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Synthesis of 4-phenylthieno[2,3-*c*]quinolines via Suzuki–Miyaura cross-couplings

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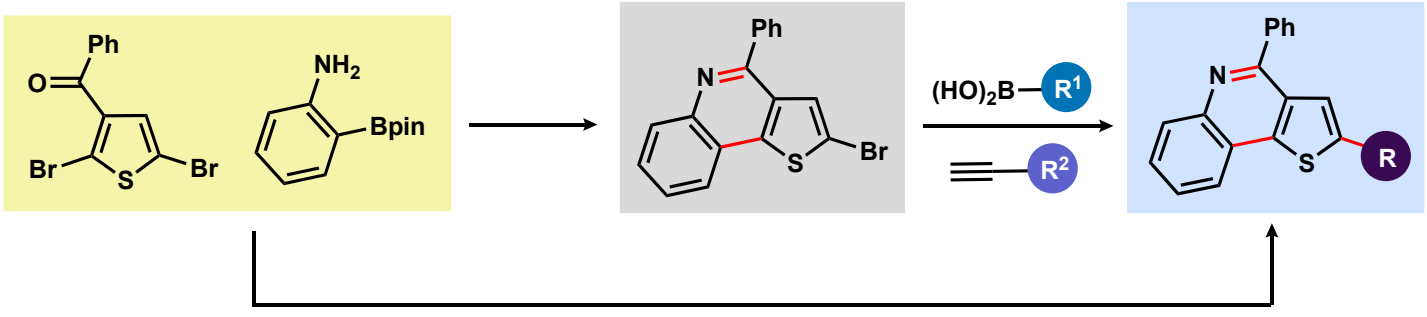
Abstract

A small library of previously unreported 4-phenylthieno[3,2-*c*]quinolines was prepared from a simple thiophene substrate via a modular synthetic strategy that exploited successive palladium-catalyzed cross-coupling reactions. These heterocycles were screened for activity against various bacterial, fungal, parasitic and cancer cell lines, which identified two original 4-(2-methoxyphenyl)-thieno[3,2-*c*]quinolines that display encouraging antibacterial activity.



Keywords: Thienoquinolines, Suzuki–Miyaura cross-coupling, heterocyclic chemistry; medicinal chemistry

Introduction

Thienoquinolines are a family of heterocycles that primarily feature two classes of structural isomers, namely, thieno[2,3-*b*]quinolines **1a** and thieno[3,2-*c*]quinolines **1b** (Figure 1).[1] These molecules have captured the attention of synthetic and medicinal chemists and they reportedly elicit an array of interesting biological activity that is consistent with their potential to serve as antimicrobial, antiviral, antiparasitic, and anti-inflammatory agents.[1-6] They also have potential application in materials science as iridium complexes of 4-phenylthieno[2,3-*b*]quinolines demonstrate intense red phosphorescence emission.[7] Two general strategies have been investigated to prepare thieno[3,2-*c*]quinolines. Specifically, a number of methods have accessed these heterocycles via quinoline substrates,[8-12] while other approaches have employed thiophene precursors.[13-19]

In this work, we deployed robust cross-coupling methodology[20-22] to establish a short, modular synthetic route enabling the efficient construction of a small library of functionalized 4-phenylthieno[3,2-*c*]quinolines from a simple thiophene starting material. These novel molecules were then screened for activity against a range of target organisms, including bacterial, fungal, parasitic and cancer cell lines.

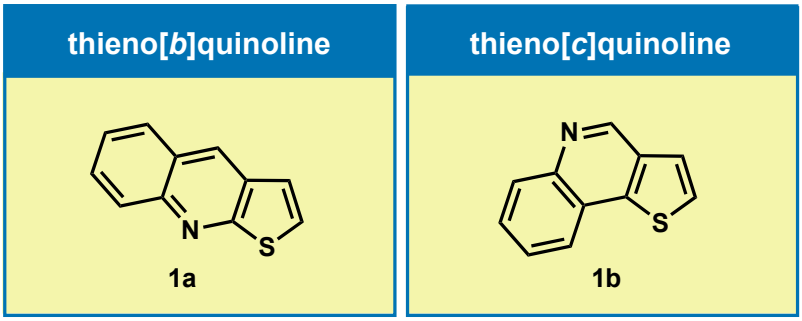


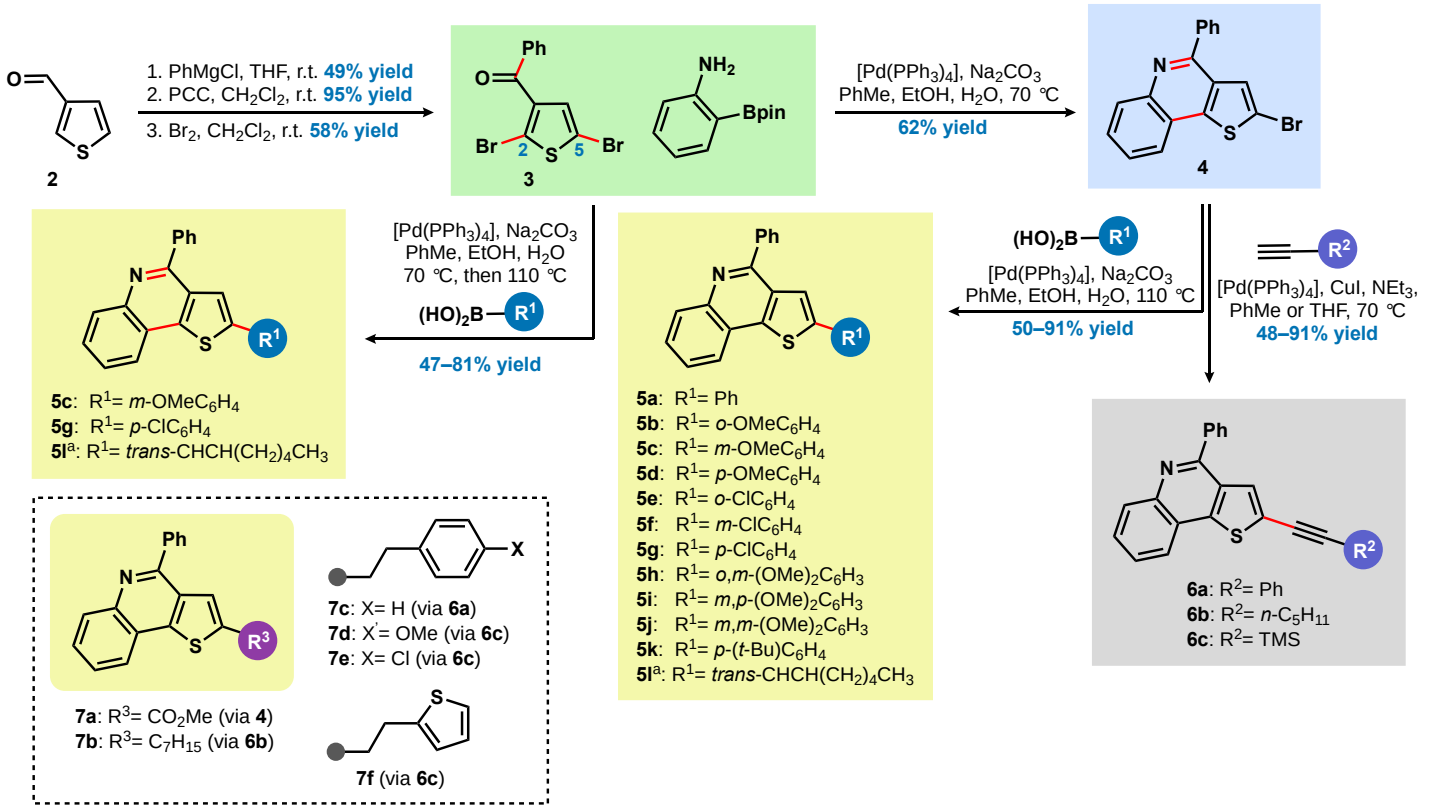
Figure 1. Parent structures of thieno[2,3-*b*]quinolines **1a** and thieno[3,2-*c*]quinolines **1b**.

