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Modulation of Amide Bond Rotamers in 5-Acyl-6,7-dihydrothieno[3,2-*c*]pyridines

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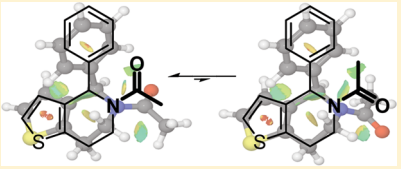
Supporting Information

ABSTRACT: 2-Substituted *N*-acyl-piperidine is a widespread and important structural motif, found in approximately 500 currently available structures, and present in nearly 30 pharmaceutically active compounds. Restricted rotation of the acyl substituent in such molecules can give rise to two distinct chemical environments. Here we demonstrate, using NMR studies and density functional theory modeling of the lowest energy structures of 5-acyl-6,7-dihydrothieno[3,2-*c*]pyridine derivatives, that the amide *E*:*Z* equilibrium is affected by non-covalent interactions between the amide oxygen and adjacent aromatic protons. Structural predictions were used to design molecules that promote either the *E*- or *Z*-amide conformation, enabling preparation of compounds with a tailored conformational ratio, as proven by NMR studies. Analysis of the available X-ray data of a variety of published *N*-acyl-piperidine-containing compounds further indicates that these molecules are also clustered in the two observed conformations. This finding emphasizes that directed conformational isomerism has significant implications for the design of both small molecules and larger amide-containing molecular architectures.



INTRODUCTION

The 2-substituted *N*-acyl-piperidine motif is present in a wide range of molecular architectures,[1] including those of biologically active compounds.[2] Restricted rotation about the amide bond affects the chemical space sampled by the acyl substituent and can therefore have an impact on molecular properties; the pharmacological influence of restricted rotation and atropisomerism is increasingly recognized in drug discovery.[3] This emerging challenge necessitates tools to analyze and manipulate the conformation of target compounds. 5-Acyl-6,7-dihydrothieno[3,2-*c*]pyridines are a known class of inhibitors of the protein Hedgehog acyltransferase, a key regulator of embryonic neurogenesis and carcinogenesis.[4] This class of compounds contains a core 2-substituted *N*-acyl-piperidine motif and exhibits an unequal distribution of rotameric species. Low-temperature selective NOE assignment of rotamers, in combination with density functional theory (DFT) modeling, indicated the existence of a non-covalent interaction (NCI) between the *ortho* position of a 2-phenyl *N*-acyl-piperidine and the amide carbonyl, altering the amide conformation. These tools were therefore used for *de novo* design and analysis of 5-acyl-6,7-dihydrothieno[3,2-*c*]pyridines with manipulated conformational preferences. Analysis of *N*-acyl-piperidine-containing molecules identified an approximately equal distribution of rotamers in non-lactam compounds that contain a rotatable amide, which would be amenable to such conformational modulation. Moreover, strategies for directing conformation are also of interest in larger peptide- and peptoid-based architectures.

RESULTS AND DISCUSSION

Compound **1** was synthesized from thiophene ethylamine by a previously reported synthetic strategy[5] with microwave assistance to promote Bischler−Napieralski cyclization (Figure 1).[6]

The ^{1}H NMR spectrum of **1** shows the presence of several additional hydrogen environments (Figure 2A). The most prominently shifted of these proton signals are a singlet and a multiplet at 5.92 and 4.86 ppm, respectively, which are separated from other hydrogen environments by >1 ppm. Additional peaks can be observed at 6.69 and 2.28 ppm (Figure 2A). To investigate the significance of the amide bond in generating these additional environments, we synthesized acrylamide derivative **2**, along with the corresponding decarbonyl derivative **3**, through reaction with allyl bromide. As postulated, the acrylamide derivative exhibits the additional hydrogen environments, whereas these are absent in the allyl derivative (Figures S7 and S12), demonstrating the dependence on the amide carbonyl and implicating restricted rotation about the N−C bond.

To confirm that the additional peaks observed in the ^{1}H NMR spectrum corresponded to isomers of **1**, we recorded the NOESY spectra to identify exchangeable proton environments (Figure S3). NOESY exchange peaks identify the prominently shifted hydrogen environments at δ = 5.92 and 4.86 ppm as corresponding to H6 and one H4 proton, respectively. In both cases, the shifted protons are adjacent to the amide nitrogen.

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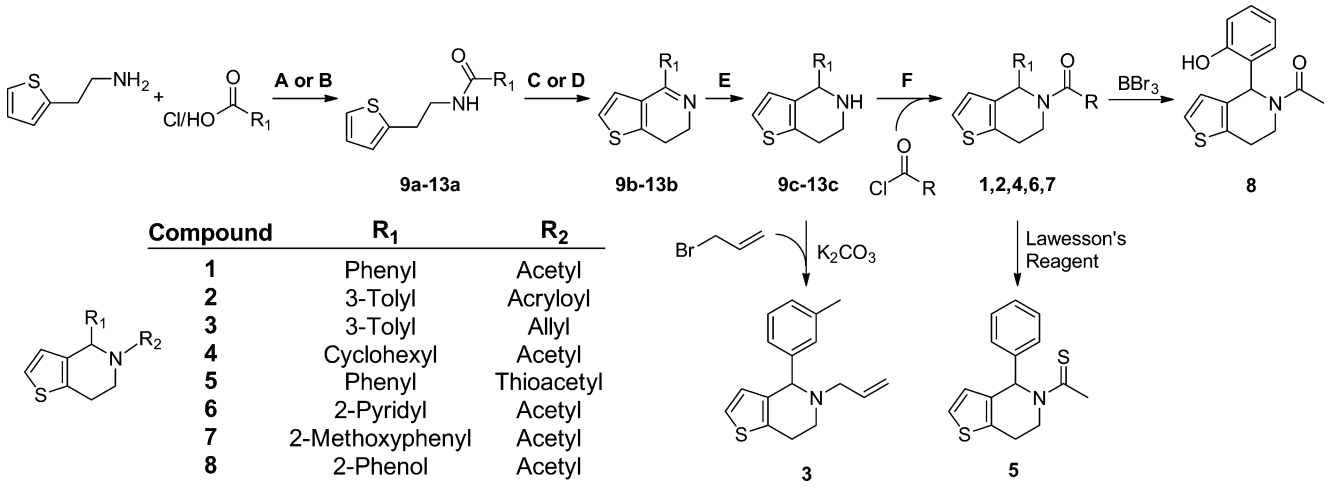

Compound	R_1	R_2
1	Phenyl	Acetyl
2	3-Tolyl	Acryloyl
3	3-Tolyl	Allyl
4	Cyclohexyl	Acetyl
5	Phenyl	Thioacetyl
6	2-Pyridyl	Acetyl
7	2-Methoxyphenyl	Acetyl
8	2-Phenol	Acetyl

Figure 1. Synthesis strategy and structures of all 6,7-dihydrothieno[3,2-*c*]pyridines. General procedures: (A) PyBOP, DIPEA, DMF, rt, overnight; (B) TEA, DCM, rt, overnight; (C) $POCl_3$, P_2O_5, toluene, microwave (140 °C, 30 min); (D) $POCl_3$, P_2O_5, toluene, 85 °C, 2 h; (E) $NaBH_4$, rt, 1 h or overnight; (F) TEA, DCM, rt, 2 h or overnight.

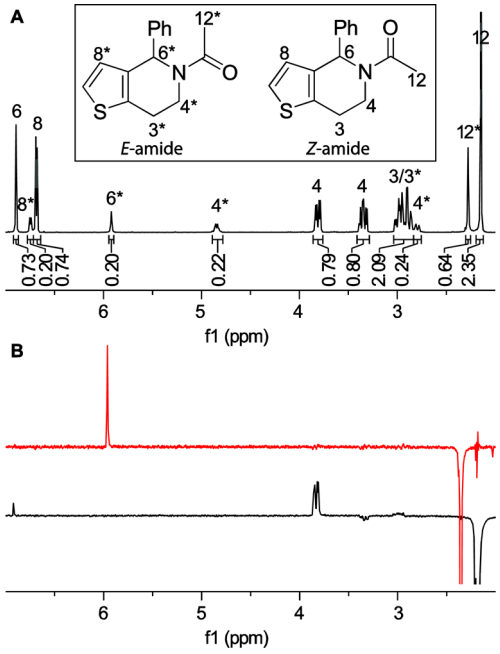

Figure 2. (A) ^{1}H NMR spectra of **1**. (B) Selective NOE pulse of methyl environments at 2.19 (black) and 2.35 (red) ppm at 218 K demonstrates the major *Z*-conformer. All NMR spectra were recorded in $CDCl_3$.

