DBU Promoted Facile Synthesis of New Thieno[2,3-*b*]pyridine/quinoline Derivatives and Their Antimicrobial Evaluation

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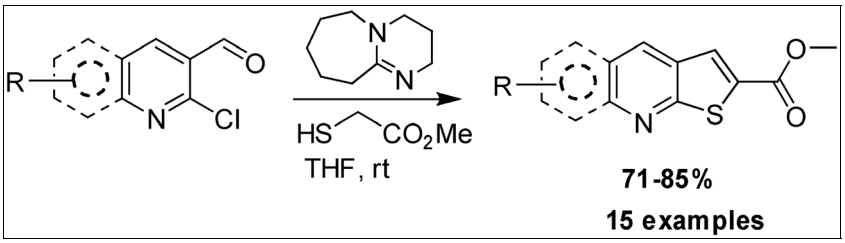

Several new thieno[2,3-*b*]pyridine and thieno[2,3-*b*]quinoline derivatives are synthesized in an efficient manner catalyzed by DBU as a base. Simple workup procedure, good yields, and mild reaction conditions are the salient features of this method. All the synthesized compounds are screened for antimicrobial activity against several organisms.

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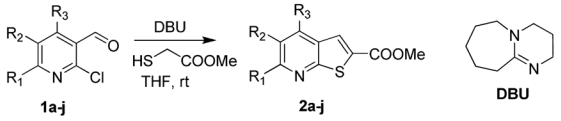
INTRODUCTION

In organic chemistry, derivatives of pyridine and its fused analogs are the important class of heterocyclic compounds, and they attract considerable interest because of their great practical usefulness, primarily, due to their various biological activities [1]. In addition, many pyridines are reported to be useful as herbicides, bactericides, fungicides, insecticides, and pharmaceuticals [2]. In particular, several thienopyridine/thienoquinoline derivatives are known to possess antibacterial [3], antifungal [4], antiviral [5], anti-inflammatory [6], antihypertensive [7], antiparasitic [8], and gonadotropin releasing hormone-antagonizing activities [9]. Due to their isosterism with indolopyridines or isoquinolines, thienopyridines have attracted much attention because of their potential biological activity as antipsychotics [10], antibacterians [11], LH-receptor agonists [12], and Src kinase inhibitors [13]. In addition, certain thienoderivatives hold promise for the treatment of osteoporosis and serve as tachykinin antagonists, 5-lipoxygenase inhibitors with a broad spectrum of action, acetylcholinesterase inhibitors [14]. Thieno[2,3-*b*]pyridines have been claimed as anticancer agents with inhibitory action against the VEGF-2 receptor tyrosine kinase [15]. The antitumor activity of 6-aryl-3-amino-thieno[2,3-*b*]pyridine derivatives is also reported by Zeng and coworkers [16]. Recently, thieno[2,3-*b*]pyridines reported as potassium channel inhibitors [17]. Thieno[2,3-*b*]pyridine derivatives have been previously prepared in a multistep procedure from either a thiophene or a pyridine ring and further ring closure leading to the other heterocyclic fused system. Unfortunately, many of these methods suffer from limitations such as long reaction times, low to moderate yields, and co-occurrence of several side products. Very few reports are available for the direct synthesis of thieno derivatives from corresponding 2-chloro 3-carbaldehydes. Suárez *et al*. [18] reported the preparation of 4,7-dihydrothieno[2,3-*b*]pyridines from the *o*-chloroformyl substituted 1,4-dihydropyridines using sodium ethoxide and dry ethanol under inert atmosphere. Bhat *et al*. [19] reported the one-step synthesis of 2-methoxycarbonylthieno[2,3-*b*]quinolines from 2-chloroquinoline-3-carbaldehydes using potassium carbonate in tetrahydrofuran with good yields.

The efficiency of DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) as a non-nucleophilic, sterically hindered, tertiary amine base in organic chemistry has been widely demonstrated [20]. In particular, it has been widely used for carrying out dehydrohalogenation reactions. In many instances, DBU itself reacted with different α,β-unsaturated systems, resulting in the formation of ε-caprolactam derivative. The reagent is commercially available and has been extensively used for carrying out a wide range of reactions [21]. Motivated by these findings, and in continuation of our ongoing efforts endowed with the discovery of nitrogenated heterocycles [22], herein we report the facile synthesis and antimicrobial activity of various thienopyridines and thienoquinolines using DBU as mild base. In the present study, we have used various 2-chloro nicotinaldehydes (**1a–e, i, j**) as active substrates which were developed in our laboratory [23]. The condensation reaction proceeded smoothly under mild conditions, upon treatment of methyl thioglycolate and DBU in THF with aldehyde.