Results and Discussion

Our synthetic approach to a range of novel thieno[3,2-*c*]quinolines **4**–**7** is outlined in Scheme 1 and commenced from commercially available thiophene-3-carbaldehyde (**2**). This substrate was subjected to a nucleophilic addition, PCC oxidation, and bromination sequence, which afforded known dibromo compound **3** in 3 steps.[23] The electron-withdrawing carbonyl group within thiophene **3** likely increases the electrophilicity of the C2-carbon relative to C5-carbon, which we exploited in performing a regioselective Suzuki–Miyaura coupling[24,25] with commercially available 2-aminophenylboronic acid, pinacol ester. This reaction furnished 4-phenylthieno[3,2-*c*]quinoline **4** in a single step. Time course experiments monitoring this transformation by ^{1}H NMR spectroscopy were consistent with an annulation process in which cross-coupling precedes Schiff base condensation. Control experiments also revealed that there was no reaction between dibromo compound **3** and 2-aminophenylboronic acid, pinacol ester in the absence of [Pd(PPh3)$_4$]. Indeed, monitoring the reaction by ^{1}H NMR spectroscopy indicated that imine formation did not occur under these conditions.

Our straightforward and concise route provided rapid and efficient access to the 4-phenylthienoquinoline core. We then exploited bromo heterocycle **4** to effect the divergent synthesis of novel functionalized thieno[3,2-*c*]quinolines via standard cross-coupling methodology. Specifically, we deployed Suzuki–Miyaura

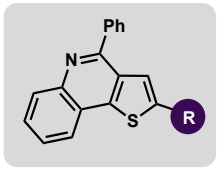
reactions to prepare 2-aryl-substituted derivatives **5a–k** in addition to alkenyl compound **5l** in moderate to high yields.[26] We also determined that products **5c**, **5g** and **5l** could be formed in 47%, 53% and 81% respective yields directly from dibromothiophene **3** via a two-stage, one-pot method. Sonogashira couplings were used to convert bromo compound **4** into alkynyl compounds **6a–c**. A palladium-catalyzed carbomethoxylation reaction, performed in the presence of CO and methanol, furnished ester **7a** from substrate **4**. Alkynes **6a** and **6b** were reduced to deliver alkyl-substituted thieno[3,2-*c*]quinolines **7b** and **7c**, respectively. The TMS-deprotection of alkyne **6c**, and subsequent Sonogashira couplings, followed by hydrogenations afforded ethylene-tethered analogues **7d–f**.



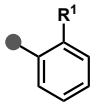
Scheme 1. Synthesis of thienoquinolines **4–7**. [a] Alkene **5l** was formed from *trans*-1-heptenylboronic acid, pinacol ester.

2,4-Diaryl-substituted thieno[3,2-*c*]quinolines **5a–k** were tested against a range of targets, including bacterial, fungal, parasitic and cancer cell lines (Table 1). Compounds **4**, **5l**, **6a**, **7a–f** were also assayed. No antifungal activity up to 100 μg/mL against *Candida albicans* and *Saccharomyces cerevisiae* and no antibacterial activity up to 100 μg/mL against *Staphylococcus aureus* was observed for any of the substrate. However, the *Bacillus subtilis* assay displayed antibacterial activity for thieno[3,2-*c*]quinolines **5a–c**, **5h** and **5j** with compounds possessing an *ortho*-methoxy group being the most active (*i.e.* **5b** and **5h**). For compounds **5a**, **5c** and **5j** these data are more consistent with bacteriostatic behavior. Heterocycles **5l** and **7c** exhibited low to moderate antigiardial activity against *Giardia duodenalis* and molecules **5b–d**, **5h**, **5l**, **7a** and **7c** only elicited low to moderate antitumor activity in a murine myeloma cell (NS-1) assay. Notably, all of the compounds screened displayed minimal effects on human neonatal fibroblast cells (NFF), which indicates that these thienoquinolines do not appear to be highly toxic to non-tumour cells. This suggests that the thieno[3,2-*c*]quinoline scaffold might represent a suitable scaffold for drug development.

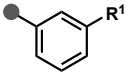
Table 1. In vitro activities of compounds **5a**–**l**, **6a**, and **7a**–**f** against *G. duodenalis*, *B. subtilis*, *S. aureus*, *C. albicans*, *S. cerevisiae*, and cytotoxicity against murine myeloma and human neonatal fibroblast cells (MIC, μg/mL)



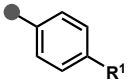
4: R = Br
5a: R = Ph
7a: R = CO_2Me
7b: R= C_7H_{15}



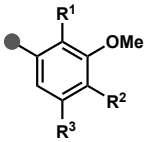
5b: R^1= OMe
5e: R^1= Cl



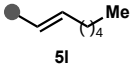
5c: R^1= OMe
5f: R^1= Cl



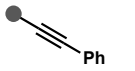
5d: R^1= OMe
5g: R^1= Cl
5k: R^1= *t*-Bu



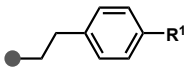
5h: R^2= R^3= H; R^1= OMe
5i: R^1= R^3= H; R^2= OMe
5j: R^1= R^2= H; R^3= OMe



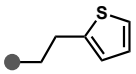
5l



6a



7c: R^1= H
7d: R^1= OMe
7e: R^1= Cl



7f

compound	*G. duodenalis*[a]	*B. subtilis*[a]		*S. aureus*[a]		*C. albicans*[a]		*S. cerevisiae*[a]		NS-1[b]	NFF[c]
	96 h	24 h	48 h	24 h	48h	24 h	48 h	24 h	48 h	96 h	96 h
4	>100	>100	>100	>100	>100	>200	>200	>200	>200	>100	>100
5a	>100	1.6	>100	>100	>100	>200	>200	>200	>200	>100	>100
5b	>100	0.8	1.6	>100	>100	>200	>200	>200	>200	12.5	>100
5c	>100	3.1	>100	>100	>100	>200	>200	>200	>200	25	>100
5d	100	>100	>100	>100	>100	>200	>200	>200	>200	50	>100
5e	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100
5f	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100
5g	>100	>100	>100	>100	>100	>200	>200	>200	>200	100	>100
5h	>100	0.8	0.8	>100	>100	>200	>200	>200	>200	12.5	>100
5i	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100
5j	>100	1.6	>100	>100	>100	>200	>200	>200	>200	>100	>100
5k	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100
5l	25	>100	>100	>100	>100	>200	>200	>200	>200	50	>100
6a	>100	>100	>100	>100	>100	>200	>200	>200	>200	>100	>100
7a	>100	>100	>100	>100	>100	>200	>200	>200	>200	50	100
7b	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100
7c	50	>100	>100	>100	>100	>200	>200	>200	>200	50	>100
7d	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100
7e	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100
7f	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100
reference[d]	6.3	0.4	0.4	0.8	0.8	1.6	1.6	1.6	1.6	0.04	0.3

[a] All compounds were tested across a concentration of range of 0.05–100 μg/mL.

[b] NS-1: murine myeloma cells.

[c] NFF: human neonatal fibroblast cells.

[d] reference compounds: metronidazole (*G. duodenalis*); tetracycline.HCl (*B. subtilis; S. aureus*); Blasticidin S.HCl (*C. albicans; S. cerevisiae*); staurosporine (NS-1; NFF).

Conclusions

In summary, we have developed a modular synthetic route that allows for the efficient preparation of a small library of previously unreported thienoquinolines. These heterocycles were evaluated for activity against bacterial, fungal, parasitic and cancer cell lines. Notably, we identified that novel thieno[3,2-*c*]quinolines **5b** and **5h** that contain an *ortho*-methoxyaryl group on C2 display encouraging antibacterial activity and all of the thieno[3,2-*c*]quinolines screened do not appear to be highly toxic to healthy non-tumour cells.

