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

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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, including those of biologically active compounds. 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. This emerging challenge necessitates tools to analyze and manipulate the conformation of target compounds. 5-Acetyl-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. 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 with microwave assistance to promote Bischler–Napieralski cyclization (Figure 1). The 1H NMR spectrum of 1 shows the presence of several additional hydrogen environments (Figure 2A). The most prominently shifted of these proton signals is a singlet at 5.92 ppm, corresponding to H6 and one H4 proton, respectively. In both cases, the shifted protons are adjacent to the amide nitrogen.

To confirm that the additional peaks observed in the 1H 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.
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. 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−π* aryl interactions between the lone pair of the carbonyl and the anti-bonding orbital of the adjacent aromatic ring. In such cases, changes in the electronics of the ring system or the nature of the lone pair donor have been used to modulate n−π* interactions. In order to probe putative n−π* 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. 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−π* amide interaction. We therefore proceeded to increase the lone pair donor capability in the molecule by exchanging the carbonyl oxygen with sulfur. The latter should exhibit increased n−π* aryl donation and thereby result in a higher population of the Z-amide. 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−π* 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, 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 than n−π* interactions.
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.\textsuperscript{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 (\textit{ω}B97XD/TZVP/SCRF = chloroform)\textsuperscript{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 \textit{Z}-configuration is not in the correct orientation to participate in an \textit{n}−\textit{π}*_{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 \textit{Z}-amide isomer is lower in free energy than the \textit{E}-amide (Table S1). The Boltzmann population distribution of the four energy minima indicates only significant population of the \textit{E}- and \textit{Z}-ground-state conformers in a 16:84 \textit{E}:\textit{Z} ratio, in good agreement with observed values (Tables S1 and S2). Prediction of the \textsuperscript{1}H NMR chemical shifts for \textit{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 \textit{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).\textsuperscript{13,14,16} In the lowest energy \textit{(Z)}-amide conformation, the amide carbonyl group forms a stabilizing NCI with the piperidine H6 proton and the \textit{ortho} aromatic proton. Additional favorable interactions are found in both conformers between the thiophene ring and the \textit{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 \textit{Z}-conformation no longer benefits from favorable interaction with the \textit{ortho} position of the cyclohexyl ring (Figure 3B). Correspondingly, the lowest energy \textit{E}- and \textit{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 \textit{E}- or \textit{Z}-conformers (Table S5), in good agreement with the observed 57:43 \textit{E}:\textit{Z} ratio. Weighting the predicted \textsuperscript{1}H NMR chemical shifts for each \textit{E}- and \textit{Z}-energy level against the predicted Boltzmann population gives an average chemical shift prediction. The calculated average resonance for the \textit{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 \textit{E}- or \textit{Z}-conformer. Replacing the \textit{ortho} CH of the phenyl moiety of 1 with 2-pyridyl derivative 6 was envisaged to promote the \textit{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 conformations of the pyridine ring.
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 1H 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, 1H 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 ΔG‡ 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 position, which was predicted to be in correct alignment to hydrogen-bond with the carbonyl with a CO–H 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 1:500:1. 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). 1H NMR spectra of 8 recorded in CDCl₃ 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 1H 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 νmax(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 1H NMR spectra of 8 recorded in DMSO-d₆ 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 (D₂O, MeOD) on the hydrogen-bonding and conformational ratio of 8 were unsuccessful due to poor solubility. Mixed-solvent D₂O:DMSO-d₆ 1H NMR analysis of 8 maintained a 40:60 E/Z ratio up to 30% D₂O, above which D₂O 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 (R₁) | cald E/Z | obsd E/Z | solvent |
|-------|-----------------|----------|----------|---------|
| 1     | phenyl          | 16:84    | 22:78    | CDCl₃   |
| 4     | cyclohexyl      | 57:43    | 57:43    | CDCl₃   |
| 6     | 2-pyridyl       | 59:41    | 48:52    | CDCl₃   |
| 7     | 2-methoxyphenyl | N/D      | 80:20    | CDCl₃   |
| 8     | 2-phenol        | 0:100    | 0:100    | CDCl₃   |
|       |                 |          |          | DMSO-d₆ |

CONCLUSION

The 2-substituted N-acetyl-piperidine motif can be found in a range of known molecular architectures and biologically active compounds. Further analysis of the 474 2-substituted N-acetyl-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-acetyl-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.
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. 1H NMR and 13C NMR spectra were recorded at room temperature at 500 and 125 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 218 and 218 K, respectively. High-temperature 1H NMR spectra were recorded at 500 MHz in 1,1,2,2-tetrachloroethane-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-yloxytrispyrrolidinophosphonium Hexafluorophosphate (PyBOP).

1-(3-Thienyl)ethylamine (0.5 mL, 543 mg, 4.3 mmol, 1 equiv) was added to a solution of the corresponding carboxylic acid chloride (5.16 mmol, 1.2 equiv) and triethylamine (TEA, 1.2 mL, 1.67 g, 12.9 mmol, 3 equiv) in dry DCM (2 mL). The reaction mixture was stirred at rt for 2 h. Afterward the solvent was removed in vacuum, the amine was used without further purification.

**General Procedure B:** Thiophene Ethylamide Preparation Using Acid Chlorides. Thiophene ethylamine (0.5 mL, 543 mg, 4.3 mmol, 1 equiv) and benzoyl chloride (657 mg, 4.7 mmol, 1.1 equiv) were 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 Reflux Conditions. A mixture of the acylated thiophene ethylamine derivative (0.84 mmol, 1 equiv), POCl3 (2.0 mL, 388 mg, 2.53 mmol, 3 equiv), and P2O5 (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 separated and dried over MgSO4, the solvent was removed in vacuum, and the residual was purified by column chromatography.