Scheme 1. Synthesis of thieno[2,3-*b*]pyridines.



2a, R_1 = H, R_2 = Me, R_3 = H
2b, R_1 = CO_2Me, R_2 = H, R_3 = H
2c, R_1 = H, R_2 = phenyl, R_3 = H
2d, R_1 = H, R_2 = *p*-tolyl, R_3 = H
2e, R_1 = Me, R_2 = phenyl, R_3 = H
2f, R_1 = Me, R_2 = CO_2Me, R_3 = phenyl
2g, R_1 = Me, R_2 = CO_2Me, R_3 = *m*-nitrophenyl
2h, R_1 = Me, R_2 = CO_2Me, R_3 = *p*-fluorophenyl
2i, R_1 = CO_2Me, R_2 = Me, R_3 = H
2j, R_1 = H, R_2 = propyl, R_3 = H

RESULTS AND DISCUSSION

During the optimization studies, the reaction was carried out in different bases such as NaH, K_2CO_3, NaOMe in MeOH, NEt_3, and also with hindered amines DABCO and DBU. It was observed that only with DBU, the desired thieno derivatives are obtained at ambient temperature in very good yields. The reaction uses other bases giving different side products along with a little amount of required product. In order to evaluate the generality of this method, several analogues of substituted thienopyridines were synthesized with different 2-chloro nicotinaldehydes (Scheme 1). The reactions proceeded very efficiently with good yields in less reaction time (0.5–2 h). To demonstrate the general utility of the method, we applied these conditions to a variety of 2-chloro quinoline-3-carbaldehydes (**1k–o**) prepared according to earlier reported procedure [24]. In all the cases, the reactions occurred smoothly, affording corresponding thienoquinolines in good yields (Scheme 2).

All the synthesized new compounds (**2a–o**) are screened for their antimicrobial activity by broth dilution method recommended by National Committee for Clinical Laboratory (NCCL) standards [25]. The antibacterial activity is tested on six different organisms (gram-positive and gram-negative), *Bacillus subtilis, Staphylococcus aureus, Staphylococcus epidermidis, Escherichia coli, Pseudomonas aeruginosa*, and *Klebsiella pneumoniae* with respect to the references penicillin and streptomycin. Interestingly, out of six organisms, almost all the thienopyridines displayed good antibacterial activity against the most compromising resistant strain, *P. aeruginosa*. Compound **2j** exhibited considerable antibacterial activity against *S. eperidimis*. Compound **2a** showed moderate activity against several strains. Some of the thienoquinolines exhibited moderate activity against *K. pneumoniae* organism. Minimum inhibitory concentration (MIC) in μg/mL values for all the compounds are listed in Table 1. It is observed that most of the thienopyridine derivatives exhibited good antibacterial activity compared to the thienoquinoline derivatives.

All the compounds are also screened for their antifungal activity against two representative microorganisms yeast and filamentous fungi, viz., *Candida albicans, Candida rugosa, Saccharomyces cerevisiae*, *Aspergillus flavus* with respect to standard Amphotericin B (50) by paper disc diffusion method. Zone of inhibition (mm) were determined for the compounds, and the screening results indicate that only compounds **2a**, **2b** and **2j** of all the compounds exhibited moderate antifungal activity (Table 2). Compounds **2a** and **2b** exhibited antifungal activity especially on *S. cerevisiae* strain, whereas compound **2j** has antifungal effect against *C. albicans* and *C. rugosa* strains (Table 2).

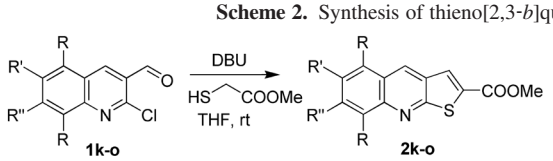
In summary, we have synthesized various new thieno derivatives in an efficient manner using DBU as a mild base. Simple workup procedure, good yields, and mild conditions are the key features of this method. All the synthesized compounds were screened for antimicrobial activity against several organisms, and most of the compounds exhibited very good antibacterial activity against *P. aeruginosa* strain compared to penicillin.