The two peaks presented by the acetyl methyl group also exhibit exchangeable hydrogen environments, and the additional environment at 6.79 ppm corresponds to the H8 proton of the thiophene ring. In order to assign *E*- and *Z*-amide conformations to the major and minor proton environments, we performed selective NOE experiments by pulsing at 2.19 or 2.35 ppm. At 298 K, significant crosstalk is observed between environments due to amide rotation (data not shown). We therefore performed low-temperature NMR experiments to limit rotation on the NMR time scale.[7] The corresponding NOESY spectra at 218 K indicate the loss of exchange between the proton peaks (Figure S4). Selective irradiation of the major methyl environment at 2.19 ppm generates an NOE at piperidine H4 (Figure 2B). Similarly, irradiation at 2.35 ppm generates an NOE at piperidine H6 (Figure 2B), thus confirming the minor and major conformations as *E* and *Z*, respectively, in a 22:78 *E*:*Z* ratio.

It has been proposed that *N*-α aromatic amides may form n$-\pi^*_{aryl}$ interactions between the lone pair of the carbonyl and the anti-bonding orbital of the adjacent aromatic ring.[8] In such cases, changes in the electronics of the ring system[8,9] or the nature of the lone pair donor have been used to modulate n$-\pi^*$ interactions.[10,11] In order to probe putative n$-\pi^*_{aryl}$ interactions in the described dihydrothieno[3,2-*c*]pyridine system, the phenyl ring was replaced with a cyclohexane moiety in compound **4** using the established synthetic route. 218 K NOESY of **4** (Figure S17) and selective NOE irradiation of the methyl peaks (Figures S18 and S19) indicate a significant increase in the proportion of the *E*-amide conformation, giving an *E*:*Z* ratio of 57:43 (Table S6).

The cyclohexane ring of **4** causes a minimal increase in steric encumbrance compared to **3**, suggesting that the altered conformational preference resulted from electronic factors.[12] This promotion of the *Z*-conformer, however, could not be definitively ascribed to the absence of the π^* orbital and a loss of a putative n$-\pi^*_{aryl}$ interaction. We therefore proceeded to increase the lone pair donor capability in the molecule by exchanging the carbonyl oxygen with sulfur.[11] The latter should exhibit increased n$-\pi^*_{aryl}$ donation and thereby result in a higher population of the *Z*-amide.[11] Thioamide **5** was synthesized by thionation of **1** with Lawesson's reagent, and the conformations were assigned using low-temperature NOESY and selective NOE experiments (Figures S24 and S25). Analysis indicates an *E*:*Z* ratio similar to that of the parent amide **1** (Figure S1), thus indicating that n$-\pi^*_{aryl}$ interactions are unlikely to modulate the amide conformation in this system.

Molecular modeling was therefore applied to better understand the factors governing the amide conformation. Although n$-$CHσ^*_{aryl} "hydrogen-bonding" interactions have been proposed to direct amide conformation in *N*-α aromatic peptoids,[12] natural bond orbital (NBO) analysis of compound **1** did not identify any substantial bonding interactions, and did not prove to be discriminatory enough to detect the weaker interactions affecting amide conformation. NBO analysis is better suited for the investigation of through-bond effects rather

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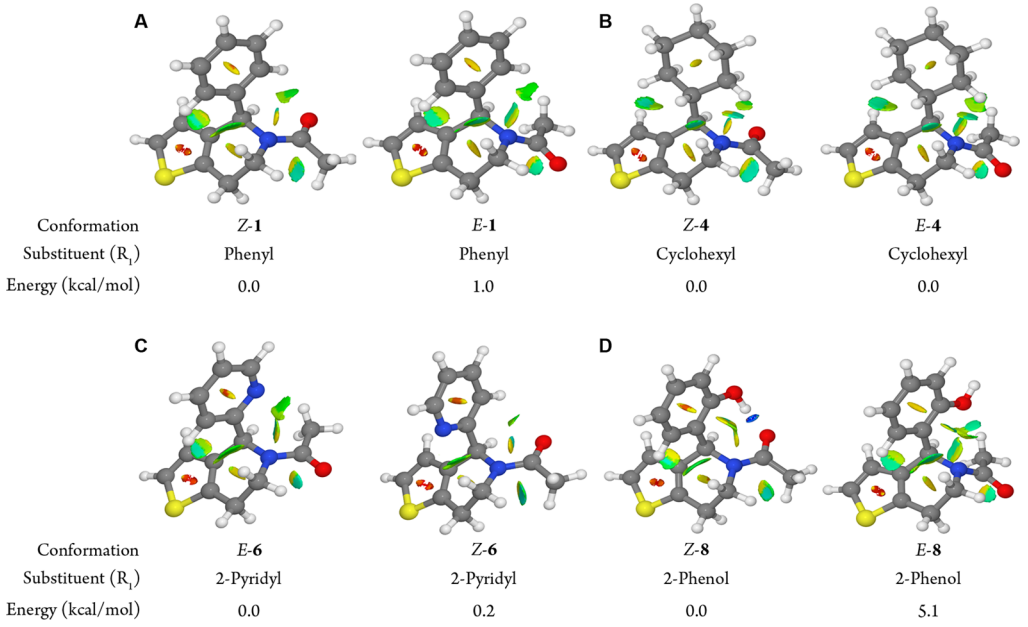

Figure 3. Computed NCI surfaces of the lowest energy conformations of **1** (A), **4** (B), **6** (C), and **8** (D). NCI surfaces are color-coded from red and yellow indicating destabilizing interactions to green and blue indicating increasing stabilization. See also Web-enhanced table table for interactive versions of these diagrams and ref 15.

than through-space effects. In the described dihydrothieno[3,2-*c*]pyridine system, the stereoselectivity is controlled by a combination of stereoelectronically controlled bond orientations that are influenced by NCIs within the molecular architecture. The balance of these interactions can be difficult to compute from total free energies alone; however, the recently introduced reduced electron density gradient is a more useful means to reveal such NCIs.[13,14] This index enables the identification and characterization of the strength of NCIs as chemically intuitive and visual isosurfaces that highlight stabilizing hydrogen-bonding interactions in blue, weaker van der Waals interactions in green, and destabilizing interactions such as steric clashes in yellow to red.

We therefore applied DFT modeling and NCI analysis (ωB97XD/TZVP/SCRF = chloroform)[15] to compare small energy differences between structures and the corresponding populations of compounds **1** and **4** (Figure 3). This model predicts that the amide lone pair in the *Z*-configuration is not in the correct orientation to participate in an n$-\pi^*_{aryl}$ interaction. Compound **1** exhibits four potential conformations, corresponding to two potential amide rotamers and the two piperidine ring-flipped conformations (cf. Web-enhanced table). Comparison of the relative energy of these conformations of **1** reveals that the *Z*-amide isomer is lower in free energy than the *E*-amide (Table S1). The Boltzmann population distribution of the four energy minima indicates only significant population of the *E*- and *Z*-ground-state conformers in a 16:84 *E*:*Z* ratio, in good agreement with observed values (Tables S1 and S2). Prediction of the ^{1}H NMR chemical shifts for *Z*-**1** provided resonances of the acetyl methyl protons at an average value of 2.01 ppm and for the equatorial H4 proton at 3.57 ppm, in good agreement with NOE results (Table S3, Figure 2B). The predicted shifts for *E*-**1** gave the methyl protons at an averaged resonance of 2.36 ppm and H6 at 6.09 ppm, also in excellent agreement with experimental data (Table S4, Figure 2B).

To understand the interactions influencing the energetic stability of each rotamer of **1**, NCI surfaces for each conformation were inspected (Figure 3A).[13,14,16] In the lowest energy (*Z*)-amide conformation, the amide carbonyl group forms a stabilizing NCI with the piperidine H6 proton and the *ortho* aromatic proton. Additional favorable interactions are found in both conformers between the thiophene ring and the *ortho* proton of the phenyl ring, as well as between the phenyl ring and the axial H4 proton of the piperidine ring. Compound **4** exhibits eight potential conformations, corresponding to combinations of two potential amide rotamers, two piperidine ring-flipped conformations, and two chair forms of the cyclohexyl ring (cf. Web-enhanced table). The NCI surfaces of the lowest energy conformations of **4** (Table S5) indicate that the *Z*-conformation no longer benefits from favorable interaction with the *ortho* position of the cyclohexyl ring (Figure 3B). Correspondingly, the lowest energy *E*- and *Z*-conformations are energetically equal, with the next highest energy levels corresponding to rotation about the C6-cyclohexyl bond. The calculated energy levels did not indicate any prominent interactions favoring *E*- or *Z*-conformers (Table S5), in good agreement with the observed 57:43 *E*:*Z* ratio. Weighting the predicted ^{1}H NMR chemical shifts for each *E*- and *Z*-energy level against the predicted Boltzmann population gives an average chemical shift prediction. The calculated average resonance for the *Z*-**4** acetyl methyl protons is 2.03 ppm (Table S7, Figure S14); low-temperature selective NOE experiments irradiating at the piperidine H4 resonances give an NOE at 2.14 ppm (Table S8, Figure S19).