Experimental Section

General. Analytical-grade solvents were used, which were purified by standard laboratory procedures. Reagents were purchased from Sigma-Aldrich, AK Scientific, Combi-Blocks, and Oakwood and were used without purification. Infrared (IR) spectroscopy was performed on a Shimadzu FTIR 8400s spectrometer. Samples for subjected to IR analysis were prepared by the deposition of a thin film of the compound onto NaCl plates following evaporation of CH_2Cl_2 or $CHCl_3$. NMR experiments were performed either on a Bruker Avance III NMR spectrometer operating at 400 MHz (^{1}H) or 100 MHz (^{13}C) or on a Bruker Avance III NMR spectrometer operating at 600 MHz (^{1}H) or 150 MHz (^{13}C). The deuterated solvents used were either $CDCl_3$ or acetone-d_6 as specified. Chemical shifts were recorded in δ (ppm). Spectra were calibrated by assignment of the residual solvent peak to δ_H 7.26 and δ_C 77.16 for $CDCl_3$ and δ_H 2.05 and δ_C 29.84 for acetone-d_6. Coupling constants (*J*) were recorded in Hz. High resolution, accurate mass spectra were acquired using a Thermo LTQ XL Orbitrap tandem mass spectrometer. Samples in methanol were analyzed by direct infusion at a rate of 20 μL/min and ionized by Electrospray ionization (ESI) in the positive mode. TLC was performed using Merck silica gel 60-F_{254} plates. Developed chromatograms were visualized by UV absorbance (254 nm) or through application of heat to a plate stained with cerium molybdate {$Ce(NH_4)_2(NO_3)_6$, $(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$, H_2SO_4, H_2O}. Flash column chromatography was performed with flash grade silica gel (60 μm) and the indicated eluent in accordance with standard techniques.[27]

Synthesis of previously unreported compounds

2-Bromo-4-phenylthieno[3,2-*c*]quinoline (4). 2-Aminophenylboronic acid, pinacol ester (835 mg, 3.81 mmol), [Pd(PPh3)$_4$] (80.0 mg, 0.0350 mmol), and Na_2CO_3 (2.5 mL of a 2 M aqueous solution) were successively added to a magnetically-stirred solution of thiophene **3**[20] (1.20 g, 3.46 mmol) in PhMe (50 mL) and EtOH (20 mL) maintained under N_2. The ensuing mixture was heated at 70 °C. After 3 h, H_2O (40 mL) was added, the phases separated, and the aqueous layer extracted with EtOAc (3 × 20 mL). The combined organic extracts were then washed with NaCl (20 mL of a saturated aqueous solution), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The ensuing residue was subjected to flash column chromatography (50% CH_2Cl_2/hexanes elution; silica gel) to provide compound **4** as a colorless solid (735 mg, 62%): ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.28 (d, *J* 8.3, 1H), 7.99 (dd, *J* 8.2, 0.9, 1H), 7.89-7.87 (m, 2H), 7.75 (t, *J* 7.0, 1H), 7.67 (s, 1H), 7.64–7.53 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.5, 147.4, 143.9, 139.6, 132.2, 130.5, 129.3, 129.2 (2C), 129.1, 128.8 (2C), 127.8, 127.2, 122.9, 122.5, 114.7; IR (NaCl): 1474, 1441, 1325, 1074, 955, 752, 692 cm^{-1}; HRMS (ESI) *m/z*: $[M + Na]^+$ Calcd for $C_{17}H_{10}NBrNaS$ 361.9615; Found 361.9608.

General procedure A. Synthesis of compounds 5a–l from bromo compound 4. Boronic acid or boronic acid, pinacol ester (1.1 equiv), [Pd(PPh3)$_4$] (1 mol %), and Na_2CO_3 (2 M aqueous solution; 1 equiv) were successively added to a magnetically-stirred solution of bromo compound **4** (0.02 M; 1 equiv) in PhMe/EtOH (5:2 v/v) maintained under N_2. The ensuing mixture was heated at 110 °C. After 2 h, the reaction mixture was cooled to rt and H_2O (10 mL) added. The aqueous layer was extracted with EtOAc (3 × 10 mL) and the combined organic fractions were washed with NaCl (10 mL of a saturated aqueous solution), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The ensuing residue was subjected to flash column chromatography (10–20% EtOAc/hexanes elution; silica gel) to provide cross-coupled products **5a**–**k**.

General procedure B. Synthesis of compounds 5c, 5g and 5l from dibromo compound 3. 2-Amino-phenylboronic acid, pinacol ester (1.1 equiv), [Pd(PPh3)$_4$] (1 mol %), and Na_2CO_3 (as a 2 M aqueous solution; 1 equiv) were successively added to a magnetically-stirred solution of dibromo compound **3** (1 equiv) in PhMe/EtOH (5:2 v/v) maintained under N_2. The ensuing mixture was heated at 70 °C. After 3 h, a second boronic acid or boronic acid, pinacol ester (1.1 equiv) was added and the ensuing mixture was heated at 110 °C. After 2 h, the reaction mixture was cooled to rt and H_2O (10 mL) added. The aqueous layer was extracted with EtOAc (3 × 10 mL) and the combined organic fractions were washed with NaCl (10 mL of a saturated aqueous solution), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The ensuing residue was subjected to flash column chromatography (10–20% EtOAc/hexanes elution; silica gel) to provide cross-coupled products **5c**, **5g** or **5l**.

General procedure C. Synthesis of compounds 7d–f from TMS-alkyne 6c

Step 1. A solution of compound **6c** in MeOH was magnetically-stirred with K_2CO_3 (2 equiv) at rt. After 3 h, the mixture was concentrated under reduced pressure. The iodo coupling partner (1.2 equiv), Et_3N (10 mL), [Pd(PPh3)$_4$] (10 mol %), and CuI (5 mol %) were added to the ensuing residue. The resultant mixture was maintained under N_2 and heated to 80 °C. After 3 h, the reaction mixture was cooled to rt and concentrated under reduced pressure. The ensuing residue was subjected to flash column chromatography (silica gel) to provide the cross-coupled alkyne precursors of compounds **7d**–**f**. These respective alkynes were each immediately subjected to the following reduction step.

Step 2. Pd/C (10 mg of a 10% w/w mixture) was added to a magnetically-stirred solution of cross-coupled alkyne in EtOH (5 mL) and the ensuing mixture was placed under an atmosphere of H_2 (balloon, 1 atm) at rt. After 16 h, the reaction mixture was filtered through a pad of Celite®, eluted with CH_2Cl_2, and the ensuing solution was concentrated under reduced pressure to provide previously unreported compounds **7d**–**f**.

2,4-Diphenylthieno[3,2-*c*]quinoline (5a). Compound **5a** was prepared from bromo compound **4** (102 mg, 0.300 mmol) and phenylboronic acid (40.0 mg, 0.330 mmol) by general procedure A to provide compound **5a** as a colorless solid (90 mg, 63%): ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.30 (d, *J* 8.3, 1H), 9.10 (dd, *J* 8.1, 0.9, 1H), 7.99 (d, *J* 7.0, 2H), 7.82 (s, 1H), 7.73–7.70 (m, 3H), 7.64–7.56 (m, 4H), 7.45 (t, *J* 7.4, 2H), 7.38 (t, *J* 7.4, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 155.6, 145.7, 144.4, 143.9, 140.1, 133.6, 133.2, 130.4, 129.4 (2C), 129.1 (3C), 128.8 (2C), 128.7 (2C), 126.9, 126.6 (2C), 123.4, 123.1, 120.4; IR (NaCl): 3059, 1554, 1476, 1453, 1331, 1252, 1027, 947, 757, 711 cm^{-1}; HRMS (ESI) *m/z*: [M + Na]$^+$ Calcd for $C_{23}H_{15}NNaS$ 360.0822; Found 360.0823.

