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In-flow photooxygenation of aminothienopyridinones generates iminopyridinedione PTP4A3 phosphatase inhibitors†

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A continuous flow photooxygenation of 7-aminothieno[3,2-*c*]pyridin-4(5*H*)-ones to produce 7-iminothieno[3,2-*c*]pyridine-4,6(5*H*,7*H*)-diones has been developed, utilizing ambient air as the sole reactant. *N*-H Imines are formed as the major products, and excellent functional group tolerance and conversion on gram-scale without the need for chromatographic purification allow for facile late-stage diversification of the aminothienopyridinone scaffold. Several analogs exhibit potent *in vitro* inhibition of the cancer-associated protein tyrosine phosphatase PTP4A3, and the SAR supports an exploratory docking model.

Introduction

Photooxygenations are considered as green alternatives to standard oxidation methods, as the former involve light and generally environmentally innocuous reagents.[1,2] Transition metal-free conditions with stoichiometric molecular oxygen or air as reactants can eliminate the need for toxic or expensive catalysts. Photosensitizers such as Rose Bengal, Methylene Blue, and tetraphenylporphyrin have been used in several natural product syntheses to generate singlet oxygen, which reacts with electron-rich alkenes and aromatic rings.[1,2] For example, a photosensitized singlet oxygen transformation was implemented in the formal synthesis of daphnane diterpene *ortho* esters and several alkaloids.[2,3] While photooxygenation is an atom-economical alternative to commonly used reagents and metal-based oxidation protocols, regioselectivity is often difficult to control, especially with alkenes,[1] and sometimes requires complex reactors,[4] photosensitizers,[5–7] photocatalysts,[8] or other additives.[1,8]

The synthesis of *N*-unsubstituted imines remains a challenging problem due to their propensity to hydrolyze under ambient conditions.[9–11] Therefore, *N*-H imines are underrepresented in the literature and are frequently only used as transient intermediates.[12] An exception are natural products such as caulibugulone E, where the imine is stabilized by conjugation to an arene and an electron-rich enamine.[13] Caulibugulone E has distinct biological properties and the *N*-H imine can be prepared by treatment of the corresponding carbonyl compound, caulibugulone A, with ammonia in the presence of Ti(O-i-Pr)$_4$.[14] Oxygenation of aryl amines represents another access point to *N*-unsubstituted imines, but often results in hydrolysis under the reaction conditions, or a mechanistically complex displacement of the amine with dioxygen.[1] Examples in the literature where the imine is preserved are scarce and low yielding.[15,16] Fremy's salt is one of many methods to mimic singlet oxygen,[17] but it is unselective for imine formation and results in hydrolysis.[18]

We recently reported that the photooxygenation of thienopyridone **1** can be performed in high yield, but on limited scale (<50 mg), to produce a novel nanomolar PTP4A3 phosphatase inhibitor,[19] 7-iminothieno[3,2-*c*]pyridine-4,6(5*H*,7*H*)-dione **2** (Scheme 1).[20] For the further investigation of the intriguing biological profile of **2**,[21] particularly through *in vivo* studies, synthetic access to gram-quantities of this material became a critical requirement. Due to the very sluggish reaction progress in the batch setup, which was aggravated by the poor solubility of both substrate and product, a flow process starting with a diluted, homogeneous solution of the reactant was investigated. Photochemical flow processes allow for a significant decrease in reaction time by increasing the exposure of the reaction mixture to light while removing light-capturing products and precipitates.[22] Herein, we describe further

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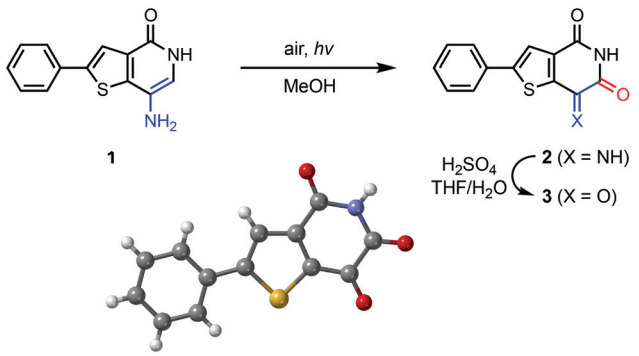
†Electronic supplementary information (ESI) available: Complete synthesis schemes, sketch of flow system and additional experimental information, concentration-PTP4A3 phosphatase inhibition response curves and assay methods, photooxygenation optimization studies, drug-likeliness calculations, docking methods, X-ray diffraction data, fluorescence and UV-VIS spectra, and copies of ^{1}H, ^{13}C, and ^{19}F NMR spectra. CCDC 1880535. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c9ob00025a



Scheme 1 Photooxygenation of thienopyridone **1** and X-ray structure of hydrolysis product **3** (CCDC 1880535†).

investigations of the scope of the photooxygenation of 4-aminothienopyridones, including the use of a macroflow photoreactor.

Table 1 Flow photooxygenation of **1** to **2**[a]

Entry	Solvent	Light source	Ratio of **2** to **3**[b]
1	1,2-DCE[c]	CFL	0 : 1
2	1,2-DCE[d]	CFL	1.5 : 1
3	$CHCl_3$ [d]	CFL	0 : 1
4	MeOH[d]	CFL	8.7 : 1
5	MeOH	CFL	10 : 1
6	i-PrOH	CFL	7.5 : 1
7	HFIP	CFL	6 : 1
8	THF	CFL	6.3 : 1
9	MeOH	Red (IR) lamp	rsm[e]
10[f]	i-PrOH	Red (IR) lamp	6.7 : 1
11	MeOH[g]	CFL	10 : 1

[a] Optimizations were performed on a 10 mg scale with 30 mL of solvent (at a concentration of 1.4 mM), utilizing an 18 W compact fluorescent lamp (CFL) with a flow rate of 1.9 mL min^{-1}. The tubing volume was 80 mL. [b] Ratios were determined by ^1H NMR integration. [c] Flow rate = 0.1 mL min^{-1}. [d] Flow rate = 0.8 mL min^{-1}. [e] Recovered starting material. [f] Three mol% methylene blue added. [g] Distilled over Mg turnings and stored over 3 Å molecular sieves for 5 days.

Results and discussion

In the original synthesis of **2**,[20] a minor by-product was observed in the batch photooxygenation process, and the identity of this compound eluded us for some time. Some reports have suggested that these type of transformations result in dimers;[23] alternatively, the corresponding carbonyl compound is also known to be the major product in related conversions, either formed directly or through hydrolysis.[18,23a]

When the reaction mixture was treated with aqueous sulfuric acid, we were able to isolate the by-product as the sole product. Furthermore, an X-ray structure confirmed its assignment as tricarbonyl compound **3** (Scheme 1). Photooxygenation of **1** in a methanol/water mixture at neutral pH still greatly favored imine formation; therefore, the formation of tricarbonyl compound **3** in the reaction mixture is unlikely to proceed substantially through the hydrolysis of **2**. While there is only a single previous report on a compound containing the thienopyridinetrione scaffold of **3** in the patent literature,[24] structurally related pyridine-, pyrrolopyridine-, and isoquinolinetriones have been obtained by oxidations of pyridines, pyrrolopyridines, and isoquinolines, respectively, as well as *via* the Beckmann rearrangement or the azido-Schmidt reaction of ninhydrin.[23b,c,25,26] Some of these compounds are of pharmaceutical interest as hepatitis C NS3 proteinase and caspase inhibitors.[23c,26]

Thienopyridone **1** was used to optimize the photooxygenation conditions leading to **2** in a photo-flow setup (Table 1; see also ESI, Fig. S1, S2, and Table S1†). Solvent, light source, flow rate, and additives were varied to minimize the formation of **3**. Additives generally increased the content of **3** or decreased the rate of conversion of **1**, and photosensitizers were not effective. As expected, conversion was not affected by the concentration of the starting material, but the low solubilities of **1** and **2** required moderate to high dilution. In MeOH, the UV-absorption band of the 353 nm peak of thienopyridone **1** extended to 500 nm into the visible range of the spectrum. The corresponding absorption maximum of imine **2** was 379 nm, and this peak extended to 450 nm. Notably, both amine **1** and imine **2** exhibited a strong green fluorescence. Combined, these data suggest that these substrates act as their own photosensitizers. Experiments with Rose Bengal and Methylene Blue were explored in an attempt enhance the reactivity of **1** and the ratio of **2** to **3**, but no substantial changes were observed when a white CFL or white LED lights were used with these photosensitizers.

Chlorinated solvents such as 1,2-dichloroethane (DCE) and $CHCl_3$ exhibited a strong preference for the formation of **3** (Table 1, entries 1–3). MeOH showed selectivity for the formation of **2**, and the ratio of **2** to **3** increased when the flow rate was accelerated (entries 4 and 5). The use of dry methanol did not appreciably affect the outcome (entry 11). Photooxygenation in hexafluoroisopropanol (HFIP) resulted in a complex mixture of products. Other protic and polar aprotic solvents, such as i-PrOH and THF, respectively, resulted in diminished selectivity (entries 6 and 8). Interestingly, imine formation was favored in solvents with short singlet oxygen lifetimes.[27] Additionally, faster flow rates often provided an increase in imine formation; although, flow rates above 1.9 mL min^{-1} led to decreased conversion.

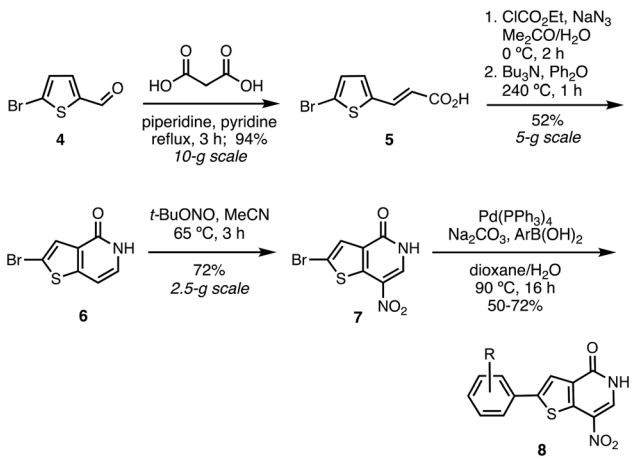
Optimized conditions required MeOH as the solvent, a household 18 W CFL light bulb as the light source, and a flow rate of 1.9 mL min^{-1}, resulting in a substrate residence time in the flow reactor of 42 min, which is a significant improvement over the previous multi-day batch process. With these conditions, the desired imine **2** was obtained in a 10 : 1 ratio over ketone **3**. It was also found that white LED lights worked just as effectively as the CFL. No additional air or oxygen was bubbled through the system; the mole fraction of O_2 in MeOH from exposure to ambient air was sufficient to keep the concentration of O_2 in the open flow system at any time at least 2

times higher than the concentration of the substrate (1.4 mM). Conversely, when the photo-flow reaction was performed under otherwise optimized conditions but under an atmosphere of argon instead of air, only 17% conversion was observed by ^{1}H NMR.

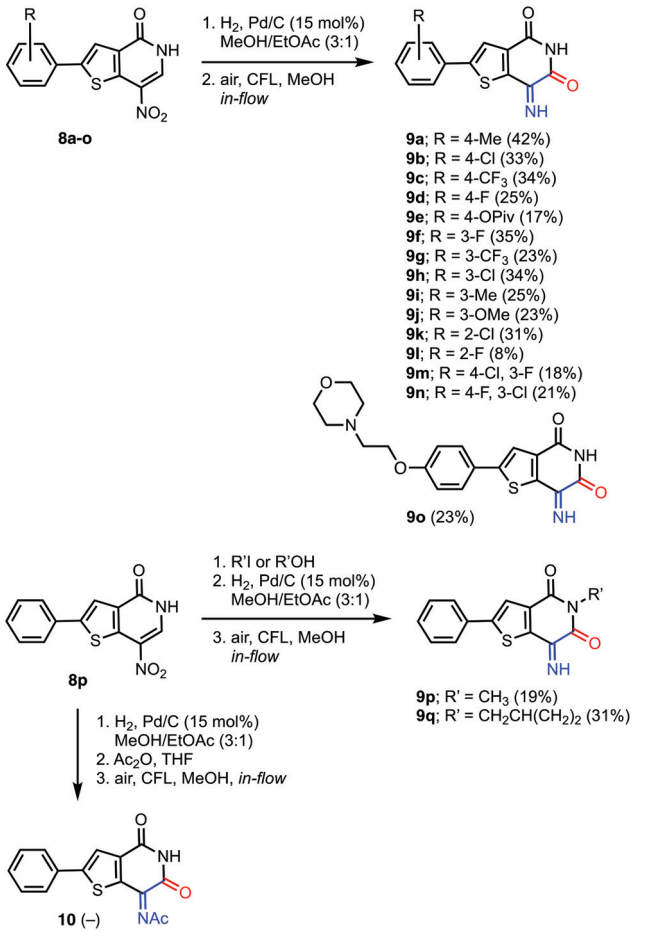
In order to examine the substrate scope of the reaction, a general synthetic route allowing for late-stage diversification of the thienopyridone scaffold was accomplished in 5 steps from commercially available aldehyde **4** (Scheme 2; for a complete schematic overview of intermediates and products, see ESI Schemes S1–8†). A Knoevenagel condensation using malonic acid afforded **5** in 94% yield. Acyl azide formation, Curtius rearrangement, and concomitant cyclization provided the thienopyridone scaffold **6** in 52% yield over 2 steps. Nitration attempts using nitric acid resulted in poor mass recovery; therefore, nitration was performed with *tert*-butyl nitrite to give the nitrated product **7** in 72% yield.[28] A late stage Suzuki–Miyaura coupling with aryl boronic acids allowed for facile substrate diversifications to give **8a–p**.

Isolation of the enamine after reduction of the nitro group in **8** proved difficult due to the formation of trace photooxygenation products during the purification step. Therefore, a 2-step procedure was implemented to examine the substrate scope (Scheme 3). By ^{1}H NMR analysis in the presence of an internal standard (1,3,5-trimethoxybenzene), **8c** and **8e** were reduced to the corresponding amine intermediates in 80% and 67% yield, respectively.

Excellent functional group tolerance was observed, as electron-rich and -deficient arenes, halides, and amines did not impede reactivity. Additionally, the photooxygenation of *N*-alkylated amides, obtained from **8p**[20] by alkylation with R'I in the presence of K_2CO_3 or under Mitsunobu reaction conditions with R'OH, produced *N*-methyl **9p** and *N*-methylcyclopropyl **9q** in 19% and 31% yield, respectively, over 3 steps. In contrast, *N*-acylation of enamine **1** obtained after reduction of the nitro group in **8p** rendered the substrate unreactive to photooxygenation, likely due to the decreased electron density at the α-carbon, and compound **10** was not observed.

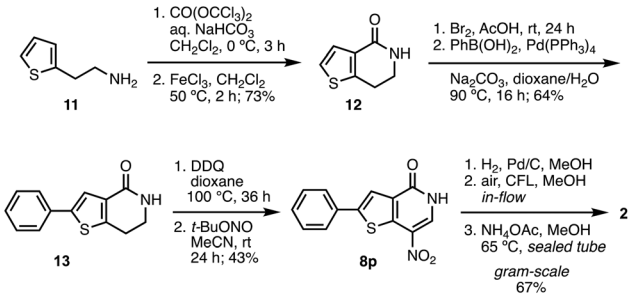


Scheme 2 Synthesis of thienopyridone scaffold enabling late-stage diversifications with aryl boronic acids.

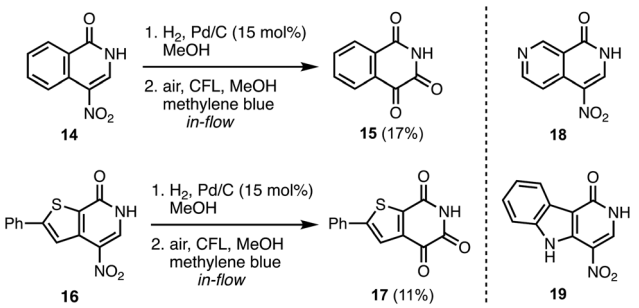


Scheme 3 Conversion of nitropyridones **8a–p** to 7-iminothieno[3,2-*c*]pyridine-4,6(5*H*,7*H*)-diones **9a–q** and attempted conversion of **8p** to acetimide **10**.

The lower yields in the telescoped conversion of nitroalkenes **8** to α-ketoimines **9** *vs.* the two-step process can be attributed to product loss in the separation of the imines from minor ketone side products during chromatography on SiO_2. Imine **9l** was exceptionally difficult to purify, resulting in a poor yield of 8%. Therefore, for scale-up purposes, it became necessary to develop a method to isolate the imine product from the ketone without chromatography. Recrystallization to enrich the imines was not successful. Amines can form adducts with $BF_3{\cdot}OEt_2$,[29] but attempts to generate an imine–boron complex proved similarly unsuccessful. An aza-Wittig reaction utilizing *P*,*P*,*P*-triphenylphosphazene,[30] or the Ti(O-i-Pr)$_4$/NH_3 protocol[14a] to convert the imine (**2**)/ketone (**3**) mixture exclusively to the imine also failed. *In situ* reaction with hexamethyldisilazene (HMDS) and CsF in DMF, or TBAF in THF,[31] provided the imine **2** in >95% selectivity over ketone **3**; however, chromatography was still needed to remove other trace impurities.