With robust systems in place to predict and measure amide conformations, molecules were designed to promote either the *E*- or *Z*-conformer. Replacing the *ortho* CH of the phenyl moiety of **1** with 2-pyridyl derivative **6** was envisaged to promote the *E*-configuration by reversing the electrostatic interactions. Compound **6** exhibits eight potential conformations, corresponding to combinations of two amide rotamers, two piperidine ring-flipped conformations, and two rotated

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conformations about the C6-pyridine bond (cf. Web-enhanced table). The NCI surface prediction for **6** indicates that the nitrogen atom induces electrostatic repulsion with the carbonyl oxygen in the *Z*-conformer (Figure 3C), resulting in no predicted preference for the *E*- or *Z*-conformer within the accuracy of the calculations. Compound **6** was synthesized from 2-picolinic acid using the established synthetic route, and the conformation was assigned using the described approach combining weighted ^{1}H NMR prediction (Tables S11 and S12), low-temperature NOESY, and selective NOE experiments (Figures S29 and S30). As predicted, **6** exhibits an increased propensity for the *E*-conformer compared to compound **1**, with an *E*:*Z* ratio of 48:52, in good agreement with the predicted absence of *Z*-conformational preference. Additionally, ^{1}H NMR spectra of compounds **4** and **6** were recorded from 297 to 378 K and from 308 to 408 K which gave coalescence temperatures of 368 and 358 K, approximately corresponding to $\Delta G^{\ddagger}$ values of 18.9 and 18.4 kcal/mol, respectively (section 2.16 in the Supporting Information). Both free activation energies are typical for hindered internal rotations in *N*,*N*-dialkylamides.[17]

Increasing the strength of the interaction between the carbonyl group and the aromatic ring should promote the *Z*-conformation.[18] A hydroxyl group was therefore inserted at the phenyl *ortho* position, which was predicted to be in correct alignment to hydrogen-bond with the carbonyl with a CO−HO bond distance of 1.71 Å and a 6° deviation from linearity in the CO−HO bond (Figure 3D).[19] Indeed, NBO analysis of the ground state of the *ortho*-hydroxy derivative indicated strong bonding interactions between both carbonyl oxygen lone pairs and the hydroxyl σ^* (16.7 and 6.5 kcal/mol for σ-character and π-character lone pairs, respectively) (cf. Web-enhanced table). Compound **8** exhibits eight potential conformations, corresponding to combinations of two amide rotamers, two piperidine ring-flipped conformations, and two rotated conformations about the C6−phenol bond (cf. Web-enhanced table). DFT analysis of the energy levels of these conformations predicted that the three lowest energy conformers exhibit the *Z*-conformation. The lowest energy *E*-conformer was less favored by 5.1 kcal/mol, equating to a relative population distribution of ∼5000:1. The required molecule was synthesized from 2-methoxybenzoic acid, initially affording 2-methoxy derivative **7**. Low-temperature NOESY and NOE spectra indicate that **7** preferentially adopted the *E*-conformation, with and *E*:*Z* of 80:20, providing a more effective means to repel the amide carbonyl into the *E*-conformation. Demethylation of **7** with tribromoborane furnished the required phenol **8** (Figure 1). ^{1}H NMR spectra of **8** recorded in $CDCl_3$ indicate that, as predicted, only a single amide conformation is observed (Table 1, Figure S37). NOESY spectroscopy and selective NOE pulsed at the methyl environment at 2.23 ppm, both at room temperature, were used to confirm the exclusive presence of the intended *Z*-conformation (Figures S39−S41). The existence of the proposed hydrogen bond between the carbonyl and hydroxyl groups was supported by good agreement between the predicted and observed chemical shifts at 9.94 and 9.83 ppm, respectively. DFT prediction of the ^{1}H chemical shift has been applied to a crystallographically validated hydrogen-bonded proton, similarly demonstrating good agreement between predicted and observed values.[20] In order to confirm the presence of the putative hydrogen bond, the solid-state IR spectrum of **8** was recorded (Figure S43). This demonstrated a ν_{max}(OH) at 3088 cm^{-1}, indicative of a strong intramolecular hydrogen bond to the hydroxyl group.[21] The lower hydroxyl vibrational frequency observed was also in agreement with DFT calculation of the lowered harmonic oscillation of the hydroxyl group of **8** (Figure S43). The ^{1}H NMR spectra of **8** recorded in DMSO-d_6 resulted in an *E*:*Z* ratio of 40:60 (Figure S42). As a polar aprotic solvent, DMSO acts as a potent hydrogen-bond acceptor, thereby disrupting the internal hydrogen bond of **8**. Attempts to assess the effect of polar protic solvents (D_2O, MeOD) on the hydrogen-bonding and conformational ratio of **8** were unsuccessful due to poor solubility. Mixed-solvent D_2O:DMSO-d_6 ^{1}H NMR analysis of **8** maintained a 40:60 *E*:*Z* ratio up to 30% D_2O, above which D_2O concentration **8** precipitated. Investigation of the conformation properties of more water-soluble 5-acyl-6,7-dihydrothieno[3,2-*c*]pyridine derivatives in polar protic solvents is therefore continuing in our laboratory.

Table 1. Comparison of Calculated and Observed Amide *E*:*Z* Ratios of 6,7-Dihydrothieno[3,2-*c*]pyridine Derivatives at 298 K

compd	substituent (R_1)	cald *E*:*Z*	obsd *E*:*Z*	solvent
1	phenyl	16:84	22:78	$CDCl_3$
4	cyclohexyl	57:43	57:43	$CDCl_3$
6	2-pyridyl	59:41	48:52	$CDCl_3$
7	2-methoxyphenyl	N/D	80:20	$CDCl_3$
8	2-phenol	0:100	0:100	$CDCl_3$
		N/D	40:60	DMSO-d_6

CONCLUSION

The 2-substituted *N*-acyl-piperidine motif can be found in a range of known molecular architectures and biologically active compounds. Further analysis of the 474 2-substituted *N*-acyl-piperidine-containing structures available in the Cambridge Crystallographic Database identifies a subset of 186 amides in which an acyclic amide bond is present. Evaluation of the torsion angle about the C−N−C−O bond in these hits indicates a clustering of the compounds in approximately equal population for the *E*- and *Z*-conformers at 0° and 180°, respectively (Figure S74).[1] These 186 compounds should be amenable to predictive and designed conformational modulation using the approach presented here. Remarkably, the *ortho* phenol 2-substituted *N*-acyl-piperidine motif of compound **8** represents a currently unreported molecular architecture. We speculate that predictable modulation of the amide conformation in this class of molecules may additionally be used to promote target binding of bioactive molecules by biasing toward the correct binding conformation. Of the 29 bioactive compounds in the DrugBank database containing the core motif, including 13 approved and 3 investigational drugs, 20 have rotatable amide substituents.[2] Strategies to lock molecules in the correct binding conformation commonly involve rigidifying the molecule through the insertion of a ring system; however, this often results in decreased solubility, through increased lattice energy and predominantly increased logP.[22] The use of heteroatom insertion presented here may be seen as an alternative to cyclization to promote the required amide conformation without concomitant increase in clogP (Table S15). Ongoing research in our laboratory is focused on assessing the effect of conformational modulation on the biological activity of the 5-acyl-6,7-dihydrothieno[3,2-*c*]-pyridines.