2-(2-Methoxyphenyl)-4-phenylthieno[3,2-*c*]quinoline (5b). Compound **5b** was prepared from bromo compound (104 mg, 0.310 mmol) and 2-methoxyphenylboronic acid (51.0 mg, 0.340 mmol) by general procedure A to provide compound **5b** as a yellow solid (109 mg, 68%): ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.18 (d, *J* 8.3, 1H), 8.05 (dd, *J* 8.1, 0.9, 1H), 7.90 (s, 1H), 7.87 (d, *J* 8.1, 2H), 7.61-7.59 (m, 2H), 7.50–7.47 (m, 3H), 7.43 (t, *J* 7.4, 1H), 7.23 (t, *J* 7.4, 1H), 6.94-6.91 (m, 2H), 3.87 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 156.1, 155.5, 146.1, 143.8, 140.2, 140.1, 132.2, 130.4, 129.7, 129.4 (2C), 129.2, 129.0, 128.7(2C), 128.4, 126.7, 123.4, 123.2, 122.7,

122.5, 121.1, 111.8, 55.8; IR (NaCl): 3055, 1712, 1551, 1491, 1480, 1333, 1248, 1117, 1026, 752, 707 cm^{-1}; HRMS (ESI) *m/z*: $[M + Na]^+$ Calcd for $C_{24}H_{17}ONNaS$ 390.0929; Found 390.0925.

2-(3-Methoxyphenyl)-4-phenylthieno[3,2-*c*]quinoline (5c). Compound **5c** was prepared from bromo compound (54.0 mg, 0.160 mmol) and 3-methoxyphenylboronic acid (27.0 mg, 0.180 mmol) by general procedure A to provide compound **5c** as a colorless solid (48 mg, 82%). Compound **5c** was synthesized in 47% yield from dibromo compound **3** employing general procedure B: ^1H NMR (400 MHz, $CDCl_3$): δ 8.19-8.17 (m, 1H), 8.15–8.13 (m, 1H), 7.97-7.95 (m, 2H), 7.84 (s, 1H), 7.72–7.74 (m, 1H), 7.65–7.55 (m, 4H), 7.39-7.34 (m, 2H), 7.28 (d, *J* 1.7, 1h) 6.96-6.94 (m, 1H), 3.91 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.1, 155.7, 144.3, 135.0, 134.8, 133.3, 130.5, 130.3, 129.3, 129.1, 128.8, 128.7, 127.0, 125.3, 123.4, 123.2, 123.1, 120.6, 119.2, 114.0, 112.5, 55.5; IR (NaCl): 1599, 1478, 1331, 1290, 1167, 1049, 768, 708 cm^{-1}; HRMS (ESI) *m/z*: $[M + Na]^+$ Calcd for $C_{24}H_{17}ONNaS$ 390.0929; Found 390.0930.

2-(4-Methoxyphenyl)-4-phenylthieno[3,2-*c*]quinoline (5d). Compound **5d** was prepared from bromo compound **4** (104 mg, 0.310 mmol) and 4-methoxyphenylboronic acid (51.0 mg, 0.340 mmol) by general procedure A to provide compound **5d** as a colorless solid (102 mg, 91%): ^1H NMR (400 MHz, $CDCl_3$): δ 8.27 (d, *J* 8.3, 1H), 8.09 (d, *J* 7.9, 1H), 7.97-7.95 (m, 2H), 7.73–7.56 (m, 8H), 6.98-6.96 (m, 2H), 3.87 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.1, 155.5, 145.1, 144.4, 143.9, 140.2, 133.4, 130.4, 129.3 (2C), 129.0, 128.7 (2C), 128.5, 127.9 (2C), 126.9, 126.3, 123.4, 123.0, 119.1, 114.5 (2C), 55.4; IR (NaCl): 1607, 1505, 1478, 1256, 1180, 1028, 824, 768, 704 cm^{-1}; HRMS (ESI) *m/z*: $[M + Na]^+$ Calcd for $C_{24}H_{17}ONNaS$ 390.0929; Found 390.0928.

2-(2-Chlorophenyl)-4-phenylthieno[3,2-*c*]quinoline (5e). Compound **5e** was prepared from bromo compound **4** (102 mg, 0.300 mmol) and 2-chlorophenylboronic acid (51.0 mg, 0.330 mmol) by general procedure A to provide compound **5e** as a colorless solid (102 mg, 65%): ^1H NMR (600 MHz, $CDCl_3$): δ 8.37 (d, *J* 8.0, 1H), 8.16 (dd, *J* 8.0, 0.9, 1H), 7.99 (d, *J* 8.0, 2H), 7.90 (s, 1H), 7.75 (ddd, *J* 8.4, 7.0, 1.4, 1H), 7.64–7.55 (m, 4H), 7.55-7.54 (m, 2H), 7.36-7.34 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 155.8, 146.6, 144.0, 140.3, 140.0, 132.8, 132.6, 132.3, 131.9, 130.7, 130.5, 129.7, 129.3 (2C), 129.2, 128.9, 128.7 (2C), 127.1, 126.9, 125.5, 123.2 (2C); IR (NaCl): 3058, 1712, 1558, 1485, 1467, 1330, 1246, 1064, 949, 756, 700 cm^{-1}; HRMS (ESI) *m/z*: $[M + Na]^+$ Calcd for $C_{23}H_{14}ClNNaS$ 394.0433; Found 394.0427.

2-(3-Chlorophenyl)-4-phenylthieno[3,2-*c*]quinoline (5f). Compound **5f** was prepared from bromo compound **4** (101 mg, 0.300 mmol) and 3-chlorophenylboronic acid (51.0 mg, 0.330 mmol) by general procedure A to provide compound **5f** as a colorless solid (104 mg, 66%): ^1H NMR (600 MHz, $CDCl_3$): δ 8.33-8.32 (m, 1H), 8.16 (d, *J* 8.3, 1H), 7.98 (d, *J* 8.0, 1H), 7.90 (s, 1H), 7.89 (s, 1H), 7.76 (t, *J* 7.8, 1H), 7.66–7.54 (m, 5H), 7.36-7.37 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 155.63, 145.9, 143.9, 142.5, 139.8, 135.3, 135.1, 133.0, 130.4, 130.3, 129.3 (3C), 128.9, 128.8 (2C), 128.5, 127.0, 126.4, 124.6, 123.2, 123.2, 121.2; IR (NaCl): 3058, 1712, 1593, 1564, 1485, 1453, 1330, 1250, 1079, 966, 767, 740, 719, 701 cm^{-1}; HRMS (ESI) *m/z*: $[M + Na]^+$ Calcd for $C_{23}H_{14}ClNNaS$ 394.0433; Found 394.0432.

2-(4-Chlorophenyl)-4-phenylthieno[3,2-*c*]quinoline (5g). Compound **5g** was prepared from bromo compound **4** (147 mg, 0.430 mmol) and 4-chlorophenylboronic acid (75.0 mg, 0.480 mmol) by general procedure A to provide compound **5g** as a colorless solid (93 mg, 58%): Compound **5g** was synthesized in 53% yield from dibromo compound **3** employing general procedure B: ^1H NMR (400 MHz, $CDCl_3$): δ 8.29 (d, *J* 8.3, 1H), 8.10 (d, *J* 7.8, 1H), 7.96-7.94 (m, 2H), 7.80 (s, 1H), 7.75-7.73 (m, 1H), 7.67–7.55 (m, 6H), 7.43–7.41 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.6, 145.7, 144.0, 142.9, 140.1, 134.6, 133.2, 132.1, 130.5, 129.3 (2C), 129.2 (3C), 128.9, 128.8 (2C), 127.7 (2C), 127.1, 123.3, 123.1, 120.8; IR (NaCl): 1474, 1331, 1250, 1171, 1094, 812, 754, 718 cm^{-1}; HRMS (ESI) *m/z*: $[M + Na]^+$ Calcd for $C_{23}H_{14}ClNNaS$ 394.0433; Found 394.0432.