Scheme 4 Scale-up of optimized in-flow photooxygenation and telescoped conversion of **8p** to give **2**.



Scheme 5 Photooxygenation of alternative heterocyclic scaffolds. Compounds **18** and **19** failed to undergo the desired oxygenation after nitro group reduction.

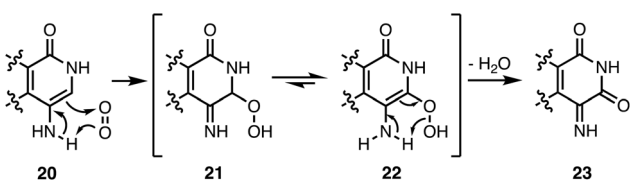
Gratifyingly, treatment of a mixture of **2** and **3** with NH_4OAc in MeOH at 65 °C resulted in quantitative formation of the imine. A homogenous solution was necessary to obtain full conversion to the imine. When the reaction was performed at reflux, decomposition was observed, likely due to evaporation of ammonia; therefore, a sealed reaction vessel was required. Interestingly, NH_4Cl did not react with the ketone, and NH_4OH and methanolic NH_3 caused decomposition.

With a modified purification protocol for the final products **9** established, the scalability of the photooxygenation was investigated next. The synthesis of **8p** was performed *via* an alternative route than previously reported,[20] with the goal being to facilitate compound throughput (Scheme 4). Commercially available thiophene **11** was treated with triphosgene to give the isocyanate, which was subjected without purification to stoichiometric ferric chloride in CH_2Cl_2 to give lactam **12** in 73% yield over the two steps. C-2 bromination of **12** in acetic acid and Suzuki–Miyaura coupling with phenylboronic acid proceeded in 64% overall yield to give **13**. The coupling product was dehydrogenated with DDQ and nitrated with *tert*-butyl nitrite to generate **8p**. The two-step nitro group reduction-photooxygenation was performed on a 500 mg and a 1 g scale, and the combined yields of **2** and **3** in these batches were 68% and 67%, respectively. Subsequently, imination of these reaction mixtures using NH_4OAc resulted in quantitative conversions, providing 322 mg and 634 mg, respectively, of iminothienopyridone **2** (Scheme 4).

We also investigated the photooxygenation of other fused pyridones (Scheme 5). Unlike the thienopyridones, these substrates were not fluorescent and required photosensitizers such as Methylene Blue to react with dioxygen. 4-Nitroisoquinoline **14** provided tricarbonyl product **15** in 17% yield, but attempts to generate the imine were unsuccessful, in agreement with previous reports.[23a] Interestingly, thieno[2,3-*c*]pyridin-7(6*H*)-one **16** behaved very differently compared to the regioisomeric thieno[3,2-*c*]pyridin-4(5*H*)-one **8**, despite their close structural similarity. Unlike **2**, the amine derived from **16** fluoresced with a pale-orange colour under a UV light, and was less reactive, as it required a photosensitizer for further conversion. The reaction profile was not clean, and the only product that could be isolated was tricarbonyl compound **17**. Isoquinolin-1(2*H*)-one **18** was unreactive in the photooxygenation after nitro group reduction, likely due to deactivation of the pyridone by the fused, electron-withdrawing pyridine ring, and only starting material was recovered. In contrast, when the very electron-rich enamine derived from the nitro group reduction of azacarbazole **19** was subjected to photooxygenation, only decomposition products were observed. These results suggest that the structure of the pyridone is critically important for the desired reactivity, and computational and spectroscopic studies to benchmark the electronic properties required for the desired reaction pathway are currently underway.

A proposed mechanism for the enamine oxygenation is shown in Scheme 6. Upon irradiation, singlet oxygen is generated, and may react with **20** *via* an ene-type reaction, in analogy to the conversion of alkenes.[32] In most of these cases, a hydroperoxide is the main product and is subsequently converted to an alcohol or carbonyl group.[1] During the course of this study, a hydroperoxide intermediate was not observed. Tautomerization of **21** to **22** should be favored due to aromatization, followed by elimination of water *via* a vinylogous Kornblum-DeLaMare rearrangement to give **23**.

The value of the photooxygenation of aminothienopyridinones is significantly enhanced by the utility of these scaffolds. Thienopyridones and their analogs are privileged structural motifs for the development of biologically active molecules.[33,34] While direct functionalizations on this heterocyclic core are rare, the biological properties of the chemotype can be significantly improved by such modifications.[35] The relatively simple thienopyridone **1** was shown to be a selective phosphatase inhibitor and to suppress tumor cell growth.[36] Our original entry into photooxygenation[20] was inspired by the



Scheme 6 Proposed mechanism for formation of 3-iminopyridine-2,6(1*H*,3*H*)-diones.

desire to diversify this scaffold by the introduction of additional carbonyl, amine, and imine substituents.

Advanced ovarian cancer and triple negative breast cancer respond poorly to existing drugs and, thus, demand new therapies. The protein tyrosine phosphatase PTP4A3 (Phosphatase of Regenerating Liver-3, PRL-3) is overexpressed in these cancer tissues.[19] PTP4A3 also promotes cancer cell migration and invasion, and is believed to be the most oncogenic of all tyrosine phosphatases.[21] Previously, we found that the iminothienopyridone, JMS-053 (**2**), is a specific, cell active small molecule PTP4A3 inhibitor superior to **1** with an *in vitro* IC_{50} for PTP4A3 of 30–40 nM.[20,21] However, the limited scope of the batch-photooxygenation method had hampered our efforts to investigate structure–activity relationships (SAR) for this scaffold. We were therefore interested to test the new analogs generated through in-flow photooxygenation in our biochemical potency assay (Table 2, Fig. S3†).

It is remarkable that 16 of the 19 newly investigated analogs generated by the flow-photooxygenation process retained the ability to inhibit the PTP4A3 phosphatase *in vitro* by at least 50% at a concentration <100 nM (IC_{50}). This finding reaffirms the robustness of this scaffold for further analog development. Three of the 19 characterized analogs, namely **9e**, **9g**, and **17** (Table 2, entries 7, 9, and 20), had IC_{50} values that were significantly poorer than **2**. The significant loss of potency in **9e** and **9g**, and the 3-fold reduced activity of **9o**, which contain bulky moieties at the *para*- and *meta*-positions of the phenyl substituent, suggests further modifications at these sites might not be productive. The >3-fold loss in potency for the inverted thiophene scaffold in **17** *vs*. the isoelectronic **3** also indicates that the arene fused to the pyridone is a critical factor for the inhibitor interaction with the protein. Some of the active halogenated analogs, *i.e.* **9b**, **9f**, and **9k**, which only show minor potency variations, may have fewer metabolic liabilities compared to **2** and are therefore worthy of further investigation. *N*-Alkyl analogs **9p** and **9q** are of particular note, as this is the first time we have seen a significant retention of phosphatase inhibition potency with modifications directly on the iminopyridone scaffold of **2**. Most of the analogs retained drug-like properties as calculated computationally (ESI, Table S3†).

We next performed exploratory docking studies with the iminopyridinedione scaffold using the A chain of PTP4A3 PDB entry 5TSR (Fig. 1).[19c] Based on the model, flexible loops play a significant role in shaping the inhibitor binding site. In the closed WPD loop (slate blue cartoon) conformation of the reduced form of the enzyme, the orientation of the P-Loop (Cys104 – Arg110; cyan cartoon) facilitates two strong hydrogen bonds with the carbonyl oxygens of inhibitor **2**, while at the same time providing sufficient steric space to accommodate small, hydrophobic substitutions on the inhibi-

Table 2 *In vitro* inhibition of PTP4A3 phosphatase activity[a]

Entry	Compound	IC_{50} (nM)	±SEM	*N*
1	JMS-053 (**2**)	34.7	2.5	6
2	**3**	49.5	2.9	6
3	**9a**	61.7	14.2	3
4	**9b**	41.9	1.2	3
5	**9c**	62.5	2.3	3
6	**9d**	71.1	2.5	3
7	**9e**	255.9	12.3	3
8	**9f**	39.1	1.3	3
9	**9g**	192.8	6.1	3
10	**9h**	65.7	4.1	6
11	**9i**	53.4	1.5	3
12	**9j**	47.7	2.7	3
13	**9k**	36.1	1.4	3
14	**9l**	53.4	1.5	3
15	**9m**	47.4	2.4	3
16	**9n**	67.7	3.0	3
17	**9o**	98.2	2.5	6
18	**9p**	48.9	12.0	6
19	**9q**	85.7	6.0	3
20	**17**	162.2	14.6	3

[a] Recombinant human PTP4A3 phosphatase was used and the enzymatic assay was performed as previously described,[20] except that it was fully automated using an Agilent Bravo Liquid Handling Platform to increase reproducibility. Results are the mean values of *N* independent assays, each comprising 10-point concentration curves conducted with six replicates (see ESI).

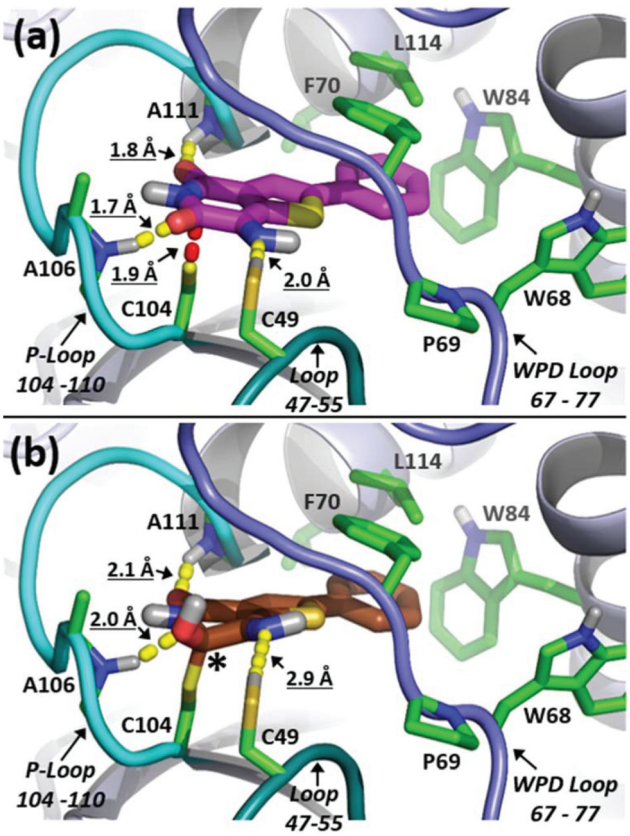


Fig. 1 Panel (a) noncovalent docking model of inhibitor **2**, shown with magenta carbons, in the closed WPD loop (slate blue cartoon) conformation of the reduced form of PTP4A3 (PDB entry 5TSR).[19c] Panel (b) covalent docking model of inhibitor **2**, shown with dark orange carbons, in the same binding pocket. Hydrogen bonds are shown in yellow dash, a potential covalent bond forming distance is highlighted in red dash (Panel (a)), and critical amino acid residues and peptide strands are labelled.

tor imide nitrogen (*e.g.*s., **9p** and **9q**). Moreover, the reorientation of the P-Loop also repositions the catalytically important Arg 110, such that it can no longer facilitate substrate binding.[19d] Concomitantly, the loop composed of residues Val47 – Lys55 (teal cartoon) orients such that Cys49 can engage in a hydrogen bond with the inhibitor's imine nitrogen. It is notable that the same three hydrogen bonds are predicted to occur for keto analog **3**. At the distal end of the compound, the phenyl ring binds in a pocket surrounded by strictly hydrophobic residues, as well as two Trp residues, one of which is located in the WPD loop (*i.e.*, Trp68). The properties of this pocket are in agreement with the SAR that was found for the new inhibitor series, *i.e.*, the size and location limitations of the substituents on the phenyl ring. For example, the model rationalizes the weaker potencies of rigid *para*-substituents on the phenyl ring. Based on the general binding mode shown in Fig. 1, the significantly reduced activity of the large, rigid 4-OPiv of **9e** is predicted to result from both steric and electrostatic incompatibilities with the binding pocket.

An interesting perspective of the docking model of inhibitor **2**, shown in Panel (a), lies in its extension to a covalent binding mode. Specifically, the more electrophilic imide carbonyl group in **2** is within covalent bond forming distance (Fig. 1, Panel (a), red dashes) to the enzyme's active site Cys104 residue (an asterisk in Fig. 1, Panel (b) highlights the covalent bond). Upon bond formation, the iminopyridinedione ring puckers, loosening the hydrogen bond framework. Therefore, it is possible that the tetrahedral intermediate would collapse and result in ring opening, converting the reversible covalent adduct into an irreversibly bound inhibitor. Related binding mechanisms have recently been suggested for cysteine protease and serine hydrolase inhibitors.[37] A covalent inhibition hypothesis may also aid in explaining the consistently potent IC_{50} values of several substituent variants of the iminopyridinedione and pyridinetrione chemotype. Furthermore, a covalent Cys104 thiophosphate intermediate that is rate-limiting for the turnover of the natural substrate is also postulated for the catalytic cycle of PTP4A;[19] therefore, these inhibitors could potentially act as pseudosubstrates of the phosphatase.

Further molecular modeling, biochemical, and *in vivo* evaluations of these new analogues and their mechanism of action are currently underway.

Conclusions

We have optimized the synthesis of 7-iminothieno[3,2-*c*]pyridine-4,6(5*H*,7*H*)-diones with photo-flow techniques, and streamlined the conversion of ketone side products to imines to allow for both the preparation of analogs for SAR purposes, as well as the generation of gram-scale material for *in vivo* biological evaluations. Full conversions were achieved for all derivatives, and moderate to satisfactory 3-step yields could be obtained when the workup of the flow reaction was coupled with a modified purification protocol. This process resolves the limitations in scope and scale-up associated with the previous light-mediated batch reaction.[20] Accordingly, we generated a series of new analogs to elucidate SAR trends, and identified several new PTP4A3 phosphatase inhibitors with low nanomolar IC_{50} values, thus significantly broadening the utility of this new heterocycle for pharmacological investigations. We also generated a binding model and explored a potential covalent active site cysteine interaction mode. Our results suggest that the iminothienopyridone chemotype may be valuable for the development of a first-in-class PTP4A3 inhibitor directed against breast and ovarian cancer.

Experimental section

General methods

Unless stated otherwise, all reactions were performed under an atmosphere of N_2 that was passed through a column (10 × 2 cm) of Drierite®. Air was used for all in-flow photooxygenation reactions, whereas the batch photooyxygenation and the nitration with *t*-BuONO used oxygen in a balloon from an O_2 tank. Prior to use, THF was freshly distilled over sodium/benzophenone, and CH_2Cl_2 was freshly distilled over CaH_2. Et_3N and i-$PrNEt_2$ were distilled over CaH_2 and stored over KOH. All glassware and stir bars were dried in an oven for 3 h prior to use. When necessary, degassed solvents were prepared by sparging with N_2 for 1 h. Reactions were monitored by TLC analysis (pre-coated silica gel 60 F_{254}) and spots were visualized (UV lamp 254 nm and 395 nm). Purifications by chromatography were performed on SiO_2. $^1H/^{13}C$ NMR spectra were recorded on Bruker Avance 300/75 MHz, Bruker Avance 400/100 MHz or Bruker Avance 500/125 MHz instruments. High resolution mass spectra were obtained on a Micromass UK Limited, Q-TOF Ultima API or a Thermo Scientific Exactive Orbitrap LC-MS. Chemical shifts were reported in parts per million (ppm) with the residual solvent peak ($CDCl_3$: 7.26 ppm for ^1H, 77.16 ppm for ^{13}C; DMSO-d_6: 2.50 ppm for ^1H, 39.52 ppm for ^{13}C) used as the internal standard. Chemical shifts were tabulated as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublet, dt = doublet of triplet, ddd = doublet of doublet of doublet, m = multiplet, brs = broad singlet), coupling constant(s), and integration. IR spectra were obtained using neat samples on a PerkinElmer 100 IR-ATR spectrometer. Melting points were obtained using a Mel-Temp instrument and are uncorrected. A variable peristaltic pump (VWR Model PP3300) was used for the photooxygenation reactions. 30 cm of silicone tubing (1/16″ ID, 3/16″ OD, 1/16″ wall thickness) in the pump were connected to 10.5 m of clear FEB tubing (4 mm ID, 5 mm OD, 0.5 mm wall thickness) *via* an adapter. The light source was a white household 18 W CFL or a 40 W-4U BestCircle (AC85-265V) LED for the scale-up reactions. For the white CFL and white LED lights, the external temperature of the capillary tubing did not exceed 42 °C.