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The computational studies presented here provide a powerful tool for the design and analysis of molecules with required conformations. NCI analysis is a superior method compared to NBO analysis for determining low-energy, through-space interactions that may have profound implications on the conformational properties of molecules. The combination of chemical shift predictions for conformers with weighting from the Boltzmann population distribution of the calculated energy levels provides an accurate method for predicting NMR signals of each conformer. Calculated NMR shifts predominantly show <0.3 ppm deviation from observed values, with the exception of the six-membered aromatic ring protons (Tables S3, S4, S7, S8, S11, S12, and S14). NCI surface visualization provides a simple visual model for the analysis of detailed intramolecular interactions that impact on the conformation, and we envisage that this approach will be adopted as a facile tool to aid synthetic chemists in the design and understanding of molecules.[15]

In summary, we have identified amide bond rotamers in 2-substituted *N*-acyl-piperidines, assigned their conformations through a combination of NOE experiments at low temperature to limit amide rotation, and established a predictive structural model that enabled design of molecules with programmed changes in conformational preference. Taken together, the *de novo* design and heteroatom insertions presented here provide a powerful method for modulation of amide conformation through either attractive hydrogen-bonding or repulsive electronic interactions.

EXPERIMENTAL SECTION

Microwave reactions were performed using a Biotage Initiator. ^{1}H NMR and ^{13}C NMR spectra were recorded at room temperature at 500 and 125 MHz, or 400 and 100 MHz, respectively. Chemical shifts (δ) are reported in parts per million (ppm) relative to residual solvent peaks as internal standard. Coupling constants (J) are reported in hertz (Hz). The peaks corresponding to the conformers are labeled with *E* or *Z*, respectively. Selective NOE and 2D-NOESY spectra were recorded at 400 and 500 MHz at room temperature or 221 and 218 K, respectively. High-temperature ^{1}H NMR spectra were recorded at 500 MHz in 1,1,2,2-tetrachloroethane-d_2 from 308 to 408 K in steps of 10 K. High-resolution mass spectrometry (HRMS) was performed using electrospray ionization (ESI) and time-of-flight (TOF) mass analysis. All details regarding the DFT modeling can be found at doi:10.6084/m9.figshare.1181739.

General Procedure A: Thiophene Ethylamide Preparation Using (Benzotriazol-1-yloxy)tripyrrolidinophosphonium Hexafluorophosphate (PyBOP). 2-(3-Thienyl)ethylamine (0.5 mL, 543 mg, 4.3 mmol, 1 equiv) was added to a solution of the corresponding carboxylic acid (4.73 mmol, 1.1 equiv), PyBOP (2.45 g, 4.73 mmol, 1.1 equiv), and *N*,*N*-diisopropylethylamine (DIPEA, 2.3 mL, 1.67 g, 12.9 mmol, 3 equiv) in DMF (2 mL). The reaction mixture was stirred at rt overnight. Afterward, DCM (30 mL) was added, and the solution was washed with an aqueous solution of LiCl (5% m/m) and brine to remove excess DMF. The organic layer was dried over $MgSO_4$, the solvent was removed in vacuum, and the residual was purified by column chromatography.

General Procedure B: Thiophene Ethylamide Preparation Using Acid Chlorides. Thiophene ethylamine (0.5 mL, 543 mg, 4.3 mmol, 1 equiv) was added dropwise (exothermic reaction) to a solution of the corresponding carboxylic acid chloride (5.16 mmol, 1.2 equiv) and triethylamine (TEA, 1.2 mL, 870 mg, 2 equiv) in dry DCM (5 mL). The reaction mixture was stirred at rt overnight. Afterward, the solvent was removed in vacuum, and the residual was purified by column chromatography.

General Procedure C: Bischler−Napieralski Reaction under Microwave Conditions. The acylated thiophene ethylamine derivative (0.38 mmol, 1 equiv) and $POCl_3$ (0.35 mL, 578 mg, 3.8 mmol, 10 equiv) were added to a suspension of P_2O_5 (160 mg, 1.14 mmol, 3 equiv) in dry toluene (2 mL). The mixture was heated by microwave irradiation at 140 °C for 0.5 h. The temperature was gradually increased. Subsequently, the reaction mixture was basified (pH = 10) using an aqueous solution of NaOH (20% v/v). The organic phase was separated and dried over $MgSO_4$, the solvent was removed in vacuum, and the residual was purified by column chromatography.

General Procedure D: Bischler−Napieralski Reaction under Reflux Conditions. A mixture of the acylated thiophene ethylamine derivative (0.84 mmol, 1 equiv), $POCl_3$ (0.23 mL, 388 mg, 2.53 mmol, 3 equiv), and P_2O_5 (359 mg, 2.53 mmol, 3 equiv) dissolved in xylene (3 mL) was heated at 85 °C for 2 h. Subsequently, the reaction mixture was basified (pH = 10) using an aqueous solution of NaOH (20% v/v). The organic phase was diluted with toluene, separated, and dried over $MgSO_4$, and the solvent was removed in vacuum. The cyclic imine was used without further purification.

General Procedure E: Reduction of the Imine. The cyclic imine obtained from general procedure C (**12b−15b**) or 7-cyclohexyl-6,7-dihydrothieno[3,2-*c*]pyridine (**16b**) (0.41 mmol, 1 equiv) was dissolved in dry methanol (1.6 mL). $NaBH_4$ (23 mg, 0.62 mmol, 1.5 equiv) was added to the solution in small portions, and the reaction mixture was stirred at rt for 1 h or overnight. Afterward, the mixture was concentrated in vacuum, and the residual was redissolved in H_2O (1 mL) and extracted using DCM. The organic phase was dried over $MgSO_4$ and the solvent removed in vacuum. The amine was used without further purification.

General Procedure F: Coupling of the Side Chain Using Acid Chlorides. The amine obtained from general procedure E (0.09 mmol, 1 equiv) and TEA (0.025 mL, 18 mg, 0.18 mmol, 2 equiv) were dissolved in dry DCM (1 mL). Subsequently, the corresponding acid chloride (0.11 mmol, 1.2 equiv) was added, and the reaction mixture was stirred at rt for 2 h. Afterward the solvent was removed in vacuum, and the residual was purified by column chromatography.

***N*-[2-(2-Thienyl)ethyl]benzamide (9a).** The amide **9a** was obtained from 2-(3-thienyl)ethylamine (0.50 mL, 543 mg, 4.3 mmol, 1 equiv) and benzoic acid (557 mg, 4.7 mmol, 1.1 equiv), using general procedure A, as a cream-colored solid (692 mg, 5.6 mmol, 70%). R_f = 0.44 (SiO_2; EtOAc:Hex, 4:6); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.77−7.67 (m, 2H), 7.57−7.44 (tt, ^3J = 7.4 Hz, ^4J = 1.4 Hz, 1H), 7.44−7.33 (m, 2H), 7.17 (dd, ^3J = 5.1 Hz, 4J = 1.2 Hz, 1H), 6.96 (dd, ^3J = 5.2, 3.4 Hz, 1H), 6.88−6.85 (m, 1H), 6.47 (s, 1H), 3.72 (q, ^3J = 6.5 Hz, 2H), 3.15 (t, ^3J = 6.5 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 167.6, 141.3, 134.6, 131.5, 128.6, 127.2, 126.9, 125.5, 124.1, 41.4, 30.0; HRMS (ESI, m/z) calcd for $C_{13}H_{14}NOS$ 232.0796, found 232.0796.

4-Phenyl-6,7-dihydrothieno[3,2-*c*]pyridine (9b). The cyclic imine **9b** was obtained from *N*-[2-(2-thienyl)ethyl]benzamide (**9a**) (290 mg, 1.3 mmol, 1 equiv), using general procedure D, as an orange oil (159 mg, 0.75 mmol, 57%). R_f = 0.43 (SiO_2; EtOAc:TEA, 100:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.69−7.65 (m, 2H), 7.46−7.40 (m, 3H), 7.09 (d, ^3J = 5.2 Hz, 1H), 7.01 (d, ^3J = 5.2 Hz, 1H), 3.97−3.93 (m, 2H), 2.95−2.91 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 162.9, 144.5, 139.2, 130.9, 129.7, 128.4, 128.2, 126.2, 121.5, 48.4, 22.4; HRMS (ESI, m/z) calcd for $C_{13}H_{11}NS$ 214.0690, found 214.0695.