EXPERIMENTAL

General. All reactions involving air-sensitive reagents were performed under nitrogen atmosphere. Solvents were freshly dried and purified by conventional methods prior to use. The progress of all the reactions was monitored by TLC, using TLC aluminum sheets precoated with silica gel 60 F_{254} to a thickness of 0.25 mm (Merck). Flash column chromatography was done using silica gel (Merck, 60–120 mesh). Melting points were determined on a MEL-TEMP II melting point apparatus and were uncorrected. IR spectra were recorded on a Perkin-Elmer FT-IR spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Gemini 200 MHz, Bruker Avance 300 MHz spectrometer, TMS was used as an internal standard, and $CDCl_3$/DMSO-d_6 are used as solvents. Mass spectra were recorded on VG Micromass 7070 H (EI), QSTAR XL High resolution mass spectrometer (HRMS), Thermofinnigan ESI ion trap Mass Spectrometer, and a GC-MS system on an Agilent 6890 series. 2-chloro nicotinaldehydes (**1f–h**) are effectively prepared by aromatization of 1,4-dihydropyridines [26] using $NaNO_2$, $NaHSO_4$, and wet silica in DCM.

General procedure for the preparation of thieno[2,3-*b*] derivatives. To a solution of 2-chloro 5-methyl nicotinaldehyde **1a** (0.15 g, 1 mmol) in THF (3 mL), DBU (0.29 mL, 2 mmol) and methyl thioglycolate (0.11 mL, 1.2 mmol) were added

Scheme 2. Synthesis of thieno[2,3-*b*]quinolines.



2k, R = H, R' = isopropyl, R" = H
2l, R = OMe, R' = H, R" = H
2m, R = H, R' = H, R" = chloro
2n, R = H, R' = H, R" = fluoro
2o, R = H, R' = bromo, R" = H

Table 1

Antibacterial activity of thieno compounds.

	MIC (μg/mL)					
Entry	*B. subtilis*	*S. aurues*	*S. epidermidis*	*E. coli*	*P. aeruginosa*	*K. pneumoniae*
2a	75	75	150	75	18.75	150
2b	150	150	150	150	9.375	150
2c	150	150	150	150	9.375	150
2d	150	150	150	150	37.5	150
2e	150	150	150	150	18.75	150
2f	150	150	150	150	9.375	150
2g	150	150	150	150	37.5	150
2h	150	150	150	150	9.375	150
2i	150	150	150	150	18.75	150
2j	150	150	37.5	150	18.75	150
2k	150	150	150	150	150	75
2l	150	150	150	150	150	75
2m	150	75	150	150	150	150
2n	150	150	150	150	150	75
2o	150	150	150	150	150	75
Penicillin	1.56	1.56	3.12	12.5	12.5	6.25
Streptomycin	6.25	6.25	3.12	6.25	1.56	3.12

sequentially and stirred at room temperature. The progress of the reaction was monitored by TLC. After completion (1 h), the reaction mixture was concentrated under reduced pressure to obtain the crude product. The crude product was purified by silica gel column chromatography (60–120 mesh, eluent: EtOAc/Hexane, 1:24) to afford 5-methyl thieno[2,3-*b*]pyridine derivative as a wheatish solid (0.15 g, 75%). A similar procedure was adopted for the preparation of other thieno derivatives.

Methyl 5-methyl thieno[2,3-*b*]pyridine-2-carboxylate (2a). Yield: 75%; wheatish solid; mp 85–87°C; IR (potassium bromide): 2951, 1719, 1511, 1248, 1058, 731 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.48 (s, 3H), 3.95 (s, 3H), 7.88–7.90 (m, 2H), 8.49 (d, 1H, J = 2.2 Hz); ^{13}C NMR ($CDCl_3$): δ 18.4, 52.6, 127.6, 129.9, 132.2, 132.9, 133.4, 150.5, 160.2, 162.8; ESI–MS: *m/z* 208 $[M+ H]^+$; HRMS (ESI): *m/z* $[M + H]^+$ Calcd. for $C_{10}H_{10}NO_2S$: 208.0432. Found: 208.0429.

Dimethyl thieno[2,3-*b*]pyridine-2,6-dicarboxylate (2b). Yield: 82%; Creamy solid; mp 180–182°C; IR (potassium bromide): 2873, 1729, 1453, 1376, 1248, 1175, 840, 720 cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.99 (s, 3H), 4.06 (s, 3H), 8.02 (s, 1H), 8.17 (d, 1H, J = 8.3 Hz), 8.26 (d, 1H, J = 8.3 Hz); ^{13}C NMR ($CDCl_3$): δ 52.8, 53.2, 121.1, 127.2, 133.7, 134.5, 137.1, 146.7, 162.3, 162.5, 165.2; ESI–MS: *m/z* 252 $[M + H]^+$; HRMS (ESI): *m/z* $[M + Na]^+$ Calcd. for $C_{11}H_9NO_4SNa$: 274.0149. Found: 274.0145.