General procedure A: photo-flow oxygenation of thienopyridones

7-Iminothieno[3,2-*c*]pyridine-4,6(5*H*,7*H*)-dione (2) and 2-phenylthieno[3,2-*c*]pyridine-4,6,7(5*H*)-trione (3). The photo-flow reactor was flushed with MeOH (50 mL). Once the solvent front entered the receiving flask, a solution of 7-amino-2-phenylthieno[3,2-*c*]pyridin-4(5*H*)-one (**1**, 10 mg)[20] in MeOH (30 mL) was passed through the tubing at a rate of 1.9 mL min^{-1} using the peristaltic pump (5 rpm). Subsequently, the tubing was flushed with additional MeOH (40 mL). The reaction mixture was concentrated to give a mixture of **2** and **3** (10 mg) and purified by chromatography on SiO_2 (EtOAc : hexanes, 7 : 3, followed by MeOH : EtOAc, 1 : 9) to give **2** (9.1 mg, 91%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.86 (s, 1H), 11.59 (s, 1H), 7.98 (s, 1H), 7.87 (dd, J = 8.1, 1.5 Hz, 2H), 7.53–7.45 (m, 3H). Spectral data were consistent with literature properties.[20]

2-Phenylthieno[3,2-*c*]pyridine-4,6,7(5*H*)-trione (3). To a solution of a mixture of **2** and **3** (6 : 1 ratio by ^{1}H NMR analysis, 0.040 g, 0.16 mmol), prepared according to General Protocol A in THF : H_2O (1 : 1, 10 mL) was added H_2SO_4 (0.083 mL, 1.6 mmol). The reaction mixture was allowed to stir at room temperature for 24 h, cooled in an ice bath and filtered. The precipitate was washed with ice-cold H_2O and dissolved in THF. The THF solution was concentrated and dried under high vacuum at 45 °C overnight to afford a brown solid that was purified by chromatography on SiO_2 (EtOAc : hexanes, 7 : 3, followed by MeOH : EtOAc, 1 : 9) to give **3** (0.031 g, 0.120 mmol, 77%) as a bright yellow solid: Mp >250 °C; IR (ATR) ν_{max} 3195, 3093, 2921, 2849, 1726, 1700, 1667, 1450, 1417, 1333, 1272 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.91 (brs, 1H), 8.09 (d, J = 3.5 Hz, 1H), 7.94 (dd, J = 8, 2 Hz, 2H), 7.54–7.50 (m, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 168.7, 159.6, 158.0, 154.4, 141.0, 139.7, 131.5, 130.4, 129.5, 126.5, 123.1; HRMS (ESI^+) m/z calcd for $C_{13}H_8O_3NS$ (M + H) 258.0219, found 258.0219.

(*E*)-3-(5-Bromothiophen-2-yl)acrylic acid (5). To a solution of 5-bromothiophene-2-carboxaldehyde (**4**) (10.15 g, 51.53 mmol) in pyridine (128 mL) were added malonic acid (16.25 g, 154.6 mmol) and piperidine (2.57 mL, 25.76 mmol). The reaction mixture was heated at reflux for 3 h, cooled to room temperature and concentrated to give a dark oil. The oil was diluted with H_2O (30 mL), at which time a solid precipitated. The suspension was then acidified to pH 2 with 6 M HCl. The precipitate was filtered and washed with H_2O (3 × 15 mL). The filter cake was dissolved in EtOAc, dried ($MgSO_4$), filtered, and concentrated to give **5** (11.29 g, 94%) as a tan solid: ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.41 (brs, 1H), 7.66 (d, J = 15.9 Hz, 1H), 7.35 (d, J = 3.9 Hz, 1H), 7.27 (d, J = 3.9 Hz, 1H), 6.15 (d, J = 15.9 Hz, 1H). Spectral data are consistent with literature properties.[38]

2-Bromothieno[3,2-*c*]pyridin-4(5*H*)-one (6). Et_3N (6.02 mL, 42.9 mmol) was added to a solution of (*E*)-3-(5-bromothiophen-2-yl)acrylic acid (**5**, 5.00 g, 21.4 mmol) in acetone (55 mL) at 0 °C (ice-bath). Ethyl chloroformate (6.25 mL, 64.3 mmol) was then added, and the reaction mixture was stirred at 0 °C for 1.5 h. A solution of NaN_3 (2.09 g, 32.1 mmol) in H_2O (16 mL) was added to this reaction mixture slowly at 0 °C (ice-bath). The mixture became homogeneous, and then a solid began to precipitate. Stirring was continued for 15 min. The reaction mixture was poured into ice-chilled H_2O (30 mL) and extracted with EtOAc (3 × 30 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated to give crude acyl azide as a tan solid that was used for the next step without further purification.

A 3-neck flask fitted with a stopper, addition funnel, and condenser was charged with Bu_3N (6.63 mL, 27.8 mmol) and Ph_2O (20 mL). The solution was heated to 240 °C. The addition funnel was charged with a solution of the crude acyl azide (5.53 g, 21.4 mmol) in CH_2Cl_2 (50 mL). The acyl azide solution was added to the hot reaction mixture over a period of *ca.* 40 min, allowing the CH_2Cl_2 to boil off. The mixture was stirred at 240 °C for another 15 min, cooled to rt, and hexanes (20 mL) was added, at which point a solid began to precipitate. The hexane layer was decanted, and the remaining residue was suspended in EtOAc (15 mL). A tan solid precipitated out of solution and was filtered to give **6** (2.56 g, 52%): Mp >250 °C; IR (ATR) ν_{max} 2809, 1637, 1607, 1513, 1472, 1274, 1222, 1144, 994, 928, 803, 762, 692 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.54 (brs, 1H), 7.54 (d, J = 0.4 Hz, 1H), 7.28–7.25 (m, 1H), 6.81 (d, J = 6.8 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 157.5, 149.7, 130.7, 130.4, 126.8, 111.4, 100.5; HRMS (ESI^+) m/z calcd for C_7H_5ONSBr (M + H) 229.9270, found 229.9270.

2-Bromo-7-nitrothieno[3,2-*c*]pyridin-4(5*H*)-one (7). A solution of 2-bromothieno[3,2-*c*]pyridin-4(5*H*)-one (**6**, 2.56 g, 11.1 mmol) in MeCN (275 mL) was heated to 65 °C in a 500 mL round-bottom flask fitted with a condenser under an O_2 atmosphere (balloon, 1 atm). After addition of *t*-BuONO (5.88 mL, 44.5 mmol), the reaction mixture was stirred for 3 h and turned from a brown heterogeneous mixture to a red homogeneous solution. The solution was cooled to room temperature and concentrated. The resulting yellow solid was suspended in MeCN (10 mL) and placed in a −20 °C freezer for 30 min. The precipitate was filtered to provide **7** as a yellow solid (2.21 g, 72%): Mp >250 °C; IR (ATR) ν_{max} 2807, 1648, 1617, 1508, 1480, 1336, 1243, 1127, 1038, 890, 764, 706 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.86 (brs, 1H), 8.75 (s, 1H), 7.71 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 156.9, 140.6, 135.9, 128.9, 126.9, 126.8, 115.9; HRMS (ESI^+) m/z calcd for $C_7H_4O_3N_2SBr$ (M + H) 274.9119, found 274.9121.

General procedure B: Suzuki coupling of 2-bromo-7-nitrothieno[3,2-*c*]pyridin-4(5*H*)-one (7)

A 25 mL round-bottom flask was charged inside a glove box with $Pd(PPh_3)_4$ (5.0 mol%). The flask was removed from the glove box and sequentially charged with 2-bromo-7-nitrothieno[3,2-*c*]pyridin-4(5*H*)-one (**7**, 1.0 equiv.), aryl boronic acid (1.1 equiv.), and Na_2CO_3 (2.3 equiv.). The flask was then purged under a stream of N_2, diluted with deoxygenated dioxane and H_2O (2 : 1, 0.1 M), fitted with a reflux condenser, and heated to 90 °C for 16 h. The reaction mixture was cooled to room temp-

erature and concentrated to give a red oil that was diluted with H_2O (10 mL) and treated with 1 M $KHSO_4$ (5 mL). The red oil changed to an orange semi-solid suspension, and the mixture was diluted with EtOAc (40 mL). The layers were separated and the aqueous phase was extracted with EtOAc (4 × 20 mL). The combined organic extracts were washed with saturated aqueous NaCl, dried ($MgSO_4$), filtered, and concentrated to give an orange solid that was suspended in MeOH (2 mL), sonicated, and heated to the boiling point. The suspension was cooled to room temperature, filtered, and the solids were washed with ice-cold MeOH (1 mL) to give the coupling product. If residual $Ph_3P(O)$ was present, the MeOH trituration protocol was repeated.

2-(3-Fluorophenyl)-7-nitrothieno[3,2-*c*]pyridin-4(5*H*)-one (8f). 2-Bromo-7-nitrothieno[3,2-*c*]pyridin-4(5*H*)-one (7, 0.075 g, 0.272 mmol) was converted according to general procedure B to give **8f** (0.040 g, 50%) as a yellow solid: Mp >250 °C; IR (ATR) ν_{max} 2798, 1653, 1611, 1502, 1476, 1340, 1263, 1241, 840, 765, 711, 673 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 12.79 (brs, 1H), 8.76 (s, 1H), 8.09 (s, 1H), 7.77 (d, J = 10.4 Hz, 1H), 6.67 (d, J = 8.0 Hz, 1H), 7.51 (q, J = 6.4 Hz, 1H), 7.26–7.21 (m, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 162.5 (d, J_{C-F} = 243.7 Hz), 157.8, 143.0, 138.8, 135.6, 134.4 (d, J_{C-F} = 8.7 Hz), 131.2 (d, J_{C-F} = 8.7 Hz), 129.7, 127.1, 122.1 (d, J_{C-F} = 2.5 Hz), 122.1, 115.4 (d, J_{C-F} = 21.2 Hz), 112.6 (d, J_{C-F} = 22.5 Hz); ^{19}F NMR (470 MHz, DMSO-d_6) δ −111.9; HRMS (ESI^+) m/z calcd for $C_{13}H_8O_3N_2FS$ (M + H) 291.0234, found 291.0232.

2-(3-Chlorophenyl)-7-nitrothieno[3,2-*c*]pyridin-4(5*H*)-one (8h). 2-Bromo-7-nitrothieno[3,2-*c*]pyridin-4(5*H*)-one (7, 0.200 g, 0.727 mmol) was converted according to general procedure B to give **8h** (0.161 g, 72%) as a yellow solid: Mp >250 °C; IR (ATR) ν_{max} 2790, 2683, 1654, 1614, 1593, 1499, 1475, 1335, 1247, 1232, 1140, 1041, 994, 763, 71 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 12.77 (brs, 1H), 8.76 (s, 1H), 8.10 (s, 1H), 7.96 (s, 1H), 7.80 (d, J = 6.0 Hz, 1H), 7.52–7.45 (m, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 157.8, 142.7, 138.8, 135.7, 134.3, 134.1, 131.0, 129.7, 128.5, 127.1, 125.5, 124.6, 121.2; HRMS (ESI^+) m/z calcd for $C_{13}H_8O_3N_2ClS$ (M + H) 306.9939, found 306.9937.

7-Nitro-2-(*m*-tolyl)thieno[3,2-*c*]pyridin-4(5*H*)-one (8i). 2-Bromo-7-nitrothieno[3,2-*c*]pyridin-4(5*H*)-one (7, 0.150 g, 0.545 mmol) was converted according to general procedure B to give **8i** (0.092 g, 59%) as a yellow solid: Mp >250 °C; IR (ATR) ν_{max} 2807, 1648, 1619, 1598, 1502, 1476, 1336, 1236, 1135, 1040, 801, 766, 712 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 12.72 (brs, 1H), 8.72 (s, 1H), 7.94 (s, 1H), 7.67 (s, 1H), 7.63 (d, J = 6.4 Hz, 1H), 7.36 (t, J = 6.4 Hz, 1H), 7.22 (d, J = 6.0 Hz, 1H), 2.38 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 157.8, 144.8, 138.7, 138.2, 135.2, 132.1, 129.8, 129.5, 129.1, 127.2, 126.4, 123.0, 119.6, 20.8; HRMS (ESI^+) m/z calcd for $C_{14}H_{11}O_3N_2S$ (M + H) 287.0485, found 287.0483.

2-(2-Chlorophenyl)-7-nitrothieno[3,2-*c*]pyridin-4(5*H*)-one (8k). 2-Bromo-7-nitrothieno[3,2-*c*]pyridin-4(5*H*)-one (7, 0.200 g, 0.727 mmol) was converted according to general procedure B to give **8k** (0.122 g, 55%) as a yellow solid: Mp >250 °C; IR (ATR) ν_{max} 2852, 1654, 1611, 1500, 1467, 1335, 1242, 1038, 872, 822, 747, 707 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 12.82 (brs, 1H), 8.79 (s, 1H), 7.84 (s, 1H), 7.79–7.75 (m, 1H), 7.67–7.64 (m, 1H), 7.49–7.46 (m, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 158.2, 140.7, 139.6, 136.1, 131.7, 131.1, 130.9, 130.6, 130.4, 128.6, 128.0, 127.1, 124.4; HRMS (ESI^+) m/z calcd for $C_{13}H_8O_3N_2SCl$ (M + H) 306.9939, found 306.9938.

2-(2-Fluorophenyl)-7-nitrothieno[3,2-*c*]pyridin-4(5*H*)-one (8l). 2-Bromo-7-nitrothieno[3,2-*c*]pyridin-4(5*H*)-one (7, 0.200 g, 0.727 mmol) was converted according to general procedure B to give **8l** (0.140 g, 66%) as a yellow solid: Mp >250 °C; IR (ATR) ν_{max} 2823, 1647, 1609, 1500, 1486, 1333, 1245, 1227, 1137, 757, 711 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 12.81 (brs, 1H), 8.77 (s, 1H), 8.01–7.96 (m, 2H with an apparent s at 8.00 ppm), 7.48–7.38 (m, 2H), 7.34 (t, J = 8.0 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 160.1 (d, J_{C-F} = 247.5 Hz), 158.0, 147.6, 139.2 (d, J_{C-F} = 6.0 Hz), 137.5 (d, J_{C-F} = 6.0 Hz), 135.7, 130.7 (d, J_{C-F} = 9.0 Hz), 129.0, 127.1, 125.4 (d, J_{C-F} = 3.0 Hz), 122.7 (d, J_{C-F} = 5.2 Hz), 119.8 (d, J_{C-F} = 12.7 Hz), 116.5 (d, J_{C-F} = 22.5 Hz); ^{19}F NMR (376 MHz, DMSO-d_6) δ −113.2; HRMS (ESI^+) m/z calcd for $C_{13}H_8O_3N_2SF$ (M + H) 291.0234, found 291.0233.

2-(4-Chloro-3-fluorophenyl)-7-nitrothieno[3,2-*c*]pyridin-4(5*H*)-one (8m). 2-Bromo-7-nitrothieno[3,2-*c*]pyridin-4(5*H*)-one (7, 0.200 g, 0.727 mmol) was converted according to general procedure B to give **8m** (0.142 g, 60%) as a yellow solid: Mp >250 °C; IR (ATR) ν_{max} 2838, 1655, 1607, 1477, 1335, 1238, 1187, 1138, 1040, 837, 808, 763, 703 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 12.81 (brs, 1H), 8.78 (s, 1H), 8.14 (s, 1H), 8.02 (dd, J = 10.4 Hz, 1.2 Hz, 1H), 7.72–7.64 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 158.1, 157.6 (d, J_{C-F} = 246.0 Hz), 141.9, 139.1, 136.2, 133.4 (d, J_{C-F} = 8.0 Hz), 131.4, 129.7, 127.1, 123.1 (d, J_{C-F} = 3.0 Hz), 121.9, 119.6 (d, J_{C-F} = 18.0 Hz), 114.2 (d, J_{C-F} = 23.0 Hz); ^{19}F NMR (376 MHz, DMSO-d_6) δ −115.0; HRMS (ESI^+) m/z calcd for $C_{13}H_7O_3N_2SFCl$ (M + H) 324.9844, found 324.9844.

2-(3-Chloro-4-fluorophenyl)-7-nitrothieno[3,2-*c*]pyridin-4(5*H*)-one (8n). 2-Bromo-7-nitrothieno[3,2-*c*]pyridin-4(5*H*)-one (7, 0.200 g, 0.727 mmol) was converted according to general procedure B to give **8n** (0.127 g, 54%) as a yellow solid: Mp >250 °C; IR (ATR) ν_{max} 2817, 1655, 1610, 1484, 1336, 1260, 1227, 1140, 1039, 895, 866, 818, 764, 712, 692 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 12.77 (brs, 1H), 8.74 (s, 1H), 8.12 (dd, J = 7.0 Hz, 2.1 Hz, 1H), 8.06 (s, 1H), 7.86–7.81 (m, 1H), 7.49 (t, J = 8.7 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 157.9, 157.2 (d, J_{C-F} = 248.0 Hz), 141.9, 138.9, 135.8, 130.2, 129.7, 127.9, 127.1, 126.7 (d, J_{C-F} = 7.0 Hz), 121.4, 120.6 (d, J_{C-F} = 18.0 Hz), 117.7 (d, J_{C-F} = 21.0 Hz); ^{19}F NMR (376 MHz, DMSO-d_6) δ −116.0; HRMS (ESI^+) m/z calcd for $C_{13}H_7O_3N_2SFCl$ (M + H) 324.9844, found 324.9843.