2-(2,3-Dimethoxyphenyl)-4-phenylthieno[3,2-*c*]quinoline (5h). Compound **5h** was prepared from bromo compound **4** (103 mg, 0.300 mmol) and 2,3-dimethoxyphenylboronic acid (61.0 mg, 0.330 mmol) by general

procedure A to provide compound **5h** as a colorless solid (113 mg, 66%): ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.19 (d, *J* 8.5, 1H), 8.09 (dd, *J* 8.1, 0.9, 1H), 7.92 (s, 1H), 7.87 (d, *J* 8.2, 2H), 7.61 (dt, *J* 6.9, 1.4, 1H), 7.53–7.48 (m, 3H), 7.44 (t, *J* 7.4, 1H), 7.25 (dd, *J* 8.0, 1.4, 1H), 7.02 (t, *J* 8.0, 1H), 6.80 (dd, *J* 8.1, 1.3, 1H), 3.84 (d, *J* 4.2, 6H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 155.6, 153.5, 146.7, 146.2, 143.9, 140.2, 139.3, 132.9, 130.4, 129.3 (2C), 129.1, 128.7 (2C), 128.6, 127.5, 126.8, 124.5, 123.5, 123.2, 122.8, 120.3, 112.4, 60.9, 56.0; IR (NaCl): 2934, 1577, 1486, 1472, 1427, 1265, 1234, 1086, 1002, 768, 703 cm^{-1}; HRMS (ESI) *m/z*: $[M + Na]^+$ Calcd for $C_{25}H_{19}O_2NNaS$ 420.1034; Found 420.1032.

2-(3,4-Dimethoxyphenyl)-4-phenylthieno[3,2-*c*]quinoline (5i). Compound **5i** was prepared from bromo compound **4** (101 mg, 0.300 mmol) and 3,4-dimethoxyphenylboronic acid (61.0 mg, 0.330 mmol) by general procedure A to provide compound **5i** as a brown solid (120 mg, 60%): ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.28 (d, *J* 8.1, 1H), 8.13 (d, *J* 8.1, 1H), 7.96 (d, *J* 8.2, 2H), 7.73-7.71 (m, 2H), 7.64–7.60 (m, 3H), 7.57-7.55 (m, 1H), 7.33 (dd, *J* 8.2, 0.8, 1H), 7.22 (d, *J* 2.1, 1H), 6.95 (d, *J* 8.4, 1H), 4.00 (s, 3H), 3.96 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 155.4, 149.8, 149.4, 145.3, 144.6, 143.8, 140.2, 134.3, 130.4, 129.3 (2C), 129.1, 128.7 (2C), 128.6, 126.9, 126.6, 123.4, 123.0, 119.5, 119.2, 111.6, 109.8, 56.2, 56.1; IR (NaCl): 2932, 1507, 1479, 1440, 1264, 1145, 1026, 767, 707 cm^{-1}; HRMS (ESI) *m/z*: $[M + Na]^+$ Calcd for $C_{25}H_{19}O_2NNaS$ 420.1034; Found 420.1031.

2-(3,5-Dimethoxyphenyl)-4-phenylthieno[3,2-*c*]quinoline (5j). Compound **5j** was prepared from bromo compound **4** (103 mg, 0.300 mmol) and 3,5-dimethoxyphenylboronic acid (61.0 mg, 0.330 mmol) by general procedure A to provide compound **5j** as a colorless solid (112 mg, 66%): ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.30 (d, *J* 7.7, 1H), 8.20 (dd, *J* 8.0, 0.8, 1H), 7.96 (d, *J* 7.4, 2H), 7.82 (s, 1H), 7.73 (t, *J* 7.0, 1H), 7.65–7.61 (m, 3H), 7.57 (t, *J* 7.4, 1H), 6.88 (d, *J* 2.2, 2H), 6.51 (t, *J* 2.2, 1H), 3.88 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 161.3, 155.6, 145.7, 144.4, 143.7, 139.9, 135.4, 133.0, 130.3, 129.3 (2C), 129.2, 128.8 (4C), 127.0, 123.3, 123.1, 120.7, 105.1 (2C), 100.5, 55.6 (2C); IR (NaCl): 2938, 1592, 1454, 1425, 1329, 1206, 1156, 1066, 832, 768, 702 cm^{-1}; HRMS (ESI) *m/z*: $[M + Na]^+$ Calcd for $C_{25}H_{19}O_2NNaS$ 420.1034; Found 420.1030.

2-[4-(*tert*-Butyl)phenyl]-4-phenylthieno[3,2-*c*]quinoline (5k). Compound **5k** was prepared from bromo compound **4** (203 mg, 0.600 mmol) and 4-(*tert*-butyl)phenylboronic acid (115 mg, 0.650 mmol) by general procedure A to provide compound **5k** as a colorless amorphous solid (118 mg, 50%):^{1}H NMR (400 MHz, $CDCl_3$): δ 8.30 (d, *J* 8.3, 1H), 8.13 (dd, *J* 8.1, 1.2, 1H), 7.97 (d, *J* 6.7, 2H), 7.81 (s, 1H), 7.75–7.54 (m, 7H), 7.49 (d, *J* 8.6, 2H), 1.40 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.5, 152.1, 145.6, 144.6, 143.8, 140.0, 133.3, 130.8, 130.3 (2C), 129.3 (2C), 128.9, 128.7, 128.6 (2C), 126.9 (2C), 126.4, 126.3, 126.1, 123.5, 123.1 119.9, 31.3; IR (NaCl): 3058, 2962, 2866, 1554, 1476, 1363, 1269, 1110, 908, 827, 767, 701 cm^{-1}; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{27}H_{24}NS$ 394.1629; Found 394.1681.

(*E*)-2-(Hept-1-en-1-yl)-4-phenylthieno[3,2-c]quinoline (5l). Compound **5l** was prepared from bromo compound **4** (106 mg, 0.310 mmol) and *trans*-1-heptenylboronic acid, pinacol ester (77.0 mg, 0.340 mmol) by general procedure A to provide compound **5l** as a yellow semi-solid (71 mg, 64%): Compound **5l** was synthesized in 81% yield from dibromo compound **3** employing general procedure B: ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.10 (d, *J* 8.3, 1H), 7.98 (d, *J* 8.0, 1H), 7.92 (d, *J* 7.2, 2H), 7.66 (t, *J* 7.7, 1H), 7.58–7.50 (m, 4H), 7.43 (s, 1H), 6.64 (d, *J* 15.7, 1H), 6.24-6.19 (m, 1H), 2.16 (q, *J* 7.2, 2H), 1.45-1.41 (m, 2H), 1.30–1.27 (m, 4H), 0.87 (t, *J* 6.6, 3H); ^{13}C NMR (100 MHz, acetone-d_6): δ 154.7, 144.2, 144.1, 143.5, 140.2, 134.6, 132.5, 130.4, 129.3 (2C), 128.9, 128.5, 128.4 (2C), 126.9, 123.3, 123.1, 122.9, 121.9, 32.7, 31.3, 28.6, 22.3, 13.5; IR (NaCl): 2930, 2859, 1713, 1674, 1557, 1481, 1453, 1331, 858, 758, 702 cm^{-1}; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{24}H_{24}NS$ 358.1629; Found 358.1629.

4-Phenyl-2-(phenylethynyl)thieno[3,2-*c*]quinoline (6a). THF (9 mL) and Et_3N (1 mL) were added to bromo compound **4** (53.0 mg, 0.156 mmol), CuI (3.0 mg, 0.016 mmol), and [Pd(PPh3)$_4$] (9.0 mg, 0.0078 mmol) maintained under N_2. Phenylacetylene (53.0 mg, 0.156 mmol) was then added and the magnetically-stirred

mixture was heated at 70 °C. After 2 h, the reaction mixture was cooled and Et_2O (10 mL) was added. The ensuing mixture was washed with H_2O (3 × 10 mL) and NaCl (10 mL of a saturated aqueous solution). The organic phase was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The resulting residue was eluted through a plug of silica gel (50% CH_2Cl_2/hexanes elution) and the ensuing solution was concentrated under reduced pressure to provide compound **6a** as a yellow solid (37 mg, 66%): ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.29 (d, *J* 8.3, 1H), 8.07 (d, *J* 8.1, 1H), 7.95-7.39 (m, 2H), 7.84 (s, 1H), 7.75 (t, *J* 7.2, 1H), 7.64–7.53 (m, 7H), 7.41–7.39 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.5, 146.7, 144.3, 139.7, 131.8, 131.6 (2C), 130.5, 129.7, 129.3 (2C), 129.2, 129.0, 128.7 (2C), 128.5 (2C), 12.1, 123.4, 123.2, 123.0, 122.2, 95.7, 82.4; IR (NaCl): 1489, 1474, 1443, 1329, 1235, 1026, 858, 752 cm^{-1}; HRMS (ESI) *m/z*: $[M + Na]^+$ Calcd for $C_{25}H_{15}NNaS$ 384.0823; Found 384.0822.