4-Phenyl-4,5,6,7-tetrahydrothiene[3,2-*c*]pyridine (9c). The cyclic amine **9c** was obtained from 4-phenyl-6,7-dihydrothiene[3,2-*c*]pyridine (**9b**) (149 mg, 0.70 mmol, 1 equiv), using general procedure, E as a yellow solid (106 mg, 0.49 mmol, 70%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.36−7.27 (m, 5H), 7.01 (d, ^3J = 5.2 Hz, 1H), 6.47 (d, ^3J = 5.2 Hz, 1H), 5.04 (s, 1H), 3.34−3.29 (m, 1H), 3.14−3.08 (m, 1H), 3.04−2.96 (m, 1H), 2.89−2.82 (m, IH), 2.09 (br s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 143.7, 136.8, 135.1, 128.6, 128.5, 127.7, 126.5, 121.9, 60.2, 42.7, 26.1; HRMS (ESI, m/z) calcd for $C_{13}H_{14}NS$ 216.0847, found 216.0855.

[2-(2-Thienyl)ethylamino](*m*-tolyl)formaldehyde (10a). The amide **10a** was obtained from 2-(3-thienyl)ethylamine (0.79 mL, 0.85 mg, 6.7 mmol, 1 equiv) and *m*-toluic acid (1000 mg, 7.3 mmol, 1.1 equiv), using general procedure A, as a white solid (1480 mg, 7.2 mmol, 98%). R_f = 0.3 (SiO_2; EtOAc:Hex, 4:6); ^{1}H NMR (400 MHz,

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$CDCl_3$) δ 7.59 (s, 1H), 7.51 (t, ^3J = 3.5 Hz, 1H), 7.32−7.30 (m, 2H), 7.20 (dd, ^3J = 5.1 Hz, ^4J = 1.0 Hz, 1H), 6.98 (dd, ^3J = 5.1 Hz, ^3J = 3.5 Hz, 1H), 6.89 (d, ^3J = 3.3 Hz, 1H), 3.74 (q, ^3J = 6.5 Hz, 2H), 3.17 (t, ^3J = 6.6 Hz, 2H), 2.40 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.7, 141.4, 138.4, 134.5, 132.2, 128.4, 127.7, 127.1, 125.5, 124.0, 123.8, 60.4, 41.3, 30.0, 21.4, 14.2; HRMS (ESI, *m*/*z*) calcd for $C_{14}H_{16}NOS$ 246.0947, found 246.0960.

4-(*m*-Tolyl)-4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine (10c). The cyclic imine, 4-(*m*-tolyl)-6,7-dihydrothieno[3,2-*c*]pyridine (**10b**), was obtained from [2-(2-thienyl)ethylamino](*m*-tolyl)formaldehyde (**10a**) (700 mg, 2.9 mmol, 1 equiv), using general procedure D, as an orange oil (620 mg, 2.7 mmol, 93%). R_f = 0.8 (MeOH:EtOAc:NEt_3, 10:90:1). The subsequent reduction was carried out without purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (s, 1H), 7.46 (d, ^3J = 7.5 Hz, 1H), 7.32 (t, ^3J = 7.5 Hz, 1H), 7.27 (d, ^3J = 7.2 Hz, 1H), 7.08 (d, ^3J = 6.7 Hz, 1H), 7.03 (d, ^3J = 5.2 Hz, 1H), 3.99−3.93 (m, 2H), 2.97−2.89 (m, 2H), 2.41 (s, 3H). The cyclic amine **10c** was obtained from **10b** (620 mg, 2.7 mmol, 1 equiv), using general procedure E, as a yellow solid (yield over two steps: 387 mg, 1.7 mmol, 63%). R_f = 0.3 (SiO_2; MeOH:EtOAc:NEt_3, 10:90:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (t, ^3J = 7.5 Hz, 1H), 7.18−7.09 (m, 2H), 7.04 (d, ^3J = 5.2 Hz, 1H), 6.53 (d, ^3J = 5.2 Hz, 1H), 5.03 (s, 1H), 3.36 (dt, ^2J = 12.0 Hz, ^3J = 4.8 Hz, 2H), 3.18−3.11 (m, 1H), 3.09−2.99 (m, 1H), 2.89 (dt, ^2J = 15.9 Hz, ^3J = 3.3 Hz, 2H), 2.39 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 143.7, 138.2, 137.0, 134.9, 129.0, 128.4, 128.4, 126.5, 125.4, 121.7, 77.5, 77.2, 76.9, 60.2, 42.7, 26.2, 21.5; HRMS (ESI, *m*/*z*) calcd for $C_{14}H_{16}NS$ 230.0998, found 230.1003.

Cyclohexanecarboxylic Acid (2-Thiophen-2-ylethyl)amide (11a). The amide **11a** was obtained from 2-(3-thienyl)ethylamine (0.46 mL, 496 mg, 3.9 mmol, 1 equiv) and cyclohexanecarboxylic acid chloride (0.64 mL, 689 mg, 4.7 mmol, 1.2 equiv), using general procedure B, as a colorless oil (881 mg, 3.7 mmol, 85%). R_f = 0.36 (SiO_2; EtOAc:Hex, 3:7); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.16 (dd, ^3J = 5.1 Hz, ^4J = 1.2 Hz, 1H), 6.95 (dd, ^3J = 5.1 Hz, ^3J = 3.4 Hz, 1H), 6.82 (dd, ^3J = 3.4 Hz, ^4J = 1.2 Hz, 1H), 5.61 (s, 1H, NH), 3.51 (q, ^3J = 6.4 Hz, 2H), 3.02 (t, ^3J = 6.4 Hz, 2H), 2.03 (tt, ^3J = 11.8 Hz, ^3J = 3.4 Hz, 1H), 1.79 (m, 4H), 1.65 (m, 1H), 1.4 (qd, ^3J = 11.8 Hz, ^3J = 2.4 Hz, 4H), 1.23 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 177.1, 141.6, 127.1, 125.4, 123.9, 45.5, 40.6, 30.0, 29.7, 25.7; HRMS (ESI, *m*/*z*) calcd for $C_{13}H_{20}NOS$ 238.1266, found 238.1257.

7-Cyclohexyl-6,7-dihydrothieno[3,2-*c*]pyridine (11b). The cyclic imine **11b** was obtained from cyclohexanecarboxylic acid (2-thiophen-2-ylethyl)amide (**11a**) (200 mg, 0.84 mmol, 1 equiv), using general procedure D, as a colorless oil (150 mg, 0.68 mmol, 81%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.13 (d, ^3J = 5.2 Hz, 1H), 7.08 (d, ^3J = 5.2 Hz, 1H), 3.78 (t, ^3J = 8.2 Hz, 2H), 2.80 (t, ^3J = 8.2 Hz, 2H), 2.66 (m, 1H), 1.87 (m, 5), 1.73 (m, 1H), 1.37 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 124.1, 122.0, 47.7, 44.6, 30.9, 26.6, 26.4, 22.4; HRMS (ESI, *m*/*z*) calcd for $C_{13}H_{18}NS$ 220.1160, found 220.1164.

7-Cyclohexyl-4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine (11c). The cyclic amine **11c** was obtained from 7-cyclohexyl-6,7-dihydrothieno[3,2-*c*]pyridine (**11b**) (90 mg, 0.41 mmol, 1 equiv), using general procedure E, as an orange oil (56 mg, 0.25 mmol, 62%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.05 (d, ^3J = 5.2 Hz, 1H), 6.81 (d, ^3J = 5.2 Hz, 1H), 3.82 (dt, ^3J = 3.7 Hz, ^3J = 1.9 Hz, 1H), 3.35−3.30 (m, 1H), 2.99−2.92 (m, 1H), 2.84−2.69 (m, 2H), 1.86−1.79 (m, 1H), 1.72−1.66 (m, 5H), 1.45−1.01 (m, 5H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 137.4, 135.0, 127.2, 125.2, 121.6, 60.1, 43.2, 42.9, 30.7, 27.1, 27.0, 26.8, 26.7, 26.4; HRMS (ESI, *m*/*z*) calcd for $C_{13}H_{20}NS$ 222.1316, found 222.1317.

2-Picolinic Acid (2-Thiophen-2-ylethyl)amide (12a). The amide **12a** was obtained from 2-(3-thienyl)ethylamine (0.50 mL, 543 mg, 4.3 mmol, 1 equiv) and 2-picolinic acid (582 mg, 4.7 mmol, 1.1 equiv), using general procedure A, as a colorless oil (638 mg, 2.8 mmol, 64%). R_f = 0.64 (SiO_2; EtOAc:TEA, 100:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.52 (dt, ^3J = 5.0 Hz, ^4J = 1.4 Hz, 1H), 8.34−8.14 (s, 1H), 8.20 (dt, ^3J = 7.8 Hz, ^4J = 0.8 Hz, 1H), 7.83 (td, ^3J = 7.8 Hz, ^4J = 1.4 Hz, 1H), 7.41 (m, 1H), 7.16 (dd, ^3J = 5.2 Hz, ^4J = 1.5 Hz, 1H), 6.95 (dd, ^3J = 5.2, 3.5 Hz, 1H), 6.91−6.84 (m, 1H), 3.76 (q, ^3J = 6.8 Hz, 2H), 3.16 (t, ^3J = 6.8 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 164.4, 149.9, 148.1, 141.3, 137.3, 127.0, 126.2, 125.3, 123.9, 122.2, 40.9, 30.1; HRMS (ESI, *m*/*z*) calcd for $C_{12}H_{13}N_2OS$ 233.0749, found 233.0752.