4-(2-(4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy) ethyl)morpholine (24). To a solution of 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (0.408 g, 1.85 mmol) in DMF (5 mL) were added 4-(2-chloroethyl)morpholine hydrochloride (0.383 g, 2.03 mmol), Cs_2CO_3 (1.52 g, 4.63 mmol), and KI (0.015 g, 0.092 mmol). The reaction mixture was heated to 65 °C for 12 h, cooled to room temperature, diluted with EtOAc (100 mL), washed with saturated aqueous $NaHCO_3$ (30 mL) and saturated aqueous NaCl (30 mL), dried ($MgSO_4$),

filtered, and concentrated to give a brown solid. Purification by chromatography on SiO_2 (MeOH : CH_2Cl_2, 1 : 9) provided **24** (0.519 g, 84%) as an off-white powdery solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, J = 8.4 Hz, 2H), 6.88 (d, J = 8.8 Hz, 2H), 4.13 (t, J = 5.6 Hz, 2H), 3.72 (t, J = 4.8 Hz, 4H), 2.80 (t, J = 5.6 Hz, 2H), 2.57 (t, J = 4.8 Hz, 4H), 1.32 (s, 12H). Spectral data are consistent with literature properties.[39]

2-(4-(2-Morpholinoethoxy)phenyl-7-nitrothieno[3,2-*c*]pyrdin-4(5*H*)-one (8o). 2-Bromo-7-nitrothieno[3,2-*c*]pyridin-4(5*H*)-one (7, 0.250 g, 0.908 mmol) was treated according to general procedure B to give **8o** (0.219 g, 60%) as a yellow solid: Mp >226 °C (dec.); IR (ATR) ν_{max} 2804, 1654, 1611, 1491, 1338, 1248, 1112, 1039, 899, 821, 762, 712 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.70 (brs, 1H), 8.71 (s, 1H), 7.83 (s, 1H), 7.76 (d, J = 8.8 Hz, 2H), 7.04 (d, J = 8.8 Hz, 2H), 4.15 (t, J = 5.6 Hz, 2H), 3.59 (t, J = 4.4 Hz, 4H), 2.72 (t, J = 5.6 Hz, 2H), 2.51–2.46 (m, 4H obstructed by DMSO signal); ^{13}C NMR (75 MHz, DMSO-d_6) δ 159.0, 158.0, 144.8, 137.6, 135.1, 130.0, 127.4, 127.3, 124.9, 118.4, 115.3, 66.1, 65.5, 56.9, 53.5; HRMS (ESI$^+$) m/z calcd for $C_{19}H_{20}N_3O_5S$ (M + H) 402.1118, found 402.1116.

General procedure C: Suzuki coupling of 2-bromo-6,7-dihydrothieno[3,2-*c*]pyridin-4(5*H*)-one

A 100 mL round-bottom flask was charged with $Pd(PPh_3)_4$ (5.0 mol%) inside a glove box. The flask was removed from the glove box and sequentially charged with 2-bromo-6,7-dihydrothieno[3,2-*c*]pyridin-4(5*H*)-one (**41**, 1.0 equiv.), aryl boronic acid (1.1 equiv.), and Na_2CO_3 (2.3 equiv.). The flask was purged under a stream of N_2, diluted with deoxygenated dioxane and H_2O (2 : 1, 0.1 M), fitted with a reflux condenser, and heated to 90 °C for 12 h. The resulting dark mixture was allowed to cool to room temperature, diluted with H_2O, and cooled in an ice-bath. The precipitate was filtered, washed with H_2O, dissolved in CH_2Cl_2, dried ($MgSO_4$), and concentrated to give a light coloured solid. Typically, a *ca.* 10 mg aliquot of the crude material was purified by chromatography on SiO_2 (EtOAc) to characterize the Suzuki products. In some cases, residual $Ph_3P(O)$ was difficult to remove prior to the next step (DDQ oxidation). Therefore, the entire batch of crude Suzuki material was purified by chromatography on SiO_2. In these cases, the Suzuki coupling and DDQ oxidation are reported with separate yields.

General procedure D: DDQ oxidation

The Suzuki coupling product (crude or purified) was suspended in dioxane (0.1 M) and treated with DDQ (2.0 equiv.). The flask was fitted with a reflux condenser and heated to 100 °C for 24 h, allowed to cool to room temperature, and concentrated to give a dark solid. The solid was dissolved in EtOAc (500 mL), and the orange solution was then washed with saturated aqueous $NaHCO_3$ (4 × 60 mL) and saturated aqueous NaCl, dried ($MgSO_4$), filtered, and concentrated to give a dark solid. The crude residue was purified as a solid by chromatography on SiO_2 (MeOH : CH_2Cl_2, 1 : 9), or suspended in CH_2Cl_2 (5 mL), sonicated for 2 min, and heated to reflux. Upon cooling to room temperature, the desired pyridone was obtained as a solid.

2-(*p*-Tolyl)-6,7-dihydrothieno[3,2-*c*]pyridin-4(5*H*)-one (25). According to procedure C, chromatography on SiO_2 (EtOAc) of an aliquot of the Suzuki reaction mixture provided **25** as a white solid: Mp 210–212 °C; IR (ATR) ν_{max} 2833, 1650, 1480, 1299, 1092, 816, 763, 694 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57 (s, 1H), 7.45 (d, J = 8.5 Hz, 2H), 7.18 (d, J = 7.5 Hz, 2H), 5.76 (brs, 1H), 3.66 (td, J = 6.5 Hz, 2.5 Hz, 2H), 3.06 (t, J = 7.0 Hz, 2H), 2.36 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.6, 145.0, 142.4, 137.9, 132.9, 130.8, 129.7, 125.7, 120.8, 41.3, 24.5, 21.2; HRMS (ESI$^+$) m/z calcd for $C_{14}H_{14}ONS$ (M + H) 244.0791, found 244.0789.

2-(4-Chlorophenyl)-6,7-dihydrothieno[3,2-*c*]pyridin-4(5*H*)-one (26). According to general procedure C, chromatography on SiO_2 (EtOAc) of an aliquot of the crude Suzuki coupling provided **26** as a white solid: Mp 219–221 °C; IR (ATR) ν_{max} 2955, 1652, 1482, 1296, 1094, 822, 775 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.59 (s, 1H), 7.49 (d, J = 11.0 Hz, 2H), 7.34 (d, J = 11.5 Hz, 2H), 5.67 (brs, 1H), 3.67 (td, J = 6.8, 3.0 Hz, 2H), 3.07 (t, J = 7.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.6, 145.9, 141.1, 134.0, 133.4, 132.4, 129.4, 127.1, 122.0, 41.5, 24.7; HRMS (ESI$^+$) m/z calcd for $C_{13}H_{11}ONSCl$ (M + H) 264.0244, found 264.0244.

2-(4-(Trifluoromethyl)phenyl)-6,7-dihydrothieno[3,2-*c*]pyridin-4(5*H*)-one (27). According to general procedure C, the product obtained from 2-bromo-6,7-dihydrothieno[3,2-*c*]pyridin-4(5*H*)-one (**41**, 1.00 g, 4.30 mmol) was purified by chromatography on SiO_2 (EtOAc) to provide **27** (1.03 g, 80%) as an off-white solid: Mp 227–229 °C; IR (ATR) ν_{max} 3192, 3072, 1653, 1485, 1319, 1163, 1108, 1065, 847, 780 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71 (s, 1H), 7.68–7.61 (m, 4H), 5.74 (brs, 1H), 3.68 (dt, J = 6.8 Hz, 2.8 Hz, 2H), 3.09 (t, J = 6.8 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.3, 146.6, 140.4, 137.0, 133.3, 129.6 (q, J_{C-F} = 31.2 Hz), 126.0 (q, J_{C-F} = 3.7 Hz), 125.1, 124.0 (q, J_{C-F} = 270 Hz), 122.8, 41.2, 24.6; ^{19}F NMR (470 MHz, $CDCl_3$) δ −62.6; HRMS (ESI$^+$) m/z calcd for $C_{14}H_{11}F_3NOS$ (M + H) 298.0508, found 298.0503.

2-(4-Fluorophenyl)-6,7-dihydrothieno[3,2-*c*]pyridin-4(5*H*)-one (28). According to general procedure C, the product obtained from 2-bromo-6,7-dihydrothieno[3,2-*c*]pyridin-4(5*H*)-one (**41**, 0.750 g, 3.23 mmol) was purified by chromatography on SiO_2 (EtOAc) to give **28** (0.673 g, 83%) as a light-brown solid: Mp 230–232 °C; IR (ATR) ν_{max} 3211, 1643, 1474, 1134, 1304, 1225, 1162, 823, 780 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54 (s, 1H), 7.54–7.50 m (2H), 7.09–7.05 (m, 2H), 5.69 (brs, 1H), 3.66 (dt, J = 6.5, 2.5 Hz, 2H), 3.07 (t, J = 6.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.4, 162.5 (d, J_{C-F} = 246.2 Hz), 145.4, 141.1, 133.1, 129.8 (d, J_{C-F} = 2.5 Hz), 127.7 (d, J_{C-F} = 7.5 Hz), 121.3, 116.0 (d, J_{C-F} = 21.2 Hz), 41.3, 24.5; ^{19}F NMR (470 MHz, $CDCl_3$) δ −113.8; HRMS (ESI$^+$) m/z calcd for $C_{13}H_{11}FNOS$ (M + H) 248.0540, found 248.0444.

2-(4-Hydroxyphenyl)-6,7-dihydrothieno[3,2-*c*]pyridin-4(5*H*)-one (29). According to general procedure C, the product obtained from 2-bromo-6,7-dihydrothieno[3,2-*c*]pyridin-4(5*H*)-one (**41**, 1.06 g, 4.56 mmol) was purified by chromatography on SiO_2

(MeOH : CH_2Cl_2, 1 : 9) to give **29** (1.02 g, 91%) as a light-orange solid: Mp >250 °C; IR (ATR) ν_{max} 3032, 1638, 1607, 1545, 1483, 1421, 1270, 1242, 1221, 1169, 1102, 983, 826, 771 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 9.68 (s, 1H), 7.58 (brs, 1H), 7.44 (d, J = 8.4 Hz, 2H), 7.36 (s, 1H), 6.79 (d, J = 8.4 Hz, 2H), 3.44 (td, J = 7.2, 2.4 Hz, 2H), 2.97 (t, J = 6.8 Hz, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 162.1, 157.3, 143.9, 141.3, 133.3, 126.7, 124.2, 119.1, 115.8, 40.2, 23.7; HRMS (ESI^+) m/z calcd for $C_{13}H_{12}O_2NS$ (M + H) 246.0583, found 246.0581.

4-(4-Oxo-4,5,6,7-tetrahydrothieno[3,2-*c*]pyridin-2-yl)phenyl pivalate (30). A solution of 2-(4-hydroxyphenyl)-6,7-dihydrothieno [3,2-*c*]pyridin-4(5*H*)-one (**29**, 1.03 g, 4.19 mmol) in THF (80 mL) was treated with Et_3N (1.18 mL, 8.39 mmol), followed by a solution of Piv_2O (1.57 g, 8.39 mmol) in THF (0.5 mL) and DMAP (0.076 g, 0.629 mmol). The flask was fitted with a reflux condenser and heated to 70 °C for 18 h. The reaction mixture was diluted with EtOAc (200 mL), washed with H_2O (50 mL), saturated aqueous NaCl (50 mL), dried ($MgSO_4$), filtered, and concentrated to give a tan solid. Purification by chromatography on SiO_2 (dry load, MeOH : CH_2Cl_2, 1 : 11) provided **30** (1.35 g, 97%) as a tan solid: Mp 233–234 °C; IR (ATR) ν_{max} 3203, 3070, 2966, 1752, 1655, 1475, 1200, 1162, 1106, 892, 842, 792 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.57 (s, 1H), 7.56 (d, J = 8.8 Hz, 2H), 7.07 (d, J = 8.8 Hz, 2H), 5.72 (brs, 1H), 3.66 (td, J = 6.8, 2.8 Hz, 2H), 3.07 (t, J = 6.8 Hz, 2H), 1.35 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.2, 163.7, 151.1, 145.7, 141.6, 133.3, 131.4, 127.0, 122.3, 121.7, 41.5, 39.4, 27.4, 24.7; HRMS (ESI^+) m/z calcd for $C_{18}H_{20}O_3NS$ (M + H) 330.1158, found 330.1158.

2-(3-(Trifluoromethyl)phenyl)-6,7-dihydrothieno[3,2-*c*]pyridin-4(5*H*)-one (31). According to general procedure C, chromatography on SiO_2 (EtOAc) of an aliquot of the crude Suzuki coupling product provided **31** as a white solid: Mp 149–151 °C; IR (ATR) ν_{max} 3191, 3067, 1650, 1482, 1327, 1121, 791, 690 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.80 (s, 1H), 7.73 (d, J = 7.6 Hz, 1H), 7.69 (s, 1H), 7.55–7.49 (m, 2H), 5.57 (brs, 1H), 3.68 (td, J = 6.4, 2.8 Hz, 2H), 3.10 (t, J = 6.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.7, 146.5, 140.5, 134.5, 133.3, 131.6 (q, J_{C-F} = 32.0 Hz), 129.6, 128.9, 126.7 (q, J_{C-F} = 276.0 Hz), 124.5 (q, J_{C-F} = 4.0 Hz), 122.6, 122.5 (q, J_{C-F} = 4.0 Hz), 41.3, 24.6; ^{19}F NMR (376 MHz, $CDCl_3$) δ −62.8; HRMS (ESI^+) m/z calcd for $C_{14}H_{11}ONSF_3$ (M + H) 298.0508, found 298.0507.

2-(*p*-Tolyl)thieno[3,2-*c*]pyridin-4(5*H*)-one (32). According to general procedures C and D, the product obtained from 2-bromo-6,7-dihydrothieno[3,2-*c*]pyridin-4(5*H*)-one (**41**, 0.625 g, 2.69 mmol) was precipitated from CH_2Cl_2 to provide **32** (0.344 g, 53% over two steps) as a tan solid: Mp 249–251 °C; IR (ATR) ν_{max} 2811, 1639, 1607, 1507, 1120, 1148, 809, 766, 746, 698 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 11.44 (brs, 1H), 7.78 (s, 1H), 7.63 (d, J = 8.0 Hz, 2H), 7.26–7.25 (m, 3H), 6.83 (d, J = 6.8 Hz, 1H), 2.33 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 157.9, 146.6, 140.8, 137.2, 131.0, 129.6, 129.2, 129.1, 125.0, 118.6, 100.2, 20.1; HRMS (ESI^+) m/z calcd for $C_{14}H_{12}NOS$ (M + H) 242.0634, found 242.0511.

2-(4-Chlorophenyl)thieno[3,2-*c*]pyridin-4(5*H*)-one (33). According to general procedures C and D, the product obtained from 2-bromo-6,7-dihydrothieno[3,2-*c*]pyridin-4(5*H*)-one (**41**, 0.625 g, 2.69 mmol) was precipitated from CH_2Cl_2 to provide **33** (0.338 g, 48% over two steps) as a tan solid: Mp >250 °C; IR (ATR) ν_{max} 2834, 1653, 1604, 1482, 1405, 1218, 1095, 813, 762, 695 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 11.50 (brs, 1H), 7.90 (s, 1H), 7.79–7.76 (m, 2H), 7.51–7.49 (m, 2H), 7.28 (d, J = 6.8 Hz, 1H), 6.86 (d, J = 6.8 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 158.5, 147.8, 139.7, 132.7, 131.9, 131.5, 130.2, 129.1, 127.4, 120.7, 100.8; HRMS (ESI^+) m/z calcd for $C_{13}H_9NOSCl$ (M + H) 262.0088, found 262.0016.

2-(4-(Trifluoromethyl)phenyl)thieno[3,2-*c*]pyridin-4(5*H*)-one (34). According to general procedure D, the product obtained from 2-(4-(trifluoromethyl)phenyl)-6,7-dihydrothieno[3,2-*c*] pyridin-4(5*H*)-one (**27**, 0.702 g, 2.36 mmol) was purified by chromatography on SiO_2 (MeOH : CH_2Cl_2, 1 : 9) to provide **34** (0.539 g, 77%) as a tan solid: Mp >250 °C; IR (ATR) ν_{max} 2830, 1643, 1607, 1323, 1106, 1067, 828, 767 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 11.53 (brs, 1H), 8.05 (s, 1H), 7.98 (d, J = 8.0 Hz, 2H), 7.79 (d, J = 8.4 Hz, 2H), 7.31 (t, J = 6.4 Hz, 1H), 6.89 (d, J = 7.2 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 159.1, 149.0, 139.6, 137.4, 131.9, 131.3, 128.5 (q, J_{C-F} = 31.2 Hz), 126.3 (q, J_{C-F} = 3.7 Hz), 124.6 (q, J_{C-F} = 271.2 Hz), 122.5, 101.3; ^{19}F NMR (470 MHz, DMSO-d_6) δ −61.0; HRMS (ESI^+) m/z calcd for $C_{14}H_9F_3NOS$ (M + H) 296.0351, found 296.0352.

