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Design and diversity-oriented synthesis of benzo- and pyrido-annulated medium-sized *N,S*-heterocycles *via* thio-Michael and Friedel-Crafts approaches

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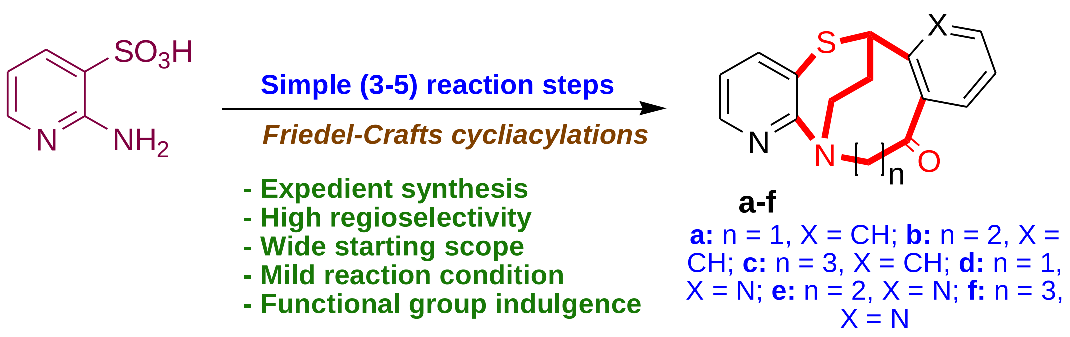
Abstract

Efficient and concise protocol for the synthesis of fused tetracyclic *N,S*-heterocycles in particular benzo- and pyrido-fused 1,4-thiazonines, 1,4-thiazecines and 1,4-thiazacycloundecanes is described. The process involves Lewis or Brønsted acids-promoted Friedel-Crafts cyclizations of heterocyclic esters. The required starting thiazepinones were obtained in moderate yields via intramolecular thio-Michael additions of mercapto-amides under mild conditions. The present study without stereochemical assignments illustrates the first example of straightforward access to promising pharmaceutical scaffolds in high yields.



Keywords: Friedel-Crafts cycliacylations, Michael additions, heteropolycycles, thiazoninones

Introduction

For more than a century, syntheses of medium-sized benzofused *N* and *S*-heterocycles have garnered more attention of both synthetic and medicinal chemists due to their scaffolds constitutes a prominent framework in numerous bioactive natural alkaloids[1] and synthetic drugs[2] possessing interesting physiological properties.[3] In the literature, a precise description of synthetic strategies in this area