 2 H, 3″-H, 5″-H), 7.69 (dd, *J* = 8.4, 4.4 Hz, 1 H, 6-H), 7.75 (d, *J* = 9.2 Hz, 2 H, 2″-H, 6″-H), 8.75 (dd, *J* = 8.4, 1.6 Hz, 1 H, 7-H), 8.79 (s, 1 H, 5′-H), 8.82 (dd, *J* = 4.4, 1.2 Hz, 1 H, 5-H).

^{13}C NMR (100.6 MHz, DMSO-d_6): δ = 13.6 (CH_3), 39.7 [$N(CH_3)_2$], 62.2 (CH_2), 112.4 (3″-CH, 5″-CH), 118.0 (C), 122.3 (5′-CH), 122.8 (6-CH), 126.2 (2″-CH, 6″-CH), 131.9 (C), 132.2 (C), 132.6 (7-CH), 132.7 (C), 146.6 (C), 148.4 (C), 149.9 (5-CH), 150.2 [*C*N(CH_3)$_2$], 160.0 (C=O).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{20}N_5O_2S$: 394.1332; found: 394.1335.

Ethyl 3-[4-(*m*-Tolyl)-1*H*-1,2,3-triazol-1-yl]thieno[3,2-*b*]pyridine-2-carboxylate (3l)

Beige solid; yield: 127 mg (75%); mp 117–118.7 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.10 (t, *J* = 7.2 Hz, 3 H, CH_3), 2.38 (s, 3 H, CH_3), 4.23 (q, *J* = 7.2 Hz, 2 H, CH_2), 7.19 (br d, 1 H, 4″-H), 7.38 (br apparent t, 1 H, 5″-H), 7.69 (dd, *J* = 8.4, 4.4 Hz, 1 H, 6-H), 7.74 (br d, 1 H, 6″-H), 7.79 (br s, 1 H, 2″-H), 8.74 (br d, 1 H, 7-H), 8.83 (br s, 1 H, 5-H), 9.01 (s, 1 H, 5′-H).

^{13}C NMR (100.6 MHz, DMSO-d_6): δ = 13.6 (CH_3), 21.1 (CH_3), 62.2 (CH_2), 122.5 (6″-CH), 122.8 (6-CH), 124.1 (5′-CH), 125.8 (2″-CH), 128.8 (4″-CH), 128.9 (5″-CH), 130.2 (C), 131.9 (C), 132.0 (C), 132.5 (7-CH), 132.7 (C), 138.2 (C), 146.0 (C), 148.3 (C), 149.9 (5-CH), 159.9 (C=O).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{17}N_4O_2S$: 365.1067; found: 365.1061.

Ethyl 3-[4-(Pyridin-2-yl)-1*H*-1,2,3-triazol-1-yl]thieno[3,2-*b*]pyridine-2-carboxylate (3m)

Beige solid; yield: 129 mg (79%); mp 139.9–140.7 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.11 (t, *J* = 7.2 Hz, 3 H, CH_3), 4.24 (q, *J* = 7.2 Hz, 2 H, CH_2), 7.40 (br s, 1 H, HetArH), 7.69 (dd, *J* = 8.4, 4.4 Hz, 1 H, 6-H), 7.97 (br t, 1 H, HetArH), 8.15 (br d, 1 H, HetArH), 8.64 (br s, 1 H, HetArH), 8.75 (br d, *J* = 8.4, 1.6 Hz, 1 H, 7-H), 8.82 (br d, *J* = 4.4, 1.6 Hz, 1 H, 5-H), 9.05 (s, 1 H, 5′-H).

^{13}C NMR (100.6 MHz, DMSO-d_6): δ = 13.6 (CH_3), 62.2 (CH_2), 119.7 (HetArCH), 122.9 (6-CH), 123.2 (HetArCH), 126.2 (5′-CH), 131.7 (C), 131.9 (C), 132.1 (C), 132.5 (7-CH), 132.7 (C), 137.3 (HetArCH), 146.7 (C), 148.5 (C), 149.7 (HetArCH), 149.9 (5-CH), 159.9 (C=O).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{14}N_5O_2S$: 352.0863; found: 352.0866.

Ethyl 3-[4-(Pyridin-3-yl)-1*H*-1,2,3-triazol-1-yl]thieno[3,2-*b*]pyridine-2-carboxylate (3n)

Beige solid; yield: 134 mg (85%); mp 136.2–137.5 °C.