2-(4-Fluorophenyl)thieno[3,2-*c*]pyridin-4(5*H*)-one (35). According to general procedure D, the product obtained from 2-(4-fluorophenyl)-6,7-dihydrothieno[3,2-*c*]pyridin-4(5*H*)-one (**28**, 0.673 g, 2.72 mmol) was purified by chromatography on SiO_2 (MeOH : CH_2Cl_2, 1 : 9) to provide **35** (0.285 g, 41%) as an off-white solid: Mp >250 °C; IR (ATR) ν_{max} 2838, 1655, 1605, 1505, 1493, 1235, 1150, 822, 750 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 11.46 (brs, 1H), 7.82 (s, 1H), 7.82–7.78 (m, 2H), 7.31–7.24 (m, 3H), 6.84 (d, J = 7.2 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 161.9 (d, J_{C-F} = 245.0 Hz), 158.5, 147.5, 140.0, 131.5, 130.0, 129.5 (d, J_{C-F} = 2.5 Hz), 127.8 (d, J_{C-F} = 8.7 Hz), 120.0, 116.0 (d, J_{C-F} = 21.2 Hz), 100.7; ^{19}F (470 MHz, DMSO-d_6) δ −113.4; HRMS (ESI^+) m/z calcd for $C_{13}H_9FNOS$ (M + H) 246.0383, found 246.0381.

4-(4-Oxo-4,5,dihydrothieno[3,2-*c*]pyridin-2-yl)phenyl pivalate (36). According to general procedure D, the product obtained from 4-(4-oxo-4,5,6,7-tetrahydrothieno[3,2-*c*]pyridin-2-yl)phenyl pivalate (**30**, 1.35 g, 4.09 mmol) was purified by chromatography on SiO_2 (MeOH : CH_2Cl_2, 1 : 9) to provide **36** (0.750 g, 56%) as a tan solid: Mp >250 °C; IR (ATR) ν_{max} 2961, 2872, 2837, 1749, 1637, 1603, 1507, 1491, 1472, 1271, 1205, 1165, 1112, 891, 840, 757 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 11.47 (brs, 1H), 7.86 (s, 1H), 7.80–7.77 (m, 2H), 7.26 (t, J = 6.4 Hz,1H), 7.19–7.17 (m, 2H), 6.85 (d, J = 6.8 Hz, 1H), 1.32 (s, 9H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 176.2, 158.5, 150.6, 147.5, 140.2, 131.5, 130.5, 129.9, 126.8, 122.4, 120.1, 100.7, 38.5, 26.6; HRMS (ESI^+) m/z calcd for $C_{18}H_{18}O_3NS$ (M + H) 328.1002, found 328.1000.

2-(3-(Trifluoromethyl)phenyl)thieno[3,2-*c*]pyridin-4(5*H*)-one (37). According to general procedures C and D, the product obtained from 2-bromo-6,7-dihydrothieno[3,2-*c*]pyridin-4(5*H*)-one (**41**, 0.625 g, 2.69 mmol) was precipitated from CH_2Cl_2 to provide **37** (0.544 g, 69% over two steps) as a tan solid: Mp

201–204 °C; IR (ATR) ν_{max} 2823, 1648, 1607, 1327, 1166, 1112, 1071, 991, 891, 756, 688 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 11.52 (brs, 1H), 8.09 (s, 1H), 8.08–8.04 (m, 2H), 7.70–7.68 (m, 2H), 7.31 (d, J = 6.8 Hz, 1H), 6.88 (d, J = 6.8 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 158.6, 148.2, 139.1, 134.1, 131.6, 130.6, 130.4, 129.9 (q, J_{C-F} = 31.2 Hz), 129.7, 124.4 (q, J_{C-F} = 3.7 Hz), 123.8 (q, J_{C-F} = 271.2 Hz), 121.9 (q, J_{C-F} = 3.7 Hz), 121.8, 100.8; ^{19}F NMR (376 MHz, DMSO-d_6) δ −61.2; HRMS (ESI^+) m/z calcd for $C_{14}H_9ONSF_3$ (M + H) 296.0351, found 296.0349.

General procedure E: nitration of pyridones

A suspension of the DDQ oxidation product (1.0 equiv.) in MeCN (0.04 M) was heated to 65 °C in a round-bottom flask fitted with a condenser under an atmosphere of O_2 (balloon, 1 atm). Neat *t*-BuONO (4.0 equiv.) was added, and the reaction mixture was stirred for 3–5 h, or until consumption of starting material was observed by TLC analysis. Typically, the reaction mixture stayed heterogeneous, but slightly darkened. The solution was cooled to room temperature and concentrated to approximately 1/2 volume. The precipitate was filtered to give the pure nitration product. In some cases when the solid was not pure, it was resuspended in MeCN, sonicated for 5 min, and filtered.

7-Nitro-2-(*p*-tolyl)thieno[3,2-*c*]pyridin-4(5*H*)-one (8a). According to general procedure E, 2-(*p*-tolyl)thieno[3,2-*c*]pyridin-4(5*H*)-one (**32**, 0.175 g, 0.725 mmol) led to **8a** (0.082 g, 39%) as a yellow solid: Mp >250 °C; IR (ATR) ν_{max} 2825, 1649, 1492, 1250, 1027, 806, 765 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 12.73 (brs, 1H), 8.73 (s, 1H), 7.91 (s, 1H), 7.74 (d, J = 8.0 Hz, 2H), 7.29 (d, J = 8.0 Hz, 2H), 2.35 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 157.9, 144.9, 138.6, 138.0, 135.2, 129.9, 129.5, 127.3, 125.9, 119.2, 20.7; HRMS (ESI^+) m/z calcd for $C_{14}H_{11}O_3N_2S$ (M + H) 287.0485, found 287.0483.

2-(4-Chlorophenyl)-7-nitrothieno[3,2-*c*]pyridin-4(5*H*)-one (8b). According to general procedure E, 2-(4-chlorophenyl)thieno[3,2-*c*]pyridin-4(5*H*)-one (**33**, 0.164 g, 0.626 mmol) led to **8b** (0.108 g, 56%) as a yellow solid: Mp >250 °C; IR (ATR) ν_{max} 2806, 1655, 1482, 1335, 1255, 1231, 1093, 815, 764, 706 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 12.79 (brs, 1H), 8.76 (s, 1H), 8.03 (s, 1H), 7.89 (d, J = 8.4 Hz, 2H), 7.53 (d, J = 8.8 Hz, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 157.8, 143.2, 138.6, 135.6, 133.3, 131.1, 129.8, 129.2, 127.7, 127.2, 120.6; HRMS (ESI^+) m/z calcd for $C_{13}H_8O_3N_2ClS$ (M + H) 306.9939, found 306.9937.

7-Nitro-2-(4-(trifluoromethyl)phenyl)thieno[3,2-*c*]pyridin-4(5*H*)-one (8c). According to general procedure E, 2-(4-(trifluoromethyl)phenyl)thieno[3,2-*c*]pyridin-4(5*H*)-one (**34**, 0.447 g, 1.51 mmol) led to **8c** (0.406 g, 79%) as a yellow solid: Mp >250 °C; IR (ATR) ν_{max} 2803, 1664, 1611, 1494, 1322, 1231, 1109, 1065, 832, 766 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 12.82 (brs, 1H), 8.78 (s, 1H), 8.17 (s, 1H), 8.10 (d, J = 8.0 Hz, 2H), 7.81 (d, J = 8.5 Hz, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 157.9, 142.5, 139.3, 136.1, 136.0, 129.7, 128.5 (q, J_{C-F} = 31.2 Hz), 127.1, 126.5, 126.1 (q, J_{C-F} = 3.7 Hz), 124.0 (q, J_{C-F} = 270.0 Hz), 121.9; ^{19}F NMR (470 MHz, DMSO-d_6) δ −61.1; HRMS (ESI^+) m/z calcd for $C_{14}H_8F_3N_2O_3S$ (M + H) 341.0202, found 341.0201.

2-(4-Fluorophenyl)-7-nitrothieno[3,2-*c*]pyridin-4(5*H*)-one (8d). According to general procedure E, 2-(4-fluorophenyl)thieno[3,2-*c*]pyridin-4(5*H*)-one (**35**, 0.230 g, 0.937 mmol) led to **8d** (0.133 g, 49%) as a yellow solid: Mp >250 °C; IR (ATR) ν_{max} 2807, 1649, 1617, 1491, 1340, 1248, 1226, 1135, 822, 764 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 12.77 (brs, 1H), 8.75 (s, 1H), 7.97 (s, 1H), 7.93–7.89 (m, 2H), 7.32 (t, J = 8.0 Hz, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 162.2 (d, J_{C-F} = 245.0 Hz), 157.8, 143.5, 138.3, 135.3, 129.8, 128.9 (d, J_{C-F} = 2.5 Hz), 128.7 (d, J_{C-F} = 8.7 Hz), 127.2, 120.0, 116.2 (d, J_{C-F} = 21.2 Hz); ^{19}F NMR (470 MHz, DMSO-d_6) δ −112.6; HRMS (ESI^+) m/z calcd for $C_{13}H_8FN_2O_3S$ (M + H) 291.0234, found 291.0233.

4-(7-Nitro-4-oxo-4,5,dihydrothieno[3,2-*c*]pyridin-2-yl)phenyl pivalate (8e). According to general procedure E, 4-(4-oxo-4,5,dihydrothieno[3,2-*c*]pyridin-2-yl)phenyl pivalate (**36**, 0.854 g, 2.60 mmol) led to **8e** (0.791 g, 81%) as a yellow solid: Mp >250 °C; IR (ATR) ν_{max} 3264, 3085, 2979, 1720, 1671, 1609, 1515, 1481, 1330, 1204, 1167, 1131, 776 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 12.78 (brs, 1H), 8.75 (d, J = 6.4 Hz, 1H), 7.99 (s, 1H), 7.91 (d, J = 8.4 Hz, 2H), 7.21 (d, J = 8.8 Hz, 2H), 1.32 (s, 9H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 176.2, 157.8, 151.1, 143.8, 138.4, 135.3, 129.8, 127.1, 122.5, 120.0, 38.5, 26.6; HRMS (ESI^+) m/z calcd for $C_{18}H_{17}O_5N_2S$ (M + H) 373.0853, found 373.0851.

7-Nitro-2-(3-(trifluoromethyl)phenyl)thieno[3,2-*c*]pyridin-4(5*H*)-one (8g). According to general procedure E, 2-(3-(trifluoromethyl)phenyl)thieno[3,2-*c*]pyridin-4(5*H*)-one (**37**, 0.354 g, 1.19 mmol) led to **8g** (0.307 g, 75%) as a yellow solid: Mp >250 °C; IR (ATR) ν_{max} 2793, 1665, 1615, 1498, 1477, 1329, 1247, 1228, 1158, 1109, 996, 892, 764 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 12.80 (brs, 1H), 8.78 (s, 1H), 8.22–8.14 (m, 3H), 7.78–7.68 (m, 2H); ^{13}C NMR (100 MHz, d_6-DMSO) δ 157.9, 142.6, 139.1, 136.0, 133.4, 130.5, 130.1 (q, J_{C-F} = 35.0 Hz), 130.0, 129.8, 127.2, 125.1 (q, J_{C-F} = 5.0 Hz), 123.9 (q, J_{C-F} = 271.0 Hz), 122.3 (q, J_{C-F} = 4.0 Hz), 121.8; ^{19}F NMR (376 MHz, DMSO-d_6) δ −61.1; HRMS (ESI^+) m/z calcd for $C_{14}H_8O_3N_2F_3S$ (M + H) 341.0202, found 341.0200.

2-(3-Methoxyphenyl)-7-nitrothieno[3,2-*c*]pyridin-4(5*H*)-one (8j). According to general procedure E, 2-(3-methoxyphenyl)thieno[3,2-*c*]pyridin-4(5*H*)-one (0.085 g, 0.330 mmol) led to **8j** (0.053 g, 53%) as a yellow solid: Mp >250 °C; IR (ATR) ν_{max} 2823, 1674, 1595, 1469, 1338, 1241, 1037, 763, 679 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 12.77 (brs, 1H), 8.76 (s, 1H), 8.04 (s, 1H), 7.40–7.38 (m, 3H), 7.00–6.96 (m, 1H), 3.85 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 159.9, 157.9, 144.5, 138.4, 135.4, 133.5, 130.4, 129.8, 127.2, 120.3, 118.3, 115.0, 110.9, 55.3; HRMS (ESI^+) m/z calcd for $C_{14}H_{11}O_4N_2S$ (M + H) 303.0434, found 303.0297.

General procedure F: nitro reduction and in-flow photooxygenation

A suspension of nitro-compound (1.0 equiv.) in MeOH : EtOAc (3 : 1, 0.05 M) was treated under a nitrogen atmosphere with 10% Pd/C (15 mol%). H_2 was bubbled through the mixture. The suspension was stirred at room temperature under H_2 (1 atm, balloon) for 6 h, filtered through Celite, and the Celite

pad was washed with MeOH (50 mL). The Pd/C was removed from the Celite, boiled in PhMe (40 mL), filtered over Celite, and eluted with MeOH. This procedure was performed twice. The combined filtrates were concentrated under reduced pressure to afford a brown solid that was used in the in-flow photooxygenation without further purification. A solution of the crude solid in MeOH (*ca.* 2–3 mL mg^{-1}) was passed through the tubing at a rate of 1.9 mL min^{-1} using the peristaltic pump (5 RPM) under white LED irradiation. The tubing was flushed with MeOH (40 mL). The mixture was concentrated to give a brown solid that was purified by chromatography on SiO_2 (dry loaded, acetone : hexanes, 1 : 2 to 1 : 1) to yield the desired imine.

2-(*p*-Tolyl)-7-iminothieno[3,2-*c*]pyridine-4,6(5*H*,7*H*)-dione (9a). According to general procedure F, the product obtained from 7-nitro-2-(*p*-tolyl)thieno[3,2-*c*]pyridin-4(5*H*)-one (**8a**, 0.080 g, 0.279 mmol) was purified by chromatography on SiO_2 (acetone : hexanes, 1 : 2) to give **9a** (0.032 g, 42%) as a yellow solid: Mp 254–255 °C; IR (ATR) ν_{max} 3288, 3225, 1712, 1687, 1612, 1391, 1301, 1194, 1153, 781 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.85 (brs, 1H), 11.56 (s, 1H), 7.92 (s, 1H), 7.76 (d, J = 8.0 Hz, 2H), 7.30 (d, J = 8.0 Hz, 2H), 2.35 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 160.0, 157.8, 153.3, 149.6, 141.3, 139.4, 136.8, 129.9, 129.2, 126.0, 121.4, 20.8; HRMS (ESI$^+$) m/z calcd for $C_{14}H_{11}N_2O_2S$ (M + H) 271.0536, found 271.0535.

2-(4-Chlorophenyl)-7-iminothieno[3,2-*c*]pyridine-4,6(5*H*,7*H*)-dione (9b). According to general procedure F, the product obtained from 2-(4-chlorophenyl)-7-nitrothieno[3,2-*c*]pyridin-4(5*H*)-one (**8b**, 0.095 g, 0.309 mmol) was purified by chromatography on SiO_2 (acetone : hexanes, 1 : 2) to give **9b** (0.030 g, 33%) as a yellow solid: Mp 237–238 °C; IR (ATR) ν_{max} 3186, 1730, 1669, 1614, 1441, 1241, 1161, 1093, 815 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.87 (brs, 1H), 11.63 (s, 1H), 8.03 (s, 1H), 7.91 (d, J = 8.4 Hz, 2H), 7.55 (d, J = 8.4 Hz, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 160.0, 157.8, 153.4, 147.7, 142.2, 136.8, 134.1, 130.8, 129.3, 127.9, 122.7; HRMS (ESI$^+$) m/z calcd for $C_{13}H_8N_2O_2ClS$ (M + H) 290.9990, found 290.9989.

7-Imino-2-(4-(trifluoromethyl)phenyl)thieno[3,2-*c*]pyridine-4,6(5*H*,7*H*)-dione (9c). According to general procedure F, the product obtained from 7-nitro-2-(4-(trifluoromethyl)phenyl) thieno-[3,2-*c*]pyridin-4(5*H*)-one (**8c**, 0.125 g, 0.367 mmol) was purified by chromatography on SiO_2 (acetone : hexanes, 1 : 2) to give **9c** (0.041 g, 34%) as a greenish/yellow solid: Mp >250 °C; IR (ATR) ν_{max} 3249, 3181, 1692, 1615, 1325, 1247, 1158, 1132, 1068, 831, 787 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.90 (s, 1H), 11.70 (s, 1H), 8.16 (s, 1H), 8.11 (d, J = 8.0 Hz, 2H), 7.84 (d, J = 8.40 Hz, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 159.9, 157.7, 153.4, 147.0, 143.1, 136.8, 135.8, 129.2 (q, J_{C-F} = 31.2 Hz), 126.9, 126.1 (q, J_{C-F} = 3.7 Hz), 124.0 (q, J_{C-F} = 270 Hz), 123.9; ^{19}F NMR (470 MHz, DMSO-d_6) δ −61.2; HRMS (ESI$^+$) m/z calcd for $C_{14}H_8F_3N_2O_2S$ (M + H) 325.0253, found 325.0252.