2-(Hept-1-yn-1-yl)-4-phenylthieno[3,2-*c*]quinoline (6b). Et_3N (10 mL) was added to bromo compound **4** (227 mg, 0.680 mmol), CuI (15.0 mg, 0.078 mmol), and [Pd(PPh3)$_4$] (43.0 mg, 0.037 mmol) in a Schlenk tube maintained under N_2. 1-Heptyne (141 mg, 1.47 mmol) was then added, the tube was sealed, and the magnetically-stirred mixture was heated at 100 °C. After 3 h, the reaction mixture was concentrated under reduced pressure. The ensuing residue was subjected to flash column chromatography (50% CH_2Cl_2/hexanes then 10% EtOAc/ CH_2Cl_2 elution; silica gel) to provide compound **6b** as an orange oil (149 mg, 63%): ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.31 (d, *J* 8.4, 1H), 8.05 (dd, *J* 8.0, 0.8, 1H), 7.91 (d, *J* 4.0, 2H), 7.74, (t, *J* 4.8, 1H), 7.67 (s, 1H), 7.63–7.52 (m, 4H), 7.42–7.35 (m, 4H), 7.29–7.25 (m, 3H), 2.50 (t, *J* 4.8, 2H), 1.67 (pentet, *J* 4.8, 2H), 1.47 (pentet, *J* 4.8, 2H), 1.40 (pentet, *J* 4.8, 2H), 0.96 (t, *J* 4.8, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.3, 146.2, 144.0, 139.5, 131.8, 130.2, 129.9 (2C), 129.3, 129.1, 128.7, 128.7 (2C), 127.1, 123.1, 123.0, 98.0, 73.6, 31.2, 28.1, 22.2, 19.8, 14.0; IR (NaCl): 2917, 2855, 1654, 1553, 1492, 1482, 1330, 1091, 1013, 908, 800, 720 cm^{-1}; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{24}H_{22}NS$ 355.1473; Found 356.1467.

4-Phenyl-2-[(trimethylsilyl)ethynyl]thieno[3,2-*c*]quinoline (6c). Et_3N (10 mL) was added to bromo compound **4** (1.10 g, 3.23 mmol), CuI (60.0 mg, 0.315 mmol), and [Pd(PPh3)$_4$] (170 mg, 0.147 mmol) in a Schlenk tube maintained under N_2. Trimethylsilylacetylene (638 mg, 6.49 mmol) was then added, the tube was sealed, and the magnetically-stirred mixture was heated at 70 °C. After 3 h, the reaction mixture was concentrated under reduced pressure. The ensuing residue was subjected to flash column chromatography (50% CH_2Cl_2/hexanes then 10% EtOAc/CH_2Cl_2 elution; silica gel) to provide compound **6c** as a yellow amorphous solid (1.05 g, 91%):^{1}H NMR (400 MHz, $CDCl_3$): δ 8.28 (d, *J* 5.6, 1H), 8.06 (d, *J* 5.4, 1H), 7.90 (d, *J* 4.9, 2H), 7.79 (s, 1H), 7.75 (t, *J* 4.8, 1H) 7.63–7.53 (m, 4H), 0.32 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.6, 146.7, 144.4, 139.6, 131.6, 130.5 (2C), 129.3, 129.2 (2C), 128.7, 127.1, 123.2, 123.1, 123.0, 102.2, 97.0, 0.23; IR (NaCl): 3059, 2958, 2898, 2147, 1548, 1475, 1452, 1420, 1329, 1249, 1177, 1153, 1027, 860, 845, 765, 757, 717 cm^{-1}; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{22}H_{20}NSSi$ 355.1086; Found 358.1080.

Methyl 4-phenylthieno[3,2-*c*]quinoline-2-carboxylate (7a). [Pd(PPh3)$_4$] (3 mg, 0.002 mmol) and Et_3N (1 mL) were added to a solution of bromo compound **4** (41.0 mg, 0.120 mmol) in MeOH (20 mL) maintained under N_2. CO was bubbled through the mixture. After 5 min, the mixture was placed under an atmosphere of CO and magnetically-stirred at 70 °C. After 16 h, the mixture was cooled then HCl (5 mL of a 2 M aqueous solution) was added. The ensuing mixture was extracted with CH_2Cl_2 (3 × 10 mL), washed with NaCl (10 mL of a saturated aqueous solution), dried ($MgSO_4$), filtered and concentrated under reduced pressure to provide compound **7a** as an off-white crystalline solid (53 mg, 69%): ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.36 (s, 1H), 8.31 (d, *J* 7.1, 2H), 8.17 (d, *J* 8.1, 1H), 7.91 (d, *J* 7.1, 2H), 7.81 (t, *J* 7.6, 1H), 7.67 (t, *J* 7.6, 1H), 7.62–7.56 (m, 3H), 4.00 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 162.6, 156.8, 149.4, 144.6, 139.3, 133.1, 131.6, 131.6 (2C), 130.5, 130.1, 129.5, 129.3 (2C), 128.9 (2C), 127.4, 123.4, 123.0, 52.7; IR (NaCl): 2922, 1727, 1453, 1257, 756 cm^{-1}; HRMS (ESI) *m/z*: $[M + Na]^+$ Calcd for $C_{19}H_{13}O_2NNaS$ 342.0565; Found 342.0564.

2-Heptyl-4-phenylthieno[3,2-*c*]quinoline (7b). Pd/C (10 mg of a 10% w/w mixture) was added to a magnetically-stirred solution of alkyne **6b** (53.0 mg, 0.150 mmol) in EtOH (5 mL) and the ensuing mixture was placed under an atmosphere of H_2 (balloon, 1 atm). After 2 h, the reaction mixture was filtered through a pad of Celite®, eluted with CH_2Cl_2. The ensuing solution was concentrated under reduced pressure to provide compound **7b** as a yellow semi-solid (50 mg, 93%):^{1}H NMR (400 MHz, $CDCl_3$): δ 8.16, (d, *J* 8.3, 1H), 7.96 (d, *J* 8.1, 1H), 7.81 (d, *J* 7.4, 2H), 7.58 (t, *J* 7.8, 1H), 7.48 (q, *J* 6.7, 3H), 7.42 (t, *J* 7.3, 1H), 7.23 (s, 1H), 2.88 (t, *J* 7.6, 2H), 1.69 (t, *J* 5.2, 2H), 1.32–1.19 (m, 8H), 0.80 (t, *J* 6.6, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.1, 145.9, 144.2, 142.6, 139.3, 131.5, 129.3 (2C), 128.2, 127.9, 127.6 (2C), 127.1, 125.6, 122.5, 121.9, 120.5, 30.7, 30.4, 29.8, 28.0, 27.9, 21.5, 13.0; IR (NaCl): 3059, 2954, 2927, 2654, 2359, 1558, 1481, 1329, 1026, 857, 766 cm^{-1}; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{24}H_{26}NS$ 360.1786; Found 360.1780.