**General Procedure D:** Bischler–Napieralski Reaction under Microwave Conditions. The acylated thiophene ethylamine derivative (0.38 mmol, 1 equiv) and POCl3 (0.35 mL, 378 mg, 3.8 mmol, 10 equiv) were added to a suspension of P2O5 (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 MgSO4, the solvent was removed in vacuum, and the residual was purified by column chromatography.

**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). NaBH4 (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 H2O (1 mL) and extracted using DCM. The organic phase was dried over MgSO4 and the solvent removed in vacuum. The cyclic imine 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.

**1H NMR (400 MHz, CDCl3) δ = 7.77–7.67 (m, 2H), 7.57–7.44 (m, 2H, J = 1.4 Hz, 1H), 7.44–7.33 (m, 2H), 7.17 (dd, J = 5.1 Hz, 4J = 1.2 Hz, 1H), 6.96 (dd, J = 5.2, 3.4 Hz, 1H), 6.88–6.85 (m, 1H, 4J = 1.2 Hz, 1H), 6.47 (s, 1H, 3J) = 6.5 Hz, 2H), 3.15 (t, J = 6.5 Hz, 2H, 1C NMR (101 MHz, CDCl3) δ = 167.6, 141.3, 134.6, 131.5, 126.8, 127.2, 126.9, 125.5, 124.1, 14.4, 30.0; HRMS (ESI, m/z) calc for C13H11NS 214.0690, found 214.0695.

**4-Phenyl-6,7-dihydrothieno[3,2-c]pyridine (9a).** The cyclic amine 9a was obtained from 2-(3-thienyl)ethylamine (0.5 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, 98%).

**4-Phenyl-4,5,6,7-tetrahydrothieno[3,2-c]pyridine (9c).** The cyclic amine 9c was obtained from 4-phenyl-6,7-dihydrothieno[3,2-c]pyridine (9b) (149 mg, 0.70 mmol, 1 equiv), using general procedure E, as a yellow oil (159 mg, 0.75 mmol, 57%). Rf = 0.43 (SiO2: EtOAc:Hex, 1:10:1).

**1H NMR (400 MHz, CDCl3) δ = 7.69–7.65 (m, 2H), 7.46–7.40 (m, 3H), 7.09 (d, J = 5.2 Hz, 1H), 7.01 (d, J = 5.2 Hz, 1H), 3.97–3.93 (m, 2H), 2.95–2.91 (m, 2H), 1C NMR (101 MHz, CDCl3) δ = 162.9, 144.5, 139.2, 130.9, 129.7, 128.4, 128.2, 126.2, 121.5, 48.2, 22.4; HRMS (ESI, m/z) calc for C13H11NS 214.0690, found 214.0695.
Cyclic imine 12b was obtained from 2-picolinic acid (2-thiophen-2-yl)amide (12a) (400 mg, 1.7 mmol, 1 equiv), using general procedure E, as a brown oil (124 mg, 0.6 mmol, 34%).

The amine 12c was obtained from 7-(2-pyridyl)-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%).

2-Methoxybenzoic Acid–Thiophene-2-ylmethylamide (13a). The amine 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%).

2-Methoxybenzoic Acid–Thiophene-2-ylmethylamide (13b). The cymine 13b was obtained from 2-methoxybenzoic acid (2-thiophen-2-yl)amide (13a) (100 mg, 0.38 mmol, 1 equiv), using general procedure C, as a colorless oil (40 mg, 0.16 mmol, 43%).

2-Methoxyphenyl–6,7-dihydrothieno[3,2-c]pyridine (12b) (235 mg, 0.97 mmol, 1 equiv), using general procedure E, as a white solid (160 mg, 0.65 mmol, 67%).

2-Picolinic Acid–(2-Thiophen-2-yl)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 (630 mg, 2.8 mmol, 44%).

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%).

2-(4-Phenyl-6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)ethanone (1). The amide 1 was obtained from 7-(4-phenyl-6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)ethanone (1) (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, 48%).

2-Picolinic Acid–(2-Thiophen-2-yl)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 (630 mg, 2.8 mmol, 44%).
equiv) dissolved in 3 mL of dry THF was added to 1-(4-phenyl-6,7-ethanethione (5).

The amide 2 was obtained from 4-(3-methylphenyl)-4,5,6,7-tetrahydrothieno[3,2-∈]pyridin-5(4H)-yl)prop-2-yn-1-ol (2). The amide 2 was obtained from 4-(3-methylphenyl)-4,5,6,7-tetrahydrothieno[3,2-∈]pyridin-5(4H)-yl)prop-2-yn-1-ol (2).

The amide 6 was obtained from 7-(2-pyridyl)-6,7-dihydrothieno[3,2-∈]pyridin-5(4H)-yl)ethanone (6).

The amide 6 was obtained from 7-(2-pyridyl)-6,7-dihydrothieno[3,2-∈]pyridin-5(4H)-yl)ethanone (6).

The amide 7 was obtained from 7-(2-methoxyphenyl)-4,5,6,7-tetrahydrothieno[3,2-∈]pyridin-5(4H)-yl)ethanone (7).

The amide 7 was obtained from 7-(2-methoxyphenyl)-4,5,6,7-tetrahydrothieno[3,2-∈]pyridin-5(4H)-yl)ethanone (7)
The authors declare no competing financial interests.

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## 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**
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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) calc for C13H10NO,S 274.0902, found 274.0893.