2-(4-Fluorophenyl)-7-iminothieno[3,2-*c*]pyridine-4,6(5*H*,7*H*)-dione (9d). According to general procedure F, the product obtained from 2-(4-fluorophenyl)-7-nitrothieno[3,2-*c*]pyridin-4(5*H*)-one (**8d**, 0.105 g, 0.361 mmol) was purified by chromatography on SiO_2 (acetone : hexanes, 1 : 2) to give **9d** (0.025 g, 25%) as a yellow solid: Mp 239–241 °C; IR (ATR) ν_{max} 3259, 2970, 1698, 1608, 1596, 1437, 1377, 1362, 1148, 908, 824 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.87 (brs, 1H), 11.60 (s, 1H), 7.97–7.92 (m, 3H), 7.34 (t, J = 8.8 Hz, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 162.6 (d, J_{C-F} = 246.0 Hz), 159.9, 157.7, 153.3, 148.1, 141.9, 136.8, 128.5 (d, J_{C-F} = 2.5 Hz), 122.2, 116.3 (d, J_{C-F} = 22.5 Hz); ^{19}F NMR (470 MHz, DMSO-d_6) δ −111.4; HRMS (ESI$^+$) m/z calcd for $C_{13}H_8N_2O_2FS$ (M + H) 275.0285, found 275.0283.

4-(7-Imino-4,6-dioxo-4,5,6,7-tetrahydrothieno[3,2-*c*]pyridin-2-yl)phenyl pivalate (9e). According to general procedure F, the product obtained from 4-(7-nitro-4-oxo-4,5,dihydrothieno[3,2-*c*] pyridin-2-yl)phenyl pivalate (**8e**, 0.175 g, 0.469 mmol) was purified by chromatography on SiO_2 (acetone : hexanes, 1 : 2) to give **9e** (0.029 g, 17%) as a tan solid: Mp 249–251 °C; IR (ATR) ν_{max} 3240, 3094, 1746, 1719, 1695, 1608, 1439, 1245, 1218, 1164, 1113, 792 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.86 (s, 1H), 11.60 (s, 1H), 7.99 (s, 1H), 7.93 (d, J = 8.8 Hz, 2H), 7.23 (d, J = 8.8 Hz, 2H), 1.32 (s, 9H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 176.3, 160.1, 157.8, 153.4, 151.6, 148.4, 142.0, 136.8, 129.6, 127.5, 122.7, 122.3, 38.6, 26.7; HRMS (ESI$^+$) m/z calcd for $C_{18}H_{17}N_2O_4S$ (M + H) 357.0904, found 357.0903.

2-(3-Methoxyphenyl)-7-iminothieno[3,2-*c*]pyridine-4,6(5*H*,7*H*)-dione (9f). According to general procedure F, the product obtained from 2-(3-fluorophenyl)-7-nitrothieno[3,2-*c*]pyridin-4(5*H*)-one (**8f**, 0.085 g, 0.292 mmol) was purified by chromatography on SiO_2 (acetone : hexanes, 1 : 2) to give **9f** (0.028 g, 35%) as a yellow solid: Mp 235–236 °C; IR (ATR) ν_{max} 3251, 3187, 3097, 1692, 1611, 1579, 1431, 1310, 1271, 1226, 1156, 962, 778 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.87 (brs, 1H), 11.64 (s, 1H), 8.09 (s, 1H), 7.81 (d, J = 13.6 Hz, 1H), 7.70 (d, J = 11.2 Hz, 1H), 7.57–7.49 (m, 1H), 7.32–7.25 (m, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 162.5 (d, J_{C-F} = 243.7 Hz), 159.8, 157.6, 153.3, 147.5 (d, J_{C-F} = 1.2 Hz), 142.4, 136.7, 134.1 (d, J_{C-F} = 8.7 Hz), 131.3 (d, J_{C-F} = 8.7 Hz), 123.1, 122.3 (d, J_{C-F} = 1.2 Hz) 116.1 (d, J_{C-F} = 20.0 Hz), 112.9 (d, J_{C-F} = 23.7 Hz); ^{19}F NMR (376 MHz, DMSO-d_6) δ −111.8; HRMS (ESI$^+$) m/z calcd for $C_{13}H_8N_2O_2FS$ (M + H) 275.0285, found 275.0283.

7-Imino-2-(3-(trifluoromethyl)phenyl)thieno[3,2-*c*]pyridine-4,6(5*H*,7*H*)-dione (9g). According to general procedure F, the product obtained from 7-nitro-2-(3-(trifluoromethyl)phenyl) thieno-[3,2-*c*]pyridin-4(5*H*)-one (**8g**, 0.128 g, 0.376 mmol) was purified by chromatography on SiO_2 (acetone : hexanes, 1 : 2) to give **9g** (0.029 g, 23%) as a yellow solid: Mp 236–238 °C; IR (ATR) ν_{max} 3188, 3103, 1731, 1680, 1617, 1426, 1335, 1242, 1177, 1161, 1128, 800, 689 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.89 (s, 1H), 11.68 (s, 1H), 8.25 (s, 1H), 8.23 (s, 1H), 8.17 (d, J = 7.6 Hz, 1H), 7.80 (d, J = 7.6 Hz, 1H), 7.73 (t, J = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 160.0, 157.8, 153.4, 147.1, 142.9, 136.8, 133.1, 130.6, 130.3 (q, J_{C-F} = 33.0 Hz), 125.8 (q, J_{C-F} = 4.0 Hz), 123.9, 123.8 (q, J_{C-F} = 270.0 Hz), 122.7 (q, J_{C-F} = 4.0 Hz); ^{19}F NMR (376 MHz, DMSO-d_6) δ −61.3; HRMS (ESI$^+$) m/z calcd for $C_{14}H_8N_2O_2F_3S$ (M + H) 325.0253, found 325.0251.

2-(3-Chlorophenyl)-7-iminothieno[3,2-*c*]pyridine-4,6(5*H*,7*H*)-dione (9h). According to general procedure F, the product

obtained from 2-(3-chlorophenyl)-7-nitrothieno[3,2-*c*]pyridin-4(5*H*)-one (**8h**, 0.040 g, 0.130 mmol) was purified by chromatography on SiO_2 (acetone : hexanes, 1 : 2) to give **9h** (0.013 g, 34%) as a yellow solid: Mp 226–228 °C; IR (ATR) ν_{max} 3211, 3079, 1725, 1676, 1610, 1565, 1433, 1300, 1236, 1220, 1156, 772, 678 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 11.87 (brs, 1H), 11.65 (s, 1H), 8.10 (s, 1H), 8.00 (s, 1H), 7.85–7.81 (m, 1H), 7.52–7.50 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 159.9, 157.7, 153.4, 147.3, 142.5, 136.7, 134.2, 133.9, 131.2, 129.2, 125.7, 124.9, 123.3; HRMS (ESI^-) *m*/*z* calcd for $C_{13}H_6N_2O_2SCl$ (M − H) 288.9833, found 288.9842.

7-Imino-2-(*m*-tolyl)thieno[3,2-*c*]pyridine-4,6(5*H*,7*H*)-dione (9i). According to general procedure F, the product obtained from 7-nitro-2-(*m*-tolyl)thieno[3,2-*c*]pyridin-4(5*H*)-one (**8i**, 0.075 g, 0.261 mmol) was purified by chromatography on SiO_2 (acetone : hexanes, 1 : 2) to give **9i** (0.018 g, 25%) as a yellow solid: Mp 234–235 °C; IR (ATR) ν_{max} 3208, 3092, 1714, 1686, 1610, 1379, 1307, 1172, 1153, 888, 772, 684 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 11.84 (brs, 1H), 11.57 (s, 1H), 7.95 (s, 1H), 7.71 (s, 1H), 7.65 (d, J = 8.4 Hz, 1H), 7.37 (t, J = 7.8 Hz, 1H), 7.26 (d, J = 7.5 Hz, 1H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 160.1, 157.8, 153.4, 149.5, 141.7, 138.8, 136.7, 131.9, 130.3, 129.3, 126.7, 123.3, 121.9, 20.9; HRMS (ESI^+) *m*/*z* calcd for $C_{14}H_{11}N_2O_2S$ (M + H) 271.0536, found 271.0533.

2-(3-Methoxyphenyl)-7-iminothieno[3,2-*c*]pyridine-4,6(5*H*,7*H*)-dione (9j). According to general procedure F, the product obtained from 2-(3-methoxyphenyl)-7-nitrothieno[3,2-*c*]pyridin-4(5*H*)-one (**8j**, 0.040 g, 0.132 mmol) was purified by chromatography on SiO_2 (acetone : hexanes, 1 : 2) to give **9j** (0.008 g, 23%) as a tan solid: Mp 226–227 °C; IR (ATR) ν_{max} 3210, 1694, 1614, 1593, 1463, 1437, 1260, 1230, 1158, 1028, 783, 680 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 11.86 (s, 1H), 11.59 (s, 1H), 8.04 (s, 1H), 7.41–7.37 (m, 3H), 7.03–7.00 (m, 1H), 3.85 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 160.0, 159.9, 157.8, 153.4, 149.2, 141.8, 136.7, 133.2, 130.5, 122.4, 118.5, 115.6, 111.1, 55.4; HRMS (ESI^+) *m*/*z* calcd for $C_{14}H_{11}N_2O_2S$ (M + H) 287.0485, found 287.0484.

2-(2-Chlorophenyl)-7-iminothieno[3,2-*c*]pyridine-4,6(5*H*,7*H*)-dione (9k). According to general procedure F, the product obtained from 2-(2-chlorophenyl)-7-nitrothieno[3,2-*c*]pyridin-4(5*H*)-one (**8k**, 0.111 g, 0.361 mmol) was purified by chromatography on SiO_2 (acetone : hexanes, 1 : 2) to give **9k** (0.033 g, 31%) as a yellow solid: Mp 220–221 °C; IR (ATR) 3226, 3192, 3080, 1724, 1678, 1608, 1408, 1307, 1224, 1165, 914, 887, 758, 731 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 11.88 (brs, 1H), 11.66 (s, 1H), 7.84 (s, 1H), 7.83–7.78 (m, 2H), 7.68–7.64 (m, 1H), 7.53–7.47 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 160.0, 157.8, 153.5, 144.9, 143.5, 135.6, 131.7, 131.1, 131.0, 130.7, 130.6, 128.1, 126.5; HRMS (ESI^+) *m*/*z* calcd for $C_{13}H_8N_2O_2SCl$ (M + H) 290.9990, found 290.9984.

2-(2-Fluorophenyl)-7-iminothieno[3,2-*c*]pyridine-4,6(5*H*,7*H*)-dione (9l). According to general procedure F, the product obtained from 2-(2-fluorophenyl)-7-nitrothieno[3,2-*c*]pyridin-4(5*H*)-one (**8l**, 0.138 g, 0.475 mmol) was purified by chromatography on SiO_2 (acetone : hexanes, 1 : 2) to give **9l** (0.011 g, 8%) as a yellow solid: Mp 225–226 °C; IR (ATR) ν_{max} 3191, 3100, 1732, 1678, 1615, 1571, 1428, 1237, 1166, 812, 794, 760, 751, 721 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 11.89 (brs, 1H), 11.65 (s, 1H), 8.06–7.99 (m, 2H), 7.56–7.40 (m, 2H), 7.35 (t, J = 7.0 Hz 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 160.0, 158.5 (d, J_{C-F} = 248.0 Hz), 157.8, 153.4, 142.9 (d, J_{C-F} = 6.0 Hz), 141.6 (d, J_{C-F} = 3.0 Hz), 140.0, 131.4 (d, J_{C-F} = 9.0 Hz), 129.2, 125.5 (d, J_{C-F} = 3.0 Hz), 124.6 (d, J_{C-F} = 4.0 Hz), 119.6 (d, J_{C-F} = 12.0 Hz), 116.6 (d, J_{C-F} = 22.0 Hz); ^{19}F NMR (376 MHz, DMSO-d_6) δ −112.7; HRMS (ESI^+) *m*/*z* calcd for $C_{13}H_8N_2O_2SF$ (M + H) 275.0285, found 275.0283.

2-(4-Chloro-3-fluorophenyl)-7-iminothieno[3,2-*c*]pyridine-4,6(5*H*,7*H*)-dione (9m). According to general procedure F, the product obtained from 2-(4-chloro-3-fluorophenyl)-7-nitrothieno-[3,2-*c*]pyridin-4(5*H*)-one (**8m**, 0.155 g, 0.477 mmol) was purified by chromatography on SiO_2 (acetone : hexanes, 1 : 2) to give **9m** (0.027 g, 18%) as a yellow solid: Mp >250 °C; IR (ATR) ν_{max} 3184, 1731, 1678, 1611, 1467, 1429, 1419, 1306, 1226, 1155, 1068, 961, 865, 808, 781 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 11.89 (s, 1H), 11.67 (s, 1H), 8.13 (s, 1H), 8.07 (dd, J = 10.6, 1.6 Hz, 1H), 7.76–7.67 (m, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 159.9, 157.7, 157.5 (d, J_{C-F} = 245.2 Hz), 153.4, 146.4 (d, J_{C-F} = 3.0 Hz), 142.8, 136.7, 133.0 (d, J_{C-F} = 7.5 Hz), 131.5, 123.8, 123.4 (d, J_{C-F} = 3.7 Hz), 120.3 (d, J_{C-F} = 17.2 Hz), 114.5 (d, J_{C-F} = 22.5 Hz); ^{19}F NMR (376 MHz, DMSO-d_6) δ −114.9; HRMS (ESI^+) *m*/*z* calcd for $C_{13}H_7N_2O_2SClF$ (M + H) 308.9895, found 308.9895.

2-(3-Chloro-4-fluorophenyl)-7-iminothieno[3,2-*c*]pyridine-4,6(5*H*,7*H*)-dione (9n). According to general procedure F, the product obtained from 2-(3-chloro-4-fluorophenyl)-7-nitrothieno-[3,2-*c*]pyridin-4(5*H*)-one (**8n**, 0.180 g, 0.554 mmol) was purified by chromatography on SiO_2 (acetone : hexanes, 1 : 2) to give **9n** (0.036 g, 21%) as a yellow solid: Mp 235–236 °C; IR (ATR) ν_{max} 3223, 2997, 2823, 1710, 1605, 1501, 1461, 1434, 1374, 1235, 1185, 1155, 908, 855, 820, 775, 734 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 11.87 (s, 1H), 11.64 (s, 1H), 8.19 (d, J = 7.0 Hz, 1H), 8.07 (s, 1H), 7.90–7.87 (m, 1H), 7.53 (t, J = 9.0 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 159.9, 157.7, 157.6 (d, J_{C-F} = 248.2 Hz), 153.3, 146.4, 142.5, 136.7, 129.8 (d, J_{C-F} = 3.7 Hz), 128.2, 127.0 (d, J_{C-F} = 7.5 Hz), 123.4, 120.7 (d, J_{C-F} = 18.0 Hz), 117.8 (d, J_{C-F} = 21.0 Hz); ^{19}F NMR (470 MHz, DMSO-d_6) δ −114.9; HRMS (ESI^+) *m*/*z* calcd for $C_{13}H_7N_2O_2SClF$ (M + H) 308.9895, found 308.9895.

7-Imino-2-(4-(2-morpholinoethoxy)phenyl)thieno[3,2-*c*]pyridine-4,6(5*H*,7*H*)-dione (9o). According to general procedure F, the product obtained from 2-(4-(2-morpholinoethoxy)phenyl-7-nitrothieno[3,2-*c*]pyrdin-4(5*H*)-one (**8o**, 0.125 g, 0.311 mmol) was purified by chromatography on SiO_2 (acetone : hexanes, 1 : 1) to give **9o** (0.028 g, 23%) as a brown solid: Mp >250 °C; IR (ATR) ν_{max} 3212, 3084, 2927, 2835, 1693, 1601, 1460, 1437, 1290, 1254, 1180, 1149, 1107, 824, 800, 777 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 11.82 (brs, 1H), 11.49 (s, 1H), 7.84 (s, 1H), 7.79 (d, J = 8.7 Hz, 2H), 7.05 (d, J = 9.0 Hz, 2H), 4.16 (t, J = 5.7 Hz, 2H), 3.60–3.56 (m, 4H), 2.71 (t, J = 5.7 Hz, 2H), 2.51–2.46 (m, 4 H covered in part by DMSO signal); ^{13}C NMR (100 MHz, DMSO-d_6) δ 160.1, 159.6, 157.9, 153.3, 149.6, 140.7, 136.9, 127.7, 124.6, 120.7, 115.3, 66.2, 65.6, 56.9, 53.6; HRMS

(ESI$^+$) *m*/*z* calcd for $C_{19}H_{20}N_3O_4S$ (M + H) 386.1169, found 386.1162.

5-Methyl-7-nitro-2-phenylthieno[3,2-*c*]pyridin-4(5*H*)-one (38). A solution of **8p** (0.200 g, 0.735 mmol) and K_2CO_3 (0.507 g, 3.67 mmol) in DMF (9 mL) was treated dropwise with iodomethane (0.23 mL, 3.7 mmol). The reaction mixture was stirred at 90 °C for 2 d, quenched with saturated aqueous NH_4Cl (5 mL) and stirred for 5 min. The mixture was diluted with EtOAc (100 mL). The layers were separated, and the organic layer was washed with H_2O (5 × 5 mL) and saturated aqueous NaCl (2 × 5 mL), dried ($MgSO_4$) and purified by chromatography on SiO_2 (dry-load, EtOAc : hexanes, 1 : 1) to yield **38** (0.146 g, 69%) as a yellow solid: Mp >250 °C; IR (ATR) ν_{max} 3079, 1655, 1603, 1482, 1296, 1256, 1075, 1044, 879 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.31 (s, 1H), 8.00 (s, 1H), 7.86 (d, J = 7.6 Hz, 2H), 7.48 (t, J = 8.4 Hz, 2H), 7.41 (t, J = 7.2 Hz, 1H), 3.69 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 157.7, 144.9, 139.6, 137.8, 132.3, 129.4, 128.9, 128.8, 126.5, 126.0, 120.1, 37.5; HRMS (ESI$^+$) *m*/*z* calcd for $C_{14}H_{11}O_3N_2S$ (M + H) 287.0483, found, 287.0485.