2-Phenethyl-4-phenylthieno[3,2-*c*]quinoline (7c). Pd/C (10 mg of a 10% w/w mixture) was added to a magnetically-stirred solution of alkyne **6a** (45.0 mg, 0.120 mmol) in EtOH (5 mL) and the ensuing mixture was placed under an atmosphere of H_2 (~30 psi in a Parr hydrogenator). After 2 h, the reaction mixture was filtered through a pad of Celite®, eluted with CH_2Cl_2, and the ensuing solution was concentrated under reduced pressure to provide compound **7c** as a yellow oil (35 mg, 77%): ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.29 (d, *J* 8.3, 1H), 8.07 (d, *J* 7.9, 1H), 7.89-7.87 (m, 2H), 7.71 (t, *J* 7.9, 1H), 7.62–7.51 (m, 4H), 7.34-7.32 (m, 2H), 7.30–7.24 (m, 4H), 3.31 (t, *J* 7.7, 2H), 3.11 (t, *J* 7.7, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.2, 145.4, 145.2, 143.8, 140.5, 140.3, 132.5, 130.4, 129.3 (2C), 128.9, 128.6 (2C), 128.4 (4C), 128.3, 126.7, 126.4, 123.6, 123.0, 122.3, 37.6, 32.6; IR (NaCl): 2922, 1481, 1453, 1412, 1331, 1026, 858, 754 cm^{-1}; HRMS (ESI) *m/z*: $[M + Na]^+$ Calcd for $C_{25}H_{19}NNaS$ 388.1136; Found 388.1134.

2-(4-Methoxyphenethyl)-4-phenylthieno[3,2-*c*]quinoline (7d). Compound **7d** was prepared from the corresponding alkyne precursor (52.0 mg, 0.130 mmol) by General Procedure C to provide after flash column chromatography (0–5% EtOAc/CH_2Cl_2; silica gel) compound **7d** as a colorless amorphous solid (50 mg, 95%): ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.26 (d, *J* 8.4, 1H), 8.06 (dd, *J* 8.0, 0.8, 1H), 7.86 (d, *J* 6.7, 2H), 7.70 (t, *J* 7.0, 1H), 7.63–7.50 (m, 4H), 7.25 (s, 1H), 7.14 (d, *J* 8.6, 2H), 6.86 (d, *J* 8.6, 2H), 3.82 (s, 3H), 3.28 (t, *J* 7.5, 2H), 3.05 (t, *J* 7.5, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.2, 155.2, 145.3, 145.2, 143.8, 140.3, 132.5, 132.4, 130.4, 129.5, 129.2, 128.9 (2C), 128.6, 128.2 (4C), 126.7, 123.6, 123.0, 122.3, 113.9, 55.3, 36.7, 32.9; IR (NaCl): 3057, 2930, 2833, 1611, 1558, 1512, 1481, 1329, 1246, 1177, 1035, 908, 768, 700 cm^{-1}; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{26}H_{22}NOS$ 396.1422; Found 396.1417.

2-(4-Chlorophenethyl)-4-phenylthieno[3,2-*c*]quinoline (7e). Compound **7e** was prepared from the corresponding alkyne precursor (71.0 mg, 0.180 mmol) by General Procedure C to provide after flash column chromatography (5% EtOAc/CH_2Cl_2; silica gel) compound **7e** as a colorless amorphous solid (65 mg, 91%):^{1}H NMR (400 MHz, $CDCl_3$): δ 8.29 (d, *J* 8.0, 1H), 8.06 (dd, *J* 8.0, 0.8, 1H), 7.83 (d, *J* 8.0, 2H), 7.71 (t, *J* 7.6, 1H), 7.63–7.51 (m, 4H), 7.29-7.28 (m, 2H), 7.22 (s, 1H), 7.15 (d, *J* 8.0, 2H) 3.29 (t, *J* 7.5, 2H), 3.08 (t, *J* 7.5, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.1, 145.5, 144.6, 143.6, 140.4, 140.0. 138.8, 132.4, 132.2, 129.3 (2C), 128.6 (2C), 126.8, 123.5 (4C), 123.0, 122.5, 36.9, 32.4; IR (NaCl): 3059, 2916, 2848, 1491, 1481, 1330, 1091, 1015, 908, 835, 767, 720, 700 cm^{-1}; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{25}H_{19}NSCl$ 400.0927; Found 400.0921.

4-Phenyl-2-[2-(thien-2-yl)ethyl]thieno[3,2-*c*]quinoline (7f). Compound **7f** was prepared from the corresponding alkyne precursor (69.0 mg, 0.190 mmol) by General Procedure C to provide after flash column chromatography (100% CH_2Cl_2; silica gel) compound **7f** as a yellow amorphous solid (50 mg, 72%):^{1}H NMR (400 MHz, $CDCl_3$): δ 8.29 (d, *J* 8.1, 1H), 8.06 (dd, *J* 7.6, 0.9, 1H), 7.90 (d, *J* 8.0, 2H), 7.72–7.52 (m, 4H), 7.34 (s, 1H), 7.19 (dd, *J* 5.1, 1.2, 1H) 6.97–6.95 (m, 1H), 6.85 (dd, *J* 3.3, 0.7, 1H), 3.32-3.37 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.20, 145.5, 144.5, 143.7, 142.9, 140.2, 132.4, 130.4, 129.3, 129.0 (2C), 128.7, 128.4 (2C), 126.9,

126.8, 125.1, 123.7, 123.5, 123.0, 122.5, 32.9, 31.7; IR (NaCl): 3500, 3059, 2918, 2847, 2359, 1558, 1481, 1441, 1329, 1235, 1026, 767, 719 cm^{-1}; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{23}H_{18}NS_2$ 372.0881; Found 372.0875.

Biological testing. Purified metabolites were dissolved in DMSO to provide stock solutions (10,000 μg/mL). An aliquot of each stock solution was transferred to the first lane of Rows B to G in a 96-well microtitre plate and two-fold serially diluted with DMSO across the 12 lanes of the plate to provide a 2,048-fold concentration gradient. Bioassay medium was added to an aliquot of each test solution to provide a 100-fold dilution into the final bioassay, thus yielding a test range of 100 to 0.05 μg/mL in 1% DMSO. Row A contained no test compound (as a reference for no inhibition) and Row H was uninoculated (as a reference for complete inhibition).

In the present study, NS-1 (ATCC TIB-18) mouse myeloma and NFF (ATCC PCS-201) human neonatal foreskin fibroblast cells were used as indicative cell lines for anti-tumour and mammalian cell toxicity, respectively. Each cell line was inoculated in 96-well microtitre plates (190 μL) at 50,000 cells/mL in DMEM (Dulbecco's Modified Eagle Medium + 10% fetal bovine serum (FBS) + 1% penicillin/streptomycin (10,000 U/mL/10,000 μg/mL, Life Technologies Cat. No. 15140122), together with resazurin (250 μg/mL; 10 μL) and incubated in 37 °C (5% CO_2) incubator. The plates were incubated for 96 h during which time the positive control wells change color from a blue to pink color. The absorbance of each well was measured at 605 nm using a Spectromax plate reader (Molecular Devices).

Bacillus subtilis (ATCC 6633) and *Staphylococcus aureus* (ATCC 25923) were used as indicative species for Gram positive antibacterial activity. A bacterial suspension (50 mL in 250 mL flask) was prepared in nutrient media by cultivation for 24 h at 250 rpm, 28 °C. The suspension was diluted to an absorbance of 0.01 absorbance units per mL, and 10 μL aliquots were added to the wells of a 96-well microtitre plate, which contained the test compounds dispersed in nutrient broth (Amyl) with resazurin (12.5 μg/mL). The plates were incubated at 28 °C for 48 h during which time the positive control wells change color from a blue to light pink color. MIC end points were determined visually. The absorbance was measured using Spectromax plate reader (Molecular Devices) at 605 nm and the MIC values determined.

The yeasts *Candida albicans* (ATCC 10231) and *Saccharomyces cerevisiae* (ATCC 9763) were used as indicative species for antifungal activity. A yeast suspension (50 mL in 250 mL flask) was prepared in 1% malt extract broth by cultivation for 24 h at 250 rpm, 24 °C. The suspension was diluted to an absorbance of 0.005 and 0.03 absorbance units per mL for *C. albicans* and *S. cerevisiae*, respectively. Aliquots (20 μL and 30 μL) of *C. albicans* and *S. cerevisiae*, respectively were applied to the wells of a 96-well microtitre plate, which contained the test compounds dispersed in malt extract agar containing bromocresol green (50 μg/mL). The plates were incubated at 24 °C for 48 h during which time the positive control wells change color from a blue to yellow color. MIC end points were determined visually. The absorbance was measured using Spectromax plate reader (Molecular Devices) at 620 nm and the MIC determined.