Methyl 5-phenyl thieno[2,3-*b*]pyridine-2-carboxylate (2c). Yield: 80%; Pale yellow solid; mp 139–141°C; IR (potassium bromide): 2953, 1727, 1450, 1376, 1256, 1171, 840, 720 cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.98 (s, 3H), 7.41–7.46 (m, 1H), 7.48–7.54 (m, 2H), 7.60–7.64 (m, 2H), 8.04–8.06 (m, 1H), 8.31–8.34 (m, 1H), 8.9 (br s, 1H); ^{13}C NMR ($CDCl_3$): δ 52.7, 127.3, 128.1, 128.2, 129.1, 130.8, 132.2, 133.8, 134.0, 137.4, 148.6, 161.7, 162.7; ESI–MS: *m/z* 270 $[M+ H]^+$; HRMS (ESI): *m/z* $[M + H]^+$ Calcd. for $C_{15}H_{12}NO_2S$: 270.0588. Found: 270.0580.

Methyl 5-(4-methyl phenyl)thieno[2,3-*b*]pyridine-2-carboxylate (2d). Yield: 81%; Creamy solid; mp 147–149°C; IR (potassium bromide): 2874, 1726, 1452, 1376, 1254, 1175, 840, 720 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.43 (s, 3H), 3.96 (s, 3H), 7.27 (d, 2H, J = 8.3 Hz), 7.48 (d, 2H, J = 8.3 Hz), 7.99 (s, 1H), 8.22 (d, 1H, J = 2.2 Hz), 8.85 (d, 1H, J = 2.2 Hz); ^{13}C NMR ($CDCl_3$): δ 21.1, 52.7, 127.1, 128.0, 129.9, 130.7, 132.3, 133.8, 134.0, 134.3, 138.2, 148.3, 161.2, 162.7; ESI–MS: *m/z* 284 $[M + H]^+$; HRMS (ESI): *m/z* $[M + H]^+$ Calcd. for $C_{16}H_{14}NO_2S$: 284.0745. Found: 284.0737.

Methyl 6-methyl-5-phenylthieno[2,3-*b*]pyridine-2-carboxylate (2e). Yield: 78%; White solid; mp 104–106°C; IR (potassium bromide): 2933, 1726, 1454, 1376, 1255, 1176, 840, 720 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.46 (s, 3H), 3.97 (s, 3H), 7.39–7.48 (m, 3H), 7.54–7.58 (m, 2H), 7.92 (s, 1H), 7.98 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 20.5, 52.5, 127.3, 127.9, 128.2, 128.4, 128.8, 129.0, 131.2, 134.4,

Table 2

Antifungal activity of thieno compounds.

	C. albicans		*C. rugosa*		*S. cerevisiae*		*A. flavus*	
Entry	100 μg	150 μg	100 μg	150 μg	100 μg	150 μg	100 μg	150 μg
2a	–	–	–	–	9	14	–	–
2b	–	–	–	–	10	15	–	–
2j	7	10	7	10	–	–	–	–
Amphotericin B (50)	23.5		21		22		25	

140.0, 159.3, 160.7, 162.7; ESI–MS: *m/z* 284 $[M + H]^+$; HRMS (ESI): *m/z* $[M + H]^+$ Calcd. for $C_{16}H_{14}NO_2S$: 284.0745. Found: 284.0740.

Dimethyl 6-methyl-4-phenylthieno[2,3-*b*]pyridine-2,5-dicarboxylate (2f). Yield: 85%; Light brown solid; mp 132–134°C; IR (potassium bromide): 2953, 1727, 1450, 1376, 1256, 1171, 840, 720 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.71 (s, 3H), 3.56 (s, 3H), 3.91 (s, 3H), 7.35–7.40 (m, 2H), 7.46–7.50 (m, 3H), 7.74 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 23.3, 52.3, 52.6, 125.9, 127.9, 128.3, 128.6, 129.0, 129.2, 132.7, 135.6, 145.2, 155.7, 162.6, 163.0, 168.6; ESI–MS: *m/z* 342 $[M + H]^+$; HRMS (ESI): *m/z* $[M + H]^+$ Calcd. for $C_{18}H_{16}NO_4S$: 342.0800. Found: 342.0793.