7-Imino-5-methyl-2-phenylthieno[3,2-*c*]pyridine-4,6(5*H*,7*H*)-dione (9p). According to general procedure F, the product obtained from 5-methyl-7-nitro-2-phenylthieno[3,2-*c*]pyridin-4(5*H*)-one (**38**, 0.120 g, 0.419 mmol) was purified by chromatography on SiO_2 (acetone : hexanes, 1 : 2) to give **9p** (0.025 g, 22%) as a brown solid: Mp 236–237 °C; IR (ATR) ν_{max} 3234, 3100, 1711, 1670, 1606, 1455, 1432, 1329, 1281, 1183, 1105, 878 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.69 (s, 1H), 8.03 (s,1H), 7.90–7.77 (m, 2H), 7.53–7.45 (m, 3H), 3.23 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 159.6, 157.9, 152.4, 149.1, 140.7, 136.5, 131.9, 129.6, 129.4, 126.2, 122.5, 27.0; HRMS (ESI$^+$) *m*/*z* calcd for $C_{14}H_{11}O_2N_2S$ (M + H) 271.0534, found, 271.0536.

5-(Cyclopropylmethyl)-7-nitro-2-phenylthieno[3,2-*c*]pyridin-4(5*H*)-one (39). A solution of 7-nitro-2-phenylthieno[3,2-*c*]pyridin-4(5*H*)-one (**8p**, 0.220 g, 0.727 mmol) in THF (15 mL) was treated with cyclopropane methanol (0.0770 mL, 0.945 mmol) and PPh_3 (0.250 g, 0.0945 mmol), cooled to 0 °C, and treated dropwise with DIAD (0.187 mL, 0.945 mmol). The reaction mixture was warmed to room temperature, stirred for 20 h, diluted with MeOH (15 mL), concentrated to $\frac{1}{4}$ volume *in vacuo*, cooled to 0 °C, and filtered. The precipitate was dried to afford **39** (0.130 g, 55%) as a yellow solid: Mp 229–231 °C; IR (ATR) ν_{max} 3087, 1654, 1595, 1514, 1484, 1449, 1333, 1304, 1230, 1137, 1025 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d$_6$) δ 9.08 (s, 1H), 8.03 (s, 1H), 7.95 (dd, J = 8.4, 1.2 Hz, 2H), 7.55–7.43 (m, 3H), 4.50 (d, J = 7.2 Hz, 2H), 1.45–1.36 (m, 1H), 0.67–0.62 (m, 2H), 0.47–0.45 (m, 2H); ^{13}C NMR (125 MHz) δ 157.3, 145.0, 138.2, 137.7, 132.2, 129.3, 129.2, 128.9, 126.8, 126.0, 120.2, 53.4, 10.7, 3.5; HRMS (ESI$^+$) *m*/*z* calcd for $C_{17}H_{14}O_3N_2S$ (M + H) 327.0798, found 327.0794.

5-(Cyclopropylmethyl)-7-imino-2-phenylthieno[3,2-*c*]pyridine-4,6(5*H*,7*H*)-dione (9q). According to general procedure F, the product obtained from 5-(cyclopropylmethyl)-7-nitro-2-phenylthieno[3,2-*c*]pyridin-4(5*H*)-one (**39**, 0.125 g, 0.383 mmol) was purified by chromatography on SiO_2 (CH_2Cl_2) to give **9q** (0.066 g, 56%) as a yellow solid: Mp 193–194 °C; IR (ATR) ν_{max} 3219, 3099, 1713, 1667, 1605, 1453, 1427, 1334, 1298, 1176, 878, 830, 752, 687 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 11.75 (s, 1H), 8.04 (s, 1H), 7.89 (dd, J = 8.4, 1.5 Hz, 2H), 7.52–7.45 (m, 3H), 3.74 (d, J = 7.0 Hz, 2H), 1.19–1.10 (m, 1H), 0.48–0.46 (m, 2H), 0.36–0.33 (m, 2H); ^{13}C NMR (125 MHz) δ 159.5, 157.7, 152.3, 149.2, 140.9, 136.3, 131.8, 129.6, 129.4, 126.2, 122.5, 44.5, 9.7, 3.7; HRMS (ESI$^+$) *m*/*z* cald for $C_{17}H_{15}O_2N_2S$ (M + H) 311.0849, found 311.0847.

***N*-(4-Oxo-2-phenyl-4,5-dihydrothieno[3,2-*c*]pyridin-7-yl)acetamide (40).** Through a suspension of 10% Pd/C (15 mol%) and 7-nitro-2-phenylthieno[3,2-*c*]pyridin-4(5*H*)-one (**8p**, 0.200 g, 0.735 mmol) in MeOH (18 mL, N_2 sparged) was bubbled H_2 gas for 10 min. The reaction mixture was stirred at room temperature under an atmosphere of H_2 (1 atm, balloon) for 6 h and filtered through Celite. The Celite pad was washed with MeOH (50 mL). The Pd/C layer was removed from the Celite, heated at reflux in PhMe (40 mL), filtered over Celite, and eluted with MeOH. This procedure was performed twice. The combined filtrates were concentrated under reduced pressure to afford a brown solid that was dissolved in Ac_2O (7 mL) and THF (7 mL), and stirred at room temperature in the dark for 16 h. The reaction mixture was concentrated under reduced pressure. Purification by chromatography on SiO_2 (dry-load, MeOH : EtOAc, 1 : 9) provided **40** (0.130 g, 62%) as a beige solid: Mp >250 °C; IR (ATR) ν_{max} 3253, 3160, 3054, 2972, 2938, 2809, 1652, 1617, 1508, 1384, 1374, 1291, 1145, 1035, 1012, 976, 947, 871, 803, 751, 687; ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 11.46 (brs, 1H), 9.71 (s, 1H), 7.87 (s, 1H), 7.76 (d, J = 7.5 Hz, 2H), 7.46 (t, J = 6.9 Hz, 2H), 7.36 (t, J = 7.2 Hz, 1H), 7.30 (s, 1H), 2.06 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d$_6$) δ 169.0, 157.4, 146.0, 141.5, 132.8, 130.9, 129.3, 128.4, 125.7, 120.3, 113.8 22.8; HRMS (ESI$^+$) *m*/*z* calcd for $C_{15}H_{13}O_2N_2S$ (M + H) 285.0692, found 285.0690.

6,7-Dihydrothieno[3,2-*c*]pyridin-4(5*H*)-one (12). A solution of thiophene-2-ethylamine (**11**, 10.0 mL, 84.5 mmol) in CH_2Cl_2 (30 mL) was added slowly over 10 min to a solution of triphosgene (9.58 g, 32.1 mmol) in CH_2Cl_2 (150 mL) in a three neck 1 L round-bottom flask (N_2 inlet, glass stopper, an outlet connected to an aqueous NH_4OH trap) at 0 °C under N_2. Then, saturated aqueous $NaHCO_3$ (180 mL) was added to the reaction mixture and the resulting biphasic mixture was stirred vigorously at 0 °C (ice-bath) under N_2 for 2.5 h. The organic layer was dried ($MgSO_4$), filtered, and concentrated to provide a crude product as a dark yellow oil. IR showed the presence of an isocyanate peak at 2259 cm^{-1}. A solution of this material (13.0 g, 84.6 mmol) in CH_2Cl_2 (150 mL) was added dropwise by addition funnel (2–3 drops per second) over 2 h to a mixture of ferric chloride (14.4 g, 88.8 mmol) in CH_2Cl_2 (450 mL) under N_2 at 50 °C in a flask connected to a reflux condenser. After an additional 2 h, the mixture was cooled to 0 °C (ice-bath) and diluted with aqueous citric acid (30 g of citric acid monohydrate in 250 mL of H_2O), and the resulting biphasic mixture was stirred for 15 min. The two layers were separated and the aqueous layer was extracted with CH_2Cl_2 (100 mL). The combined organic layers were washed with satu-

rated aqueous NaCl (350 mL), dried ($MgSO_4$), and concentrated to a dark oil. Purification by chromatography on basic Al_2O_3 (CH_2Cl_2 to load the sample, elution with MeOH : CH_2Cl_2, 1 : 19) provided **12** (9.90 g, 73% over two steps) as a brown liquid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 (d, J = 5.5 Hz, 1H), 7.11 (d, J = 5.5 Hz, 1H), 5.57 (brs, 1H), 3.65 (dt, J = 6.5, 2.5 Hz, 2H), 3.08 (t, J = 6.5 Hz, 2H). Spectral data were consistent with literature properties.[20]

2-Bromo-6,7-dihydrothieno[3,2-*c*]pyridin-4(5*H*)-one (41). In a 250 mL round-bottom flask, a solution of **12** (4.80 g, 31.3 mmol) in AcOH (60 mL) was treated with Br_2 (1.77 mL, 34.5 mmol). The red reaction mixture was shielded from light with foil and stirred at room temperature. Reaction progress was monitored by LC-MS. Additional Br_2 (1.00 mL) was added every 24 h until starting material was consumed. The reaction mixture was diluted with PhMe (250 mL) and concentrated. The resulting brown solid was dissolved in CH_2Cl_2 (300 mL), washed with saturated aqueous $NaHCO_3$ (100 mL), 1 M $Na_2S_2O_3$ (100 mL), and saturated aqueous NaCl (100 mL), dried ($MgSO_4$), and concentrated to give a crude tan solid that was purified by chromatography on SiO_2 (CH_2Cl_2 to load sample, EtOAc : hexanes, 4 : 1 to 1 : 0) to provide **41** (4.70 g, 65%) as a tan solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 (s, 1H), 5.69 (brs, 1H), 3.64 (dt, J = 6.8, 2.8 Hz, 2H), 2.99 (t, J = 6.8 Hz, 2H). Spectral data were consistent with literature properties.[20]

2-Phenyl-6,7-dihydrothieno[3,2-*c*]pyridin-4(5*H*)-one (13). To a 1 L round-bottom flask containing $Pd(PPh_3)_4$ (1.72 g, 1.64 mmol,) were added **41** (9.77 g, 42.1 mmol), phenylboronic acid (6.28 g, 50.5 mmol), and Na_2CO_3 (10.3 g, 96.8 mmol). The flask was evacuated and purged with N_2 (3×), diluted with deoxygenated dioxane and H_2O (2 : 1, 420 mL), fitted with a reflux condenser, and heated to 90 °C for 15 h. The resulting dark mixture was cooled to room temperature, diluted with H_2O (1 L), cooled in an ice-bath, and filtered. The brown residue was washed with cold H_2O (2 × 100 mL) and dissolved in EtOAc. The H_2O washes were extracted with CH_2Cl_2 (2 × 50 mL), and the combined organic layers were dried ($MgSO_4$), filtered, concentrated, and dried under high vacuum to afford a black solid that was purified by chromatography on SiO_2 (CH_2Cl_2 to load sample, EtOAc : hexanes, 1 : 1 to 1 : 0) to provide **13** (9.58 g, 99%) as a tan solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59 (s, 1H), 7.58 (d, J = 5.1 Hz, 2H), 7.38 (tt, J = 9.0, 1.2 Hz, 2H), 7.33–7.29 (m, 1H), 5.65 (brs, 1H), 3.67 (dt, J = 6.8, 2.8 Hz, 2H), 3.09 (t, J = 6.8 Hz, 2H). Spectral data were consistent with literature properties.[20]

2-Phenylthieno[3,2-*c*]pyridin-4(5*H*)-one (42). In a 500 mL round-bottom flask equipped with a condenser, a solution of **13** (9.58 g, 41.8 mmol) and DDQ (19.0 g, 83.6 mmol) in 1,4-dioxane (260 mL) was stirred at 100 °C for 36 h. The reaction mixture was cooled to room temperature, concentrated, diluted with EtOAc (300 mL), saturated aqueous $NaHCO_3$ and H_2O (4 : 1, 500 mL), and stirred for 24 h. The organic layer was washed with saturated aqueous $NaHCO_3$ (3 × 100 mL) and saturated aqueous NaCl (100 mL), dried ($MgSO_4$), filtered, and concentrated give a light brown solid. Acetone was added to the solid to yield a black solution with a tan precipitate. The mixture was sonicated and filtered. The filtrate was concentrated, the process was repeated, and the precipitates were combined to provide **42** as a tan solid (2.88 g). The aqueous phase was extracted with CH_2Cl_2 until the suspended solid was no longer present. The combined CH_2Cl_2 washes were dried ($MgSO_4$), filtered, and concentrated to provide additional **42** (4.94 g; combined yield: 7.82 g, 82%) as a tan solid: ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.46 (s, 1H), 7.85 (s, 1H), 7.75 (d, J = 7.2 Hz, 2H), 7.45 (t, J = 7.2 Hz, 2H), 7.38–7.34 (m, 1H), 7.26 (dd, J = 6.6, 5.4 Hz, 1H), 6.85 (d, J = 7.2 Hz, 1H). Spectral data were consistent with literature properties.[20]

7-Nitro-2-phenylthieno[3,2-*c*]pyridin-4(5*H*)-one (8p). To a 1 L round-bottom flask charged with a stir bar were added **42** (2.80 g, 12.3 mmol), MeCN (246 mL) and *t*-BuONO (6.51 mL, 49.3 mmol), and the flask was flushed with O_2 and stirred at room temperature under O_2 (1 atm, balloon, 10 min flush) for 24 h. Reaction progress was monitored by TLC analysis (50% EtOAc : hexanes, R_f = 0.70). The solution was partially concentrated (*ca.* 1/4 volume). The resulting slurry was cooled in an ice bath for 20 min and filtered. The precipitate was washed with MeOH (3 × 5 mL) and dried under high vacuum to provide **8p** (1.78 g, 53%) as a yellow-brown solid: ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.76 (brs, 1H), 8.74 (d, J = 6.9 Hz, 1H), 7.98 (s, 1H), 7.85 (dt, J = 6.9,1.5 Hz, 2H), 7.52–7.41 (m, 3H). Spectral data were consistent with literature properties.[20]

7-Imino-2-phenylthieno[3,2-*c*]pyridine-4,6(5*H*,7*H*)-dione (2). A suspension of **8p** (1.00 g, 3.67 mmol) in MeOH (90 mL) was bubbled with N_2 for 5 min, and then treated with 10% Pd/C (0.597 g, 0.551 mmol). The reaction mixture was bubbled with H_2 for 10 min, stirred at room temperature under a H_2 atmosphere (1 atm, balloon) for 16 h, and filtered through Celite. The Celite pad was washed with MeOH (100 mL). The Pd/C layer was removed from the Celite, boiled in PhMe (40 mL), filtered over Celite, and eluted with MeOH. This procedure was performed twice. The combined filtrates were concentrated under reduced pressure to afford a brown solid that was dissolved in MeOH (2 L). The solution was passed through the tubing at a rate of 1.9 mL min^{-1} using the peristaltic pump (5 RPM) under LED irradiation. The tubing was flushed with MeOH (40 mL). The mixture was concentrated to give a brown solid that was filtered through a short SiO_2 plug (dry load, MeCN : CH_2Cl_2, 1 : 6) to provide the imine/ketone mixture as a dark orange solid (0.634 g, 2.47 mmol). A solution of this mixture and NH_4OAc (3.81 g, 49.5 mmol) in MeOH (180 mL) in an oven-dried pressure vessel was stirred at 60–65 °C. Due to residual solid still present after 24 h, the solution was decanted and additional MeOH (180 mL) and NH_4OAc (3.81 g, 49.5) were added. The reaction mixture was stirred for an additional 24 h. The process was repeated until the solution was homogeneous. The reaction mixture was cooled to room temperature and concentrated. The solid residue was suspended in EtOAc (300 mL) and saturated aqueous $NaHCO_3$ (150 mL), and vigorously stirred until all solids dissolved. The layers were separated, and the aqueous layer was extracted with EtOAc (2 × 50 mL). The combined organic layers were washed with H_2O (2 × 50 mL) and concentrated to provide **2**

(0.634 g, 67% over three steps) as a reddish-brown solid: ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.86 (s, 1H), 11.59 (s, 1H), 7.98 (s, 1H), 7.88 (dd, J = 8.1, 1.5 Hz, 2H), 7.53–7.44 (m, 3H). Spectral data were consistent with literature properties.[20]

4-Nitroisoquinolin-1(2*H*)-one (14). To a solution of 1-hydroxyisoquinoline (2.00 g, 13.5 mmol) in AcOH (13.5 mL) was added HNO_3 (2.68 mL, 40.5 mmol). The solution was stirred at room temperature for 5 min, then heated to 65 °C for 16 h in a round-bottom flask equipped with a reflux condenser. The reaction mixture was poured over ice and filtered. The residue was washed with ice-cold H_2O (2 × 5 mL) and dried under high vacuum to provide **14** (1.53 g, 59%) as a yellow solid: Mp 236–237 °C; IR (ATR) ν_{max} 3061, 2864, 1655, 1631, 1509, 1470, 1439, 1317, 1285, 1225, 1139, 1039 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.42 (brs, 1H), 8.64 (d, J = 6.3 Hz, 1H), 8.57 (dd, J = 7.2, 0.3 Hz, 1H), 8.31 (ddd, J = 8.1, 1.5, 0.6 Hz, 1H), 7.94 (td, J = 7.2, 1.5 Hz, 1H), 7.68 (td, J = 7.2, 0.9 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 161.4, 136.2, 134.3, 129.4, 128.2, 128.0, 127.7, 124.2, 123.1; HRMS (ESI$^+$) m/z calcd for $C_9H_7O_3N_2$ (M + H) 191.0451, found, 191.0451.