7-(2-Pyridyl)-6,7-dihydrothieno[3,2-*c*]pyridine (12b). The cyclic imine **12b** was obtained from 2-picolinic acid (2-thiophen-2-ylethyl)amide (**12a**) (400 mg, 1.7 mmol, 1 equiv), using general procedure C, as a brown oil (124 mg, 0.6 mmol, 34%). R_f = 0.38 (SiO_2; EtOAc:TEA, 100:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.68 (dt, ^3J = 5.1 Hz, ^4J = 1.5 Hz, 1H), 8.00 (dd, ^3J = 7.7 Hz, ^4J = 1.3 Hz, 1H), 7.81 (td, ^3J = 7.7 Hz, ^4J = 1.5 Hz, 1H), 7.54 (d, ^3J = 5.3 Hz, 1H), 7.36 (m, 1H), 7.12 (d, ^3J = 5.3 Hz, 1H), 4.03 (t, ^3J = 8.5 Hz, 2H), 2.97 (t, ^3J = 8.5 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 161.4, 156.9, 148.5, 144.6, 136.7, 130.0, 127.1, 124.1, 122.6, 121.2, 48.5, 22.2; HRMS (ESI, *m*/*z*) calcd for $C_{12}H_{11}N_2S$ 215.0643, found 215.0655.

7-(2-Pyridyl)-4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine (12c). The amine **12c** was obtained from 7-(2-pryidyl)-6,7-dihydrothieno-[3,2-*c*]pyridine (**12b**) (105 mg, 0.5 mmol, 1 equiv), using general procedure E, as a brown oil (61 mg, 0.3 mmol, 58%). R_f = 0.10 (SiO_2; EtOAc:TEA, 100:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.60 (dt, ^3J = 4.9 Hz, ^4J = 1.5 Hz, 1H), 7.66 (td, ^3J = 7.7 Hz, ^4J = 1.5 Hz, 1H), 7.25 (dd, ^3J = 7.7 Hz, ^4J = 1.0 Hz 1H), 7.18−7.22 (m, 1H), 7.05 (d, ^3J = 5.2 Hz, 1H), 6.58 (d, ^3J = 5.2 Hz, 1H), 5.19 (t, ^3J = 2.0 Hz, 1H), 3.32 (dt, ^3J = 12.4 Hz, ^3J = 4.9 Hz, 1H), 3.22−3.09 (m, 1H), 3.06−2.95 (m, 1H), 2.93−2.86 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.2, 149.5, 136.6, 135.3, 135.3, 125.9, 122.5, 122.5, 122.1, 61.0, 42.2, 25.9; HRMS (ESI, *m*/*z*) calcd for $C_{12}H_{13}N_2S$ 217.0803, found 217.0799.

2-Methoxybenzoic Acid (2-Thiophen-2-ylethyl)amide (13a). The amide **13a** was obtained from 2-(3-thienyl)ethylamine (0.5 mL, 543 mg, 4.3 mmol, 1 equiv) and 2-methoxybenzoic acid (719 mg, 4.73 mmol, 1.1 equiv), using general procedure A, as a colorless oil (769 mg, 3.1 mmol, 73%). R_f = 0.52 (SiO_2; EtOAc:Hex, 4:6); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.22 (dd, ^3J = 7.8 Hz, ^4J = 1.9 Hz, 1H), 8.04 (s, 1H, NH), 7.45−7.40 (m, 1 H), 7.19 (dd, ^3J = 5.1 Hz, ^4J = 1.2 Hz, 1H), 7.09−7.05 (m, 1H), 6.98−6.89 (m, 3H), 3.82 (s, 1H), 3.77 (q, ^3J = 6.8 Hz, ^3J = 12.2 Hz, 2H), 3.15 (t, ^3J = 6.8 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 165.3, 157.6, 142.1, 132.8, 132.4, 127.1, 125.5, 124.0, 121.6, 121.4, 111.4, 110.1, 55.8, 41.2, 30.1; HRMS (ESI, *m*/*z*) calcd for $C_{14}H_{16}NO_2S$ 262.0902, found 262.0916.

7-(2-Methoxyphenyl)-6,7-dihydrothieno[3,2-*c*]pyridine (13b). The cyclic imine **13b** was obtained from 2-methoxybenzoic acid (2-thiophen-2-ylethyl)amide (**13a**) (100 mg, 0.38 mmol, 1 equiv), using general procedure C, as a colorless oil (40 mg, 0.16 mmol, 43%). R_f = 0.48 (SiO_2; EtOAc:TEA, 100:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.40−7.34 (m, 2H), 7.01 (td, ^3J = 7.5 Hz, ^4J = 1.0 Hz, 1H), 6.97−6.93 (m, 2H), 6.69 (d, ^3J = 5.2 Hz, 1H), 4.00 (t, ^3J = 8.2 Hz, 2H), 3.73 (s, 3H), 2.96 (t, ^3J = 8.2 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 162.1, 157.2, 142.4, 132.2, 130.4, 130.0, 129.0, 127.1, 126.2, 121.2, 120.9, 111.2, 110.1, 55.6, 48.3, 43.0, 22.2; HRMS (ESI, *m*/*z*) calcd for $C_{14}H_{14}NOS$ 244.0796, found 244.0805.

7-(2-Methoxyphenyl)-4,5,6,7-tetrahydrothieno[3,2-*c*]-pyridine (13c). The amine **13c** was obtained from 7-(2-methoxyphenyl)-6,7-dihydrothieno[3,2-*c*]pyridine (**13b**) (235 mg, 0.97 mmol, 1 equiv), using general procedure E, as a white solid (160 mg, 0.65 mmol, 67%). R_f = 0.40 (SiO_2; EtOAc:TEA, 100:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.29−7.24 (m, 1H), 7.05 (d, ^3J = 5.2 Hz, 1H), 6.95−6.93 (m, 2H), 6.87 (td, ^3J = 7.4 Hz, ^4J = 1.1 Hz, 1H), 6.56 (d, ^3J = 5.2 Hz, 1H), 5.51 (s, 1H), 3.90 (s, 3H), 3.20−3.14 (m, 1H), 3.10−3.04 (m, 1H), 2.93−2.90 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 157.2, 136.3, 135.4, 131.6, 129.5, 128.5, 126.6, 121.7, 120.3, 110.5, 55.5, 53.0, 41.4, 26.3; HRMS (ESI, *m*/*z*) calcd for $C_{14}H_{16}NOS$ 246.0953, found 246.0952.

1-[4-Phenyl-6,7-dihydrothieno[3,2-*c*]pyridin-5(4*H*)-yl]-ethanone (1). The amide **1** was obtained from 7-phenyl-4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine (**9c**) (30 mg, 0.14 mmol, 1 equiv) and acetyl chloride (0.012 mL, 13 mg, 0.17 mmol, 1.2 equiv), using general procedure G, as a white solid (16 mg, 0.06 mmol, 44%). R_f = 0.50 (SiO_2; EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.34−7.21 (m, 5H), 7.12 (d, ^3J = 5.1 Hz, 1H), 6.89 (s, 1H, *ma*), 6.75 (d, ^3J = 5.1 Hz, 1H, *mi*), 6.69 (d, ^3J = 5.1 Hz, 1H, *ma*), 5.92 (s, 1H, *mi*), 4.86−4.82 (m, 1H, *mi*), 3.81 (dd, ^3J = 14.0, 5.2 Hz, 1H, *ma*), 3.39−3.31 (m, 1H, *ma*),

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3.02−2.85 (m, 2H), 2.82−2.78 (m, 1H, *mi*), 2.28 (s, 3H, *mi*), 2.15 (s, 3H, *ma*); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 168.9, 141.2, 134.3, 133.9, 128.8, 128.7, 128.3, 128.0, 127.7, 127.3, 126.7, 126.1, 123.3, 123.3, 58.8, 53.4, 40.2, 36.3, 25.7, 24.7, 22.2, 21.8; HRMS (ESI, *m*/*z*) calcd for $C_{15}H_{16}NOS$ 258.0953, found 258.0965.