^{1}H NMR (400 MHz, DMSO-d_6, *T* = 100 °C): δ = 1.14 (t, *J* = 7.2 Hz, 3 H, CH_3), 4.27 (q, *J* = 7.2 Hz, 2 H, CH_2), 7.55 (br s, 1 H, HetArH), 7.67 (dd, *J* = 8.4, 4.4 Hz, 1 H, 6-H), 8.31 (br d, 1 H, HetArH), 8.70 (dd, *J* = 8.4, 1.6 Hz and br s, 2 H, 7-H, HetArH), 8.83 (dd, *J* = 4.4, 1.6 Hz, 1 H, 5-H), 9.03 (s, 1 H, 5′-H), 9.23 (br s, 1 H, HetArH).

^{13}C NMR (100.6 MHz, DMSO-d_6, *T* = 100 °C): δ = 13.0 (CH_3), 61.7 (CH_2), 122.2 (6-CH), 124.22 (5′-CH, HetArCH), 131.1 (C), 131.7 (7-CH), 131.8 (C), 132.0 (HetArCH), 132.3 (C), 142.8 (C), 146.2 (C), 147.9 (C), 148.5 (HetArCH), 149.3 (5-CH), 159.4 (C=O).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{14}N_5O_2S$: 352.0863; found: 352.0862.

Ethyl 3-[4-(Thiophen-3-yl)-1*H*-1,2,3-triazol-1-yl]thieno[3,2-*b*]pyridine-2-carboxylate (3o)

Beige solid; yield: 128 mg (80%); mp 114.6–116.5 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.13 (t, *J* = 7.2 Hz, 3 H, CH_3), 4.24 (q, *J* = 7.2 Hz, 2 H, CH_2), 7.60 (dd, *J* = 4.8, 1.2 Hz, 1 H, 5″-H), 7.68–7.71 (m, 2 H, 4″-H, 6-H), 7.97 (dd, *J* = 3.2, 1.2 Hz, 1 H, 2″-H), 8.75 (dd, *J* = 8.4, 1.6 Hz, 1 H, 7-H), 8.83 (dd, *J* = 4.4, 1.6 Hz, 1 H, 5-H), 8.90 (s, 1 H, 5′-H).

^{13}C NMR (100.6 MHz, DMSO-d_6): δ = 13.6 (CH_3), 62.2 (CH_2), 121.3 (2″-CH), 122.9 (HetArCH), 123.9 (5′-CH), 125.8 (5″-CH), 127.4 (HetArCH), 131.5 (C), 131.8 (C), 132.0 (C), 132.6 (7-CH), 132.7 (C), 142.5 (C), 148.3 (C), 150.0 (5-CH), 159.9 (C=O).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{13}N_4O_2S_2$: 357.0474; found: 357.0479.

Methyl 6-[(2-Fluorophenyl)ethynyl]-3-[4-(3-methoxyphenyl)-1*H*-1,2,3-triazol-1-yl]thieno[3,2-*b*]pyridine-2-carboxylate (4a)

From ethyl 3-amino-6-[(2-fluorophenyl)ethynyl]thieno[3,2-*b*]pyridine-2-carboxylate (66.0 mg, 2.00 mmol) following the general procedure gave **4a** as a beige solid; yield: 80.0 mg (84%); mp 185–187 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.82 (s, 3 H, OCH_3), 3.84 (s, 3 H, OCH_3), 6.95–6.98 (m, 1 H, ArH), 7.30–7.34 (m, 1 H, ArH), 7.37–7.44 (m, 2 H, 2 ArH), 7.52–7.58 (m, 3 H, 3 ArH), 7.70–7.74 (m, 1 H, ArH), 8.97 (d, *J* = 1.6 Hz, 1 H, HetArH), 9.03 (d, *J* = 1.6 Hz, 1 H, HetArH), 9.07 (s, 1 H, 5′-H).