Isoquinoline-1,3,4(2*H*)-trione (15). A suspension of **14** (0.200 g, 1.05 mmol) in EtOH : EtOAc (8 mL, 1 : 1) was bubbled with N_2 for 10 min before adding 10% Pd/C (0.171 g, 0.158 mmol). Then, H_2 was bubbled through the mixture for 5 min. The solution was stirred at room temperature under H_2 (1 atm, balloon) for 24 h and filtered over Celite. The Celite pad was washed consecutively with PhMe and MeOH until coloured material stopped eluting. The filtrate was concentrated to give a solid that was dissolved in in MeOH (400 mL) and treated with methylene blue (0.010 g, 0.032 mmol). The solution was passed through the tubing under at a rate of 1.9 mL min^{-1} using the peristaltic pump (5 RPM) under LED irradiation. The tubing was flushed with MeOH (50 mL). The reaction mixture was concentrated to give a blue solid which was purified by chromatography on SiO_2 (dry load, EtOAc : hexanes, 1 : 2.5) to give **15** (0.032 g, 17%) as a green solid: Mp 226–228 °C; IR (ATR) ν_{max} 3194, 3114, 2923, 1685, 1589, 1332, 1272, 1129, 974, 823, 794 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.94 (brs, 1H), 8.13 (dd, J = 8.4, 1.2 Hz, 1H), 8.05 (dd, J = 7.2, 1.2, Hz, 1H), 7.95–7.85 (m, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 175.5, 163.2, 157.5, 134.9, 134.0, 132.3, 129.8, 128.1, 126.7; HRMS (ESI$^-$) m/z calcd for $C_9H_4O_3N$ (M-H) 174.0192, found, 174.0186.

5-Bromothiophene-3-carbaldehyde (43). To a solution of thiophene-3-carbaldehyde (2.00 mL, 22.1 mmol) in CH_2Cl_2 (80 mL) was added $AlCl_3$ (8.86 g, 66.4 mmol). The dark solution was stirred for 10 min, and Br_2 (1.25 mL, 24.4 mmol) was added. The mixture was stirred at room temperature for 12 h, and slowly quenched with H_2O at 0 °C. The aqueous phase was extracted with CH_2Cl_2 (2 × 30 mL). The combined organic phases were washed with saturated aqueous $Na_2S_2O_3$ (30 mL) and saturated aqueous NaCl (30 mL), dried ($MgSO_4$), and concentrated. The dark oil was purified by chromatography on SiO_2 (EtOAc : hexanes, 1 : 19) to provide **43** (2.85 g, 67%) as a yellow liquid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.77 (s, 1H), 7.99 (d, J = 1.5 Hz, 1H), 7.50 (d, J = 1.2 Hz, 1H). Spectral data were consistent with literature properties.[40]

(*E*)-3-(5-Bromothiophen-3-yl)acrylic acid (44). To a solution of **43** (3.39 g, 17.7 mmol) in a round-bottom flask equipped with a reflux condenser were added pyridine (40 mL) and malonic acid (5.59 g, 53.2 mmol). At 110 °C, piperidine (0.88 mL, 8.9 mmol) was added. After 3 h (reaction progress was monitored by TLC, EtOAc : hexanes, 1 : 9), the reaction mixture was concentrated, diluted with H_2O (45 mL), and neutralized with 6 M HCl to pH 2. The precipitate was filtered, washed with H_2O (3 × 10 mL), and dissolved in MeOH. This solution was concentrated and dried under high vacuum to provide **44** (2.35 g, 57%) as a tan solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.34 (brs, 1H), 7.93 (d, J = 1.5 Hz, 1H), 7.71 (d, J = 1.5 Hz, 1H), 7.48 (d, J = 15.9 Hz, 1H), 6.37 (d, J = 15.9 Hz, 1H). Spectral data were consistent with literature properties.[37]

2-Bromothieno[2,3-*c*]pyridin-7(6*H*)-one (45). A solution of Et_3N (2.81 mL, 20.2 mmol) and **44** (2.35 g, 10.1 mmol) in acetone (21 mL) was treated at 0 °C with ethyl chloroformate (2.94 mL, 30.2 mmol). The reaction mixture was stirred at 0 °C for 1 h. A solution of NaN_3 (0.983 g, 15.1 mmol) in H_2O (6 mL) was added slowly at 0 °C, and stirring was continued at 0 °C for 1 h. The mixture was poured into ice-cold H_2O, extracted with EtOAc, dried ($MgSO_4$), and concentrated to give the crude azide intermediate as a tan solid. To a solution of Bu_3N (3.15 mL, 13.1 mmol) in Ph_2O (10 mL) heated to 240 °C was added a solution of the crude azide (2.60 g, 10.1 mmol) in CH_2Cl_2 (20.2 mL) over a period of *ca.* 30 min, allowing the CH_2Cl_2 to boil off. The reaction mixture was stirred at 240 °C for another 1 h, cooled to room temperature, diluted with hexanes (70 mL), and stirred for 15 min. The precipitate was filtered, washed with hexanes (2 × 10 mL) and dried under vacuum to give the crude product as a sticky brown solid. Purification by chromatography on SiO_2 (CH_2Cl_2 to load sample, EtOAc to elute impurities, then MeOH : EtOAc, 1 : 9) provided **45** (1.29 g, 56%) as a brown solid: Mp 246–248 °C; IR (ATR) ν_{max} 3131.3, 2957.1, 2838.5, 1627.6, 1609.6, 1521.9, 1470.6, 1418.7, 1238.5, 1059.5, 948.3, 935.8, 888.1 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.65 (brs, 1H), 7.57 (s, 1H), 7.29 (d, J = 7.2 Hz, 1H), 6.64 (d, J = 6.9, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 157.1, 146.7, 131.4, 130.1, 128.4, 121.0, 101.5; HRMS (ESI$^+$) m/z calcd for C_7H_5BrNOS (M + H) 229.9275, found, 229.9266.

2-Bromo-4-nitrothieno[2,3-*c*]pyridin-7(6*H*)-one (46). To a solution of **45** (1.20 g, 5.21 mmol) in MeCN (104 mL) was added *t*-BuONO (2.76 mL, 20.9 mmol). The flask was flushed with O_2 and the solution was stirred for 15 h at rt under O_2 (1 atm, balloon), concentrated, and suspended in MeCN (10 mL). The resulting slurry was filtered and washed with MeCN (3 × 5 mL) to provide **46** (0.730 g, 51%) as a tan solid: Mp 203–205 °C; IR (ATR) ν_{max} 3189, 3083, 1744, 1700, 1674, 1519, 1430, 1389, 1369, 1260, 880, 867, 821, 797, 746 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.88 (brs, 1H), 8.69 (s, 1H), 8.06 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 157.1, 138.4, 137.3, 130.7, 128.2, 127.5, 124.8; HRMS (ESI$^+$) m/z calcd for $C_7H_4BrN_2O_3S$ (M + H) 274.9126, found, 274.9106.

4-Nitro-2-phenylthieno[2,3-*c*]pyridin-7(6*H*)-one (16). To a 100 mL round-bottom flask containing $Pd(PPh_3)_4$ (0.134 g,

0.127 mmol) were added **46** (0.700 g, 2.54 mmol), phenylboronic acid (6.28 g, 50.5 mmol), and Na_2CO_3 (0.623 g, 5.85 mmol). The flask was evacuated and purged with N_2 (3×), diluted with deoxygenated dioxane and H_2O (2 : 1, 26 mL), fitted with a reflux condenser, and heated to 90 °C for 16 h. The solution was concentrated to give a red oil that was diluted with H_2O (50 mL) and 1 M $KHSO_4$ (5 mL), at which time the red oil converted to an orange semi-solid suspension. The mixture was diluted with EtOAc (40 mL), and the layers were separated. The aqueous phase was extracted with EtOAc (3 × 100 mL). The combined organic extracts were washed with saturated aqueous NaCl (50 mL), dried ($MgSO_4$), filtered, and concentrated to give a yellow solid. The solid was then partially dissolved in MeOH (15 mL), sonicated, and heated to reflux, cooled to room temperature, and kept in a −20 °C freezer for 30 min. The yellow precipitate was filtered and washed with cold MeOH to give **16** (0.354 g, 52%): Mp >250 °C; IR (ATR) ν_{max} 3308, 1646, 1626, 1530, 1504, 1489, 1459, 1439, 1401, 1348, 1306, 1246, 1153, 1100, 1064, 1025, 998, 964 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 12.75 (brs, 1H), 8.70 (s, 1H), 8.28 (s, 1H), 7.88 (dd, J = 8.1, 1.8 Hz, 2H), 7.57–7.50 (m, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 157.5, 152.6, 138.4, 136.6, 132.0, 130.0, 129.5, 127.9, 127.6, 126.6, 120.0; HRMS (ESI^+) m/z calcd for $C_{13}H_9O_3N_2S$ (M + H) 273.0328, found, 273.0334.

2-Phenylthieno[2,3-*c*]pyridine-4,5,7(6*H*)-trione (17). To a suspension of **16** (0.170 g, 0.468 mmol) in degassed MeOH (10 mL) was added 10% Pd/C (0.076 g, 0.070 mmol). Then, H_2 was bubbled through the mixture for 5 min. The suspension was stirred at room temperature under H_2 (1 atm, balloon) for 17 h, and filtered over Celite. The Pd/C layer was removed, boiled in PhMe (10 mL) for 10 seconds, filtered over Celite, and washed with MeOH. The process was repeated two more times. The combined filtrates were concentrated under reduced pressure to give a residue that was suspended in MeCN (20 mL) and treated with *meso*-tetraphenylporphine (0.0086 g, 0.014 mmol). The solution was irradiated with two CFL lamps, flushed with O_2, and allowed to stir under O_2 (1 atm, balloon) for 6 d. The reaction mixture was concentrated and purified by chromatography on SiO_2 (dry load, MeCN : CH_2Cl_2, 0 : 1 to 1 : 6) to provide **17** (0.025 g, 21%) as a yellow solid. The reaction was also performed in-flow following the general procedure F with 3% methylene blue to provide **17** (11%) as a yellow solid: Mp >250 °C; IR (ATR) ν_{max} 3079, 2851, 1737, 1701, 1671, 1535, 1502, 1454, 1415, 1360, 1265, 1120, 1078, 998, 954 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 12.01 (brs, 1H), 8.05 (s, 1H), 7.90 (dd, J = 8.1, 2.1 Hz, 2H), 7.53–7.47 (m, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 170.1, 159.0, 158.1, 151.1, 141.6, 140.1, 131.5, 129.9, 129.5, 126.4, 121.3; HRMS (ESI^+) m/z calcd for $C_{13}H_6O_3NS$ (M + H) 256.0063, found, 256.0063.

(*E*)-4-(2-(Dimethylamino)vinyl)nicotinonitrile (47). A solution of 3-cyano-4-methylpyridine (1.00 g, 8.21 mmol) and Bredereck's reagent (2.07 mL, 9.03 mmol) in DMF (12 mL), was heated at 140 °C under N_2 in a 20 mL microwave vial for 2 d. After addition of EtOAc (200 mL), the mixture was washed with H_2O (5 × 24 mL). The combined organic layers were washed with saturated aqueous NaCl (10 mL), dried ($MgSO_4$), concentrated, and dried under high vacuum to give **47** (1.27 g, 89%) as a light red solid: ^1H NMR (300 MHz, DMSO-d_6) δ 8.48 (s, 1H), 8.22 (dd, J = 6, 0.6 Hz, 1H), 7.83 (d, J = 13.2 Hz, 1H), 7.45 (d, J = 6 Hz, 1H), 5.05 (d, J = 13.2 Hz, 1H), 2.98 (s, 6H). Spectral data were consistent with literature properties.[41,42]

2,7-Naphthyridin-1(2*H*)-one (48). To a solution of **47** (1.27 g, 7.33 mmol) in AcOH (3.50 mL) was added H_2SO_4 (3.50 mL). The reaction mixture was stirred at 110 °C for 1 h, cooled to room temperature, diluted with H_2O (10 mL), and then slowly added to NH_4OH (15 mL). The solution was neutralized to pH 7–8 with additional NH_4OH and was cooled in an ice bath. The precipitate was filtered and washed with small amounts of cold H_2O (2 × 3 mL) and dried under high vacuum to afford **48** (0.899 g, 84%) as a tan solid: ^1H NMR (300 MHz, DMSO-d_6) δ 11.61 (brs, 1H), 9.31 (t, J = 0.8 Hz, 1H), 8.70 (d, J = 5.4 Hz, 1H), 7.59 (dd, J = 5.4, 0.8 Hz, 1H), 7.42 (dd, J = 6.9, 6.0 Hz, 1H), 6.56 (d, J = 7.2 Hz, 1H). Spectral data were consistent with literature properties.[42]

4-Nitro-2,7-naphthyridin-1(2*H*)-one (18). To a microwave vial charged with a stir bar were added **48** (0.882 g, 6.03 mmol) and H_2SO_4 (5.50 mL), followed by HNO_3 (1.20 mL, 18.1 mmol). The vial was capped and stirred at 85 °C for 16 h. The reaction mixture was cooled to 0 °C (ice-bath), diluted with H_2O (10 mL), and basified to pH 7 with NH_4OH. The resulting precipitate was filtered, washed with minimal amounts of cold H_2O (2 × 5 mL), and dried under high vacuum to provide **18** (0.393 g, 34%) as a yellow solid: Mp >250 °C; IR (ATR) ν_{max} 3187, 3130, 3060, 2879, 1677, 1631, 1589, 1509, 1471, 1415, 1348, 1296, 1247, 1204, 1187, 1107, 1038, 895, 790 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 12.66 (brs, 1H), 9.38 (s, 1H), 8.91 (t, J = 5.5 Hz, 2H), 8.41 (d, J = 5.5 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 161.7, 152.9, 150.4, 141.7, 135.5, 125.9, 118.4, 115.9; HRMS (ESI^+) m/z calcd for $C_8H_6O_3N_3$ (M + H) 191.0403, found, 191.0404.

2,5-Dihydro-1*H*-pyrido[4,3-*b*]indol-1-one (49). A solution of 2,4-dihydroxypyridine (0.500 g, 4.41 mmol) and phenylhydrazine (1.49 mL, 14.7 mmol) in Ph_2O (3.5 mL) was stirred for 15 h at 240 °C. The solution was cooled to room temperature and diluted with hexanes (20 mL), stirred for 15 min, and filtered. The solid was washed with hexanes and collected to give crude **49** as a dark gray solid that was washed with MeOH (2 × 3 mL) and filtered to provide **49** (0.393 g, 48%) as a black solid: ^1H NMR (400 MHz, DMSO-d_6) δ 11.70 (s, 1H), 11.08 (s, 1H), 8.09 (d, J = 7.8 Hz, 1H), 7.48 (d, J = 7.8 Hz, 1H), 7.30–7.25 (m, 2H), 7.18 (t, J = 7.2 Hz, 1H), 6.50 (d, J = 6.9 Hz, 1H). Spectral data were consistent with literature properties.[43]

4-Nitro-2,5-dihydro-1*H*-pyrido[4,3-*b*]indol-1-one (19). To a solution of **49** (0.100 g, 0.543 mmol) in MeCN (11 mL) was added *t*-BuONO (0.287 mL, 2.17 mmol). The flask was flushed with O_2, and the solution was stirred for 15 h at room temperature under O_2 (1 atm, balloon). The solvent was evaporated, and the orange residue was purified by chromatography on SiO_2 (dry load, EtOAc : hexanes, 1 : 1 to 1.5 : 1) to provide **19** (0.052 g, 42%) as a yellow-orange powder: Mp >250 °C; IR (ATR) ν_{max} 3376, 3013, 2924, 2815, 1630, 1608, 1509, 1250,

1191, 1020 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 12.41 (brs, 1H), 12.29 (brs, 1H), 8.72 (s, 1H), 8.14 (d, J = 7.8 Hz, 1H), 7.72 (d, J = 8.1 Hz, 1H), 7.39 (td, J = 8.1, 0.9 Hz, 1H), 7.28 (t, J = 8.4 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 159.3, 137.7, 137.1, 135.7, 124.7, 123.3, 122.0, 121.8, 120.3, 112.8, 106.1; HRMS (ESI^+) m/z calcd for $C_{11}H_8O_3N_3$ (M + H) 230.0559, found, 230.0560.

Conflicts of interest

The authors are co-inventors of patents on the composition of matter and the use of 7-iminothieno[3,2-*c*]pyridine-4,6(5*H*,7*H*)-diones and related compounds, filed and held by the University of Pittsburgh and the University of Virginia.

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