1-[4-(3-Methylphenyl)-6,7-dihydrothieno[3,2-*c*]pyridin-5(4*H*)-yl]prop-2-en-1-one (2). The amide **2** was obtained from 4-(3-methylphenyl)-4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine (**10c**) (20 mg, 0.09 mmol, 1 equiv) and acryloyl chloride (0.0089 mL, 9.9 mg, 0.11 mmol, 1.2 equiv), using general procedure F, as a colorless oil (16 mg, 0.056 mmol, 63%). R_f = 0.38 (SiO_2; EtOAc:Hex, 3:7); ^{1}H NMR (500 MHz, $CDCl_3$) 7.19 (d, ^3J = 7.5 Hz, 1H, *E*), 7.15 (d, ^3J = 5.2 Hz, 2H, *E*), 7.10−7.05 (dd, ^3J = 15.8 Hz, ^3J = 7.5 Hz, 3H, *E*), 6.94 (s, 1H, *E*), 6.85 (dd, ^3J = 15.6 Hz, ^3J = 11.4 Hz, 1H, *Z*), 6.77 (s, 1H, *Z*), 6.72 (d, ^3J = 4.7 Hz, 1H, *E*), 6.61 (dd, ^3J = 16.7 Hz, ^3J = 10.4 Hz, 1H, *E*), 6.42 (s, 1H, *Z*), 6.35 (d, ^3J = 16.7 Hz, 1H, *E*), 6.09 (s, 1H, *Z*), 5.79 (s, 1H, *Z*), 5.73 (d, ^3J = 10.4 Hz, 1H, *E*), 4.86 (s, 1H, *Z*), 4.01 (dd, ^2J = 13.8 Hz, ^3J = 4.2 Hz, 1H, *E*), 3.40 (td, ^3J = 13.8 Hz, ^3J = 4.2 Hz, 1H, *E*), 3.08−2.83 (m, 2H, *E*), 2.32 (s, 3H, *Z*/*E*); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 165.5, 141.1, 138.2, 134.4, 133.9, 129.5, 128.8, 128.3, 128.3, 128.1, 128.0, 126.8, 126.2, 125.9, 124.7, 123.4, 57.9, 54.1, 39.8, 36.8, 26.2, 24.9, 21.6; HRMS (ESI, *m*/*z*) calcd for $C_{17}H_{18}NOS$ 284.1109, found 284.1119.

1-[4-(3-Methylphenyl)-6,7-dihydrothieno[3,2-*c*]pyridin-5(4*H*)-yl]prop-2-en-1-one (3). A mixture of 4-(3-methylphenyl)-4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine (**10c**) (20 mg, 0.087 mmol, 1 equiv), allyl bromide (0.012 mL, 17 mg, 0.14 mmol, 1.6 equiv), and K_2CO_3 (19 mg, 0.14 mmol, 1.6 equiv) dissolved in 1 mL of acetone was stirred at rt overnight. A precipitate formed that was removed by filtration. Afterward, the solvent was removed in vacuum and the residual purified by column chromatography to afford the tertiary amine **3** as a colorless oil (12 mg, 0.045 mmol, 52%). R_f = 0.73 (SiO_2; EtOAc:Hex, 3:7); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.19 (t, ^3J = 7.5 Hz, 1H), 7.11 (s, 1H), 7.08 (t, ^3J = 7.5 Hz, 2H), 6.94 (d, ^3J = 5.2 Hz, 1H), 6.33 (d, ^3J = 5.2 Hz, 1H), 5.91−5.83 (m, 1H), 5.18−5.13 (m, 2H), 4.45 (s, 1H), 3.28−3.24 (m, 2H), 3.09−3.03 (m, 1H), 2.90−2.84 (m, 2H), 2.68−2.63 (m, 1H), 2.33 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 141.3, 140.8, 135.6, 134.4, 134.0, 129.4, 128.1, 128.0, 126.8, 126.0, 122.0, 117.5, 66.2, 57.0, 47.8, 25.0, 21.4; HRMS (ESI, *m*/*z*) calcd for $C_{17}H_{20}NS$ 270.1316, found 270.1326.

1-(4-Cyclohexyl-6,7-dihydrothieno[3,2-*c*]pyridin-5(4*H*)-yl)-ethanone (4). The amide **4** was obtained from 7-cyclohexyl-4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine (**11c**) (30 mg, 0.14 mmol, 1 equiv) and acetyl chloride (0.015 mL, 16 mg, 0.21 mmol, 1.5 equiv), using general procedure F, as a colorless oil (20 mg, 0.076 mmol, 54%). R_f = 0.28 (SiO_2; EtOAc:Hex, 3:7); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.08 (d, ^3J = 5.2 Hz, 1H, *E*), 7.06 (d, ^3J = 5.2 Hz, 1H, *Z*), 6.82 (d, ^3J = 5.2 Hz, 1H, *Z*), 6.80 (d, ^3J = 5.2 Hz, 1H, *E*), 5.38 (d, ^3J = 8.6 Hz, 1H, *Z*), 4.88 (dd, ^2J = 12.6 Hz, ^3J = 5.8 Hz, 1H, *E*), 4.38 (d, ^3J = 8.9 Hz, 1H, *E*), 3.95 (dd, ^2J = 14.1 Hz, ^3J = 5.9 Hz, 1H, *Z*), 3.55 (m, 1H, *Z*), 3.03 (td, ^2J = 12.2 Hz, ^3J = 4.4 Hz, 1H, *E*), 2.98−2.89 (m, 1H, *Z*/*E*), 2.86−2.81 (m, 1H, *Z*), 2.76−2.72 (m, 1H, *E*), 2.17 (s, 3H, *Z*), 2.12 (s, 3H, *E*), 1.91−1.63 (m, 7H, *Z*/*E*), 1.27−0.99 (m, 5H, *Z*/*E*); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 170.0, 169.4, 136.1, 135.1, 134.9, 132.7, 127.5, 126.8, 122.1, 122.0, 61.3, 55.4, 43.2, 42.8, 41.0, 35.7, 31.0, 30.7, 30.4, 29.8, 26.4, 26.4, 26.4, 26.3, 26.3, 26.3, 25.8, 24.7, 21.9; ^{1}H NMR (500 MHz, $C_2D_2Cl_4$) δ = 7.11 (d, ^3J = 5.1 Hz, 1H, *Z*/*E*), 6.84 (d, ^3J = 5.1 Hz, 1H, *Z*), 6.82 (d, ^3J = 5.2 Hz, 1H, *E*), 5.32 (d, ^3J = 8.6 Hz, 1H, *Z*), 4.85−4.82 (m, 1H, *E*), 4.36 (d, ^3J = 8.9 Hz, 1H, *E*), 3.92 (dd, ^2J = 14.3 Hz, ^3J = 5.8 Hz, 1H, *Z*), 3.52 (m, 1H, *Z*), 3.01 (td, ^2J = 12.3 Hz, ^3J = 4.6 Hz, 1H, *E*), 2.95−2.82 (m, 2H, *Z*/*E*), 2.76 (dd, ^3J = 16.2 Hz, ^3J = 4.2 Hz, 1H, *E*), 2.14 (s, 3H, *Z*), 2.11 (s, 3H, *E*), 1.89−1.60 (m, 7H, *Z*/*E*), 1.26−1.00 (m, 5H, *Z*/*E*); ^{13}C NMR (125 MHz, $C_2D_2Cl_4$) δ = 169.6, 169.2, 135.7, 134.7, 134.7, 132.8, 127.2, 126.7, 122.1, 122.0, 60.9, 55.0, 42.8, 42.2, 40.7, 35.4, 30.7, 30.5, 30.2, 29.5, 26.2, 26.1, 26.0, 25.5, 24.5, 22.1, 21.7; HRMS (ESI, *m*/*z*) calcd for $C_{15}H_{22}NOS$ 264.1422, found 264.1431.