Dimethyl 6-methyl-4-(3-nitrophenyl)thieno[2,3-*b*]pyridine-2,5-dicarboxylate (2g). Yield: 74%; Pale yellow solid; mp 147–149°C; IR (potassium bromide): 2951, 1728, 1531, 1438, 1351, 1252, 1166, 1127, 818, 738 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.74 (s, 3H), 3.65 (s, 3H), 3.93 (s, 3H), 7.63 (s, 1H), 7.71–7.74 (m, 2H), 8.28–8.30 (m, 1H), 8.34–8.40 (m, 1H); ^{13}C NMR ($CDCl_3$): δ 23.6, 52.4, 52.7, 123.5, 123.9, 125.9, 126.5, 128.6, 129.8, 134.0, 134.4, 137.5, 148.5, 155.9, 161.6, 162.1, 163.4, 167.8; ESI–MS: *m/z* 387 $[M + H]^+$; HRMS (ESI): *m/z* $[M + Na]^+$ Calcd. for $C_{18}H_{14}N_2O_6SNa$: 409.0470. Found: 409.0476.

Dimethyl 4-(4-fluorophenyl)-6-methylthieno[2,3-*b*]pyridine-2,5-dicarboxylate (2h). Yield: 82%; Brown solid; mp 122–124°C; IR (potassium bromide): 2956, 1727, 1500, 1435, 1298, 1272, 1162, 1115, 1065, 840, 746 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.72 (s, 3H), 3.62 (s, 3H), 3.93 (s, 3H), 7.2 (t, 2H, *J* = 9.0 Hz), 7.35–7.41 (m, 2H), 7.72 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 23.3, 52.4, 52.7, 115.7, 116.0, 127.5, 128.7, 129.2, 130.2, 130.3, 130.8, 131.6, 132.9, 144.0, 155.7, 161.3, 162.5, 163.0, 164.7, 168.5; ESI–MS: *m/z* 360 $[M + H]^+$; HRMS (ESI): *m/z* $[M + H]^+$ Calcd. for $C_{18}H_{15}NO_4FS$: 360.0705. Found: 360.0704.

Dimethyl 5-methylthieno[2,3-*b*]pyridine-2,6-dicarboxylate (2i). Yield: 80%; White solid; mp 127–129°C; IR (potassium bromide): 2958, 2924, 1722, 1436, 1283, 1261, 1205, 1130, 1040, 728 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.68 (s, 3H), 3.97 (s, 3H), 4.01 (s, 3H), 7.92 (s, 1H), 8.02 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 20.1, 52.8, 52.9, 126.8, 131.3, 134.1, 135.8, 136.7, 146.9, 159.6, 162.4, 166.0; ESI–MS: *m/z* 266 $[M + H]^+$; HRMS (ESI): *m/z* $[M + H]^+$ Calcd. for $C_{12}H_{12}NO_4S$: 266.0487. Found: 266.0482.

Methyl 5-propylthieno[2,3-*b*]pyridine-2-carboxylate (2j). Yield: 83%; White solid; mp 77–79°C; IR (potassium bromide): 2951, 2864, 1718, 1510, 1450, 1254, 1195, 1062, 882, 734 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.99 (t, 3H, *J* = 7.5 Hz), 1.72 (sextet, 2H, *J* = 7.5 Hz), 2.72 (t, 2H, *J* = 7.5 Hz), 3.95 (s, 3H), 7.88 (d, 1H, *J* = 2.2 Hz), 7.91 (s, 1H), 8.48 (d, 1H, *J* = 2.2 Hz); ^{13}C NMR ($CDCl_3$): δ 13.6, 24.5, 34.9, 52.6, 127.9, 132.2, 133.3, 134.6, 139.3, 150.6, 160.7, 163.0; ESI–MS: *m/z* 236 $[M + H]^+$; HRMS (ESI): *m/z* $[M + H]^+$ Calcd. for $C_{12}H_{14}NO_2S$: 236.0745. Found: 236.0750.

Methyl 6-isopropylthieno[2,3-*b*]quinoline-2-carboxylate (2k). Yield: 81%; Creamy solid; mp 119–120°C; IR (potassium bromide): 3413, 2923, 2853, 1714, 1533, 1433, 1255, 1052, 926, 752 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.38 (d, 6H, *J* = 6.8 Hz), 3.12 (septet, 1H, *J* = 6.8, 13.6 Hz), 3.98 (s, 3H), 7.65–7.71 (m, 2H), 8.03–8.09 (m, 2H), 8.54 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 23.7, 34.0, 52.7, 124.3, 125.8, 128.0, 128.2, 130.8, 130.9, 132.5, 134.0, 146.3, 147.3, 162.7, 162.8; ESI–MS: *m/z* 286 $[M + H]^+$; HRMS (ESI): *m/z* $[M + H]^+$ Calcd. for $C_{16}H_{16}NO_2S$: 286.0901. Found: 286.0905.