^{13}C NMR (100.6 MHz, DMSO-d_6): δ = 53.4 (OCH_3), 55.2 (OCH_3), 87.3 (C), 90.8 (C), 109.6 (d, *J* = 15.0 Hz, 1‴-C), 110.5 (CH), 114.0 (CH), 115.9 (d, *J* = 21.0 Hz, 3‴-CH), 117.6 (C), 117.7 CH), 124.4 (5′-CH), 125.0 (d, *J* = 4.0 Hz, 5‴-CH), 130.2 (CH), 131.5 (C), 131.9 (C), 132.0 (d, *J* = 8 Hz, 4‴-CH), 132.2 (C), 132.8 (C), 133.7 (CH), 135.1 (CH), 145.9 (C), 147.4 (C), 151.6 (CH), 159.8 (C), 160.0 (C), 161.9 (d, *J* = 250 Hz, CF).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{26}H_{18}FN_4O_3S$: 485.1078; found: 485.1077.

Methyl 3[4-(3-Methoxyphenyl)-1*H*-1,2,3-triazol-1-yl]-6-[(3-methoxyphenyl)ethynyl]thieno[3,2-*b*]pyridine-2-carboxylate (4b)

From ethyl 3-amino-6-[(3-methoxyphenyl)ethynyl]thieno[3,2-*b*]pyridine-2-carboxylate (58.0 mg, 1.70 mmol) following the general procedure gave **4b** as a beige solid; yield: 60.0 mg, (71%); mp 146.1–148.2 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.80 (s, 3 H, OCH_3), 3.81 (s, 3 H, OCH_3), 3.84 (s, 3 H, OCH_3), 6.95–6.97 (br d, 1 H, ArH), 7.04–7.07 (br d, 1 H, ArH), 7.19–7.22 (m, 2 H, 2 ArH), 7.36–7.44 (m, 2 H, 2 ArH), 7.52–7.54 (m, 2 H, 2 ArH), 8.96 (br s, 1 H, HetArH), 8.98 (br s, 1 H, HetArH), 9.07 (s, 1 H, 5″-H).

^{13}C NMR (100.6 MHz, DMSO-d_6): δ = 53.4 (OCH_3), 55.2 (OCH_3), 55.3 (OCH_3), 85.8 (C), 94.1 (C), 110.5 (CH), 114.0 (CH), 116.2 (CH), 116.3 (CH), 117.7 (CH), 118.1 (C), 122.3 (C), 124.0 (CH), 124.4 (5″-CH), 130.1 (CH), 130.2 (CH), 131.5 (C), 131.9 (C), 132.3 (C), 132.5 (C), 134.8 (CH), 145.9 (C), 147.2 (C), 151.7 (CH), 159.2 (C), 159.8 (C), 160.0 (C).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{27}H_{21}N_4O_4S$: 497.1278; found: 497.1278.

Methyl 3-[4-(3-Methoxyphenyl)-1*H*-1,2,3-triazol-1-yl]-6-(3-thienyl)thieno[3,2-*b*]pyridine-2-carboxylate (5)

From methyl 3-amino-6-(3-thienyl)thieno[3,2-*b*]pyridine-2-carboxylate (52.0 mg, 1.78 mmol) following the general procedure gave **5** as a yellow solid; yield: 70.0 mg (88%); mp 171.6–172.1 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.81 (s, 3 H, OCH_3), 3.84 (s, 3 H, OCH_3), 6.95–6.98 (m, 1 H, 4‴-H), 7.42 (apparent t, *J* = 8.4 Hz, 1 H, 5‴-H), 7.53–7.55 (m, 2 H, 2‴-H, 6‴-H), 7.75–7.79 (m, 2 H, 2 ArH), 8.23–8.24 (m, 1 H, ArH), 9.06 (br d, *J* = 2 Hz, 1 H, 7-H), 9.08 (s, 1 H, 5″-H), 9.26 (d, *J* = 2 Hz, 1 H, 5-H).

^{13}C NMR (100.6 MHz, DMSO-d_6): δ = 55.2 (OCH_3), 55.2 (OCH_3), 110.5 (ArCH), 113.9 (4‴-CH), 117.6 (ArCH), 124.0 (ArCH), 124.4 (5″-CH), 126.2 (ArCH), 128.2 (ArCH), 128.3 (7-CH), 130.0 (C), 130.2 (5‴-CH), 130.6 (C), 131.6 (C), 133.2 (C), 137.3 (C), 145.9 (C), 146.8 (C), 148.6 (5-CH), 159.8 (C), 160.2 (C).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{17}N_4O_3S_2$: 449.0742; found: 449.0737.

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Supporting Information

^{1}H and ^{13}C NMR spectra of all the compounds are presented at http://dx.doi.org/10.1055/s-0035-1562093.

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