1-(4-Phenyl-6,7-dihydrothieno[3,2-*c*]pyridin-5(4*H*)-yl)-ethanethione (5). Lawesson's reagent (26 mg, 0.064 mmol, 0.75 equiv) dissolved in 3 mL of dry THF was added to 1-(4-phenyl-6,7-dihydrothieno[3,2-*c*]pyridin-5(4*H*)-yl)ethanone (**1**) (20 mg, 0.077 mmol, 1 equiv) dissolved in 1.5 mL of dry THF. The reaction was stirred at rt over 72 h. Removing the solvent in vacuum and purifying the residual by column chromatography provided the thioamide **5** as a colorless oil (19 mg, 0.069 mmol, 89%). R_f = 0.56 (SiO_2; EtOAc:Hex, 3:7); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.21 (s, 1H, *E*), 7.45−7.44 (m, 1H, *E*), 7.38−7.36 (m, 1H, *Z*), 7.35−7.34 (m, 1H, *Z*), 7.33−7.32 (m, 1H, *Z*), 7.31 (m, 1H, *E*), 7.30−7.29 (m, 2H, *Z*), 7.23−7.22 (m, 1H, *Z*), 7.22−7.21 (m, 2H, *Z*), 7.20 (d, ^3J = 5.5 Hz, 1H, *Z*/*E*), 6.81 (d, ^3J = 5 Hz, 1H, *Z*), 6.78 (d, ^3J = 5.5 Hz, 1H, *E*), 6.43 (s, 1H, *Z*), 5.78−5.75 (m, 1H, *E*), 4.22 (m, 1H, *E*), 3.56−3.50 (m, 1H, *E*), 3.33−3.23 (m, 2H, *Z*), 3.00−2.95 (m, 1H, *E*), 2.93 (s, 1H, *E*), 2.89−2.85 (m, 1H, *Z*), 2.75 (s, 3H, *E*); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 199.5, 198.9, 140.0, 138.7, 136.2, 134.1, 133.5, 132.7, 129.1, 128.6, 128.5, 128.4, 127.5, 126.8, 125.9, 124.3, 124.1, 62.1, 60.7, 44.1, 43.5, 33.2, 32.4, 25.9, 24.1; HRMS (ESI, *m*/*z*) calcd for $C_{15}H_{16}NS_2$ 274.0724, found 274.0714.

1-[4-(2-Pyridyl)-6,7-dihydrothieno[3,2-*c*]pyridin-5(4*H*)-yl]-ethanone (6). The amide **6** was obtained from 7-(2-pyridyl)-4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine (**12c**) (19 mg, 0.09 mmol, 1 equiv) and acetyl chloride (0.01 mL, 11 mg, 0.14 mmol, 1.5 equiv), using general procedure G, as a colorless oil (12 mg, 0.05 mmol, 55%). R_f = 0.32 (SiO_2; EtOAc:TEA, 100:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.61 (d, ^3J = 5.7 Hz, 1H, *mi*), 8.53 (d, ^3J = 4.7 Hz, 1H, *ma*), 7.64 (m, 1H), 7.45 (d, ^3J = 7.8 Hz, 1H, *ma*), 7.21 (dd, ^3J = 7.6, 4.8 Hz, 1H, *mi*), 7.18−7.12 (m, 2H), 7.10 (t, ^3J = 6.4 Hz, 2H), 6.93 (d, ^3J = 5.1 Hz, 1H, *mi*), 6.75 (d, ^3J = 5.1 Hz, 1H, *ma*), 6.70 (s, 1H, *ma*), 6.05 (s, 1H, *mi*), 5.00 (dd, ^3J = 14.0, 3.7 Hz, 1H, *mi*), 4.03−3.97 (m, 1H, *ma*), 3.97−3.87 (m, 1H, *ma*), 3.06 (dd, ^3J = 11.6, 3.7 Hz, 1H, *mi*), 3.02−2.91 (m, 2H), 2.86 (dd, ^3J = 16.7, 3.1 Hz, 1H, *mi*), 2.33 (s, 3H, *mi*), 2.20 (s, 3H, *ma*); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 170.7, 169.3, 160.0, 159.9, 149.8, 149.6, 136.8, 136.6, 135.6, 134.0, 133.4, 132.7, 126.4, 126.3, 123.3, 123.1, 122.9, 122.8, 122.5, 121.0, 60.6, 55.8, 42.0, 36.7, 25.7, 24.9, 22.5, 22.0; HRMS (ESI, *m*/*z*) calcd for $C_{14}H_{15}N_2OS$ 259.0905, found 259.0909.

1-[4-(2-Methoxyphenyl)-6,7-dihydrothieno[3,2-*c*]pyridin-5(4*H*)-yl]ethanone (7). The amide **7** was obtained from 7-(2-methoxyphenyl)-4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine (**13c**) (80 mg, 0.37 mmol, 1 equiv) and acetyl chloride (0.039 mL, 43 mg, 0.55 mmol, 1.5 equiv), using general procedure F, as a white solid (79 mg, 0.27 mmol, 74%). R_f = 0.44 (SiO_2; EtOAc:Hex, 6:4); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.29−7.23 (m, 1H, *Z*), 7.10 (d, ^3J = 5.2 Hz, 1H, *Z*), 7.07−7.06 (m, 2H, *E*), 6.93 (d, ^3J = 8.0 Hz, 1H, *Z*), 6.91−6.88 (m, 2H, *E*), 6.86−6.81 (m, 2H, *Z*), 6.67 (s, 1H, *E*), 6.66 (d, ^3J = 5.2 Hz, 1H, *Z*), 6.33 (s, 1H, *Z*), 4.80−4.73 (m, 1H, *Z*), 3.91 (s, 3H, *Z*), 3.87 (m, 1H, *E*), 3.84 (s, 3H, *E*), 3.55 (m, 1H, *E*), 3.04−2.97 (m, 2H, *Z*), 2.91 (td, ^2J = 16.6 Hz, ^2J = 15.9 Hz, ^3J = 4.4 Hz 1H, *E*), 2.84−2.77 (m, 1H, *Z*), 2.31 (s, 3H, *Z*), 2.16 (s, 3H, *E*); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 170.7, 168.8, 157.7, 156.8, 135.9, 135.5, 134.3, 133.3, 130.0, 129.6, 129.4, 129.1, 128.9, 126.6, 125.9, 123.2, 122.9, 120.4, 120.1, 111.1, 110.6, 55.7, 55.3, 53.7, 49.6, 41.1, 36.3, 25.9, 24.8, 22.2, 21.7; HRMS (ESI, *m*/*z*) calcd for $C_{16}H_{18}NO_2S$ 288.1058, found 288.1051.

1-[4-(2-Hydroxyphenyl)-6,7-dihydrothieno[3,2-*c*]pyridin-5(4*H*)-yl]ethanone (8). BBr_3 (0.93 mL of 1 M BBr_3 in DCM, 0.93 mmol, 9 equiv) was added dropwise to a solution of 1-[4-(2-methoxyphenyl)-6,7-dihydrothieno[3,2-*c*]pyridin-5(4*H*)-yl]ethanone (**7**) (30 mg, 0.10 mmol, 1 equiv) in 2 mL of dry DCM at −78 °C (isopropanol−dry ice bath) under an argon atmosphere. The reaction mixture was allowed to warm to room temperature while being stirred overnight under argon. A 1:1 mixture of methanol and water (1 mL) was added to quench the reaction. Afterward, the organic phase was washed with brine and dried over $MgSO_4$, and the organic solvent was removed in vacuum. The residual was purified by column chromatography to provide the product **8** as a white solid (15 mg, 0.055 mmol, 55%). R_f = 0.69 (SiO_2; EtOAc:Hex, 6:4); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 9.83 (s, 1H), 7.22−7.19 (m, 1H), 7.15 (d, ^3J = 5.2 Hz, 1H), 6.98 (d, ^3J = 8.1 Hz, 1H), 6.75−6.71 (m, 3H), 6.59 (d, ^3J = 5.2 Hz, 1H), 3.86 (dd, ^2J = 14.1 Hz, ^3J = 4.8 Hz, 1H), 3.50 (td, ^2J = 14.1 Hz, ^3J = 13.2 Hz, ^3J = 4.4 Hz, 1H), 3.09−2.97 (m, 2H), 2.20 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 171.7, 156.1, 133.7, 230.1,

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129.8, 126.6, 125.7, 124.0, 119.3, 117.9, 50.9, 40.7, 25.5, 21.6; HRMS (ESI, m/z) calcd for $C_{15}H_{16}NO_2S$ 274.0902, found 274.0893.

■ ASSOCIATED CONTENT

Supporting Information

Supplemental Figures S1−74 and supplementary Tables S1−15. This material is available free of charge via the Internet at http://pubs.acs.org. Full information for the systems reported in the Web-enhanced table is available via the links to the digital repository. The function of this repository is explained in ref 15.

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Notes

The authors declare no competing financial interest.

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