Giardia duodenalis (strain 713) was used as indicative species for antiparasitic activity. *G. duodenalis* was inoculated in 96-well microtitre plates (200 μL) at 4×10^5 cells/mL in *Giardia* medium (0.2% tryptone, Oxoid; 0.1% yeast extract, Difco; 0.5% glucose; 0.106% L-Arginine; 0.1% L-cysteine; 0.2% NaCl; 0.1% K_2HPO_4; 0.06% KH_2PO_4; 0.02% ascorbic acid; 0.0023% Ferric ammonium citrate; 0.01% Bile (Sigma); 1% penicillin/streptomycin (10,000 U/mL/10,000 μg/mL, Life Technologies Cat. No. 15140122), 10% new born calf serum (NBCS), Life Technologies). The plates were incubated in anaerobic jars (Oxoid AG25) containing Anaerogen satchel (Oxoid AN25) in 37 °C (5% CO_2) incubator. At 96 h, *G. duodenalis* proliferation was counted and % inhibition graphed to determine the MIC values.

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Supplementary Material

^{1}H and ^{13}C NMR spectra for compounds **4**, **5a-l**, **6a-c** and **7a-f** are provided.

References

1. For a recent review of the synthesis of thienoquinolines, see: Teja, C.; Nawaz Khan, F.-R. *Asian J. Org. Chem.* **2020**, *9*, 1889–1900. https://doi.org/10.1002/ajoc.202000427
2. Moretto, A. F.; Kirincich, S. J.; Xu, W. X.; Smith, M. J.; Wan, Z. K.; Wilson, D. P.; Follows, B. C.; Binnun, E.; Joseph-McCarthy, D.; Foreman, K.; Erbe, D. V.; Zhang, Y. L.; Tam, S. K.; Tam, S. Y.; Lee, J. *Bioorg. Med. Chem.* **2006**, *14*, 2162–2177. https://doi.org/10.1016/j.bmc.2005.11.005
3. Pierre, F.; Regan, C. F.; Chevrel, M.-C.; Siddiqui-Jain, A.; Macalino, D.; Streiner, N.; Drygin, D.; Haddach, M.; O'Brien, S. E.; Rice, W. G.; Ryckman, D. M. *Bioorg. Med. Chem. Lett*. **2012**, *22*, 3327–3331. https://doi.org/10.1016/j.bmcl.2012.02.099
4. Abdel-Wadood, F. K.; Abdel-Monem, M. I.; Fahmy, A. M.; Geies, A. A. *Arch. Pharm. Chem. Life Sci.* **2014**, *347*, 142–152. https://doi.org/10.1002/ardp.201300167
5. Chatterjee, A.; Cutler, S. J.; Doerksen, R. J.; Khan, I. A.; Williamson, J. S. *Bioorg. Med. Chem*. **2014**, *22*, 6409–6421. https://doi.org/10.1016/j.bmc.2014.09.043
6. Salvati, E.; Botta, L.; Amato, J.; Di Leva, F. S.; Zizza, P.; Gioiello, A.; Pagano, B.; Graziani, G.; Tarsounas, M.; Randazzo, A.; Novellino, E.; Biroccio, A.; Cosconati, S. *J. Med. Chem*. **2017**, *60*, 3626–3635. https://doi.org/10.1021/acs.jmedchem.6b01563
7. Jiang, B.; Ning, X.; Gong, S.; Jiang, N.; Zhong, C.; Lu, Z.-H.; Yang, C. *J. Mater. Chem. C* **2017**, *5*, 10220-10224. ttps://doi.org/10.1039/C7TC03667A
8. Mekheimer, R. A.; Sadek, K. U.; El-Nabi, H. A. A.; Mohamed, A. A. E. H.; Ebraheem, E. A.; Smith, M. B. *J. Heterocycl. Chem.* **2005**, *42*, 567–574. https://doi.org/10.1002/jhet.5570420415
9. Avetisyan, A.; Aleksanyan, I.; Sargsyan, K. *Russ. J. Org. Chem.* **2007**, *43*, 422–425. https://doi.org/10.1134/S1070428007030165
10. Mekheimer, R. A.; Hameed, A. M. A.; Sadek, K. U. *ARKIVOC* **2008**, *xvi*, 144–153. https://doi.org/10.3998/ark.5550190.0009.g14

11. Selvi, G.; Rajendram, S. P. *Heterocycl. Commun.* **2009**, *15*, 349-350. https://doi.org/10.1515/HC.2009.15.5.349
12. Mphahlele, M. J.; Maluleka, M. M.; Makhafola, T. J.; Mabeta, P. *Molecules* **2014**, *19*, 18527–18542. https://doi.org/10.3390/molecules191118527
13. Yang, Y.; Hornfeldt, A.; Gronowitz, S. *J. Heterocycl. Chem*. **1989**, *26*, 865–868. https://doi.org/10.1002/jhet.5570260366
14. Martin, A. R.; Yang, Y. *Acta Chem. Scand.* **1993**, *47*, 221–221. https://doi.org/10.3891/acta.chem.scand.47-0221
15. Marzinzik, A.; Rademacher, P. *Synthesis* **1995**, *1995*, 1131–1134. https://doi.org/10.1055/s-1995-4062
16. Youn, S. W.; Bihn, J. H. *Tetrahedron Lett.* **2009**, *50*, 4598-4601. https://doi.org/10.1016/j.tetlet.2009.05.071
17. Beydoun, K.; Doucet, H. *Eur. J. Org. Chem*. **2012**, *2012*, 6745–6751. https://doi.org/10.1002/ejoc.201201142
18. Akula, M.; Yogeeswari, P.; Sriram, D.; Jha, M.; Bhattacharya, A. *RSC Adv.* **2016**, *6*, 46073–46080. https://doi.org/10.1039/C6RA03187K
19. Hernández-Ruiz, R.; Rubio-Presa, R.; Suárez-Pantiga, S.; Pedrosa, M. R.; Fernández-Rodríguez, M. A.; Tapia M. J.; Sanz, R. *Chem. – Eur. J.* **2021**, *27*, 13613–13623. https://doi.org/10.1002/chem.202102000
20. Suzuki, A. *Chem. Commun.* **2005**, 4759–4763. https://doi.org/10.1039/B507375H
21. Banwell, M. G.; Goodwin, T. E.; Ng. S; Smith, J. A.; Wong, D. J. *Eur. J. Org. Chem.* **2006**, 3043-3060. https://doi.org/10.1002/ejoc.200500911
22. Rossi. R.; Bellina. F; Lessi, M. *Adv. Synth. Catal.* **2012**, 1181-1255. https://doi.org/10.1002/adsc.201100942
23. He, C.; Zhang, X.; Huang, R.; Pan, J.; Li, J.; Ling, X.; Xiong, Y.; Zhu, X. *Tetrahedron Lett.* **2014**, *55*, 4458–4462. https://doi.org/10.1016/j.tetlet.2014.06.047
24. Handy, S. T.; Sabatini, J. J. *Org. Lett.* **2006**, *8*, 1537-1539. https://doi.org/10.1021/ol0530981
25. Handy, S. T.; Zhang, Y. *Synthesis* **2006**, *22*, 3883-3887. https://doi.org/10.1055/s-2006-950305
26. Suzuki–Miyaura cross-coupling conditions were adapted from: Bissember, A. C.; Phillis, A. T.; Banwell, M. G.; Willis, A. C. *Org. Lett.* **2007**, *9*, 5421–5424. https://doi.org/10.1021/ol7021774
27. Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem*. **1978**, *43*, 2923–2925. https://doi.org/10.1021/jo00408a041