Methyl 5,8-dimethoxythieno[2,3-*b*]quinoline-2-carboxylate (2l). Yield: 82%; Yellowish brown solid; mp 185–187°C; IR (potassium bromide): 3413, 2924, 1717, 1621, 1476, 1303, 1262, 1167, 1058, 912, 790 cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.99 (s, 3H), 4.01 (s, 3H), 4.08 (s, 3H), 6.67 (d, 1H, *J* = 8.5 Hz), 6.94 (d, 1H, *J* = 8.5 Hz), 8.08 (s, 1H), 8.99 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 52.7, 55.7, 56.2, 101.9, 107.6, 119.7, 128.1, 128.4, 130.6, 134.4, 140.4, 148.5, 149.2, 162.8, 163.0; ESI–MS: *m/z* 304 $[M + H]^+$; HRMS (ESI): *m/z* $[M + H]^+$ Calcd. for $C_{15}H_{14}NO_4S$: 304.0643. Found: 304.0632.

Methyl 7-chlorothieno[2,3-*b*]quinoline-2-carboxylate (2m). Yield: 74%; Light yellow solid; mp 191–193°C; IR (potassium bromide): 3436, 2923, 2856, 1710, 1528, 1434, 1294, 1055, 912, 744 cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.92 (s, 3H), 7.42–7.44 (m, 1H), 7.75–7.77 (m, 1H), 7.99 (s, 1H), 8.02–8.03 (m, 1H), 8.32 (s, 1H); ^{13}C NMR ($CDCl_3$ + DMSO-d_6): δ 51.9, 122.8, 124.7, 126.0, 127.2, 127.3, 128.1, 129.3, 132.2, 138.9, 146.9, 147.1, 161.4; ESI–MS: *m/z* 278 $[M + H]^+$; HRMS (ESI): *m/z* $[M + H]^+$ Calcd. for $C_{13}H_9ClNO_2S$: 278.1322. Found: 278.1332.

Methyl 7-fluorothieno[2,3-*b*]quinoline-2-carboxylate (2n). Yield: 80%; Pale yellow solid; mp 189–190°C; IR (potassium bromide): 3418, 2923, 1729, 1629, 1537, 1253, 1145, 1058, 909, 746 cm^{-1}; ^1H NMR ($CDCl_3$ + DMSO-d_6): δ 3.99 (s, 3H), 7.38–7.45 (m, 1H), 7.70 (d, 1H, *J* = 9.5 Hz), 8.10–8.15 (m, 1H), 8.16 (s, 1H), 8.86 (s, 1H); ^{13}C NMR (DMSO-d_6): δ 53.0, 110.9, 111.1, 116.8, 117.1, 122.4, 122.5, 124.6, 124.7, 129.2, 130.9, 132.1, 132.2, 134.6, 164.8, 169.0; ESI–MS: *m/z* 262 $[M + H]^+$; HRMS (ESI): *m/z* $[M + H]^+$ Calcd. for $C_{13}H_9FNO_2S$: 262.0338. Found: 262.0329.

Methyl 6-bromothieno[2,3-*b*]quinoline-2-carboxylate (2o). Yield: 71%; pale yellow solid; mp >220°C; IR (potassium bromide): 3417, 2923, 1719, 1528, 1258, 1055, 915, 744 cm^{-1}; ^1H NMR ($CDCl_3$): δ 4.0 (s, 3H), 7.81–7.86 (dd, 1H, *J* = 9.1, 2.7 Hz), 8.02 (d, 1H, *J* = 9.1 Hz), 8.08 (s, 1H), 8.13 (d, 1H, *J* = 2.7 Hz), 8.55 (s, 1H); ^{13}C NMR (DMSO-d_6): δ 52.1, 118.9, 120.5, 123.1, 125.3, 127.7, 127.8, 132.8, 133.1, 138.9, 142.0, 156.5, 162.4; ESI–MS: *m/z* 322 $[M + H]^+$; HRMS (ESI): *m/z* $[M + H]^+$ Calcd. for $C_{13}H_9BrNO_2S$: 322.0348. Found: 322.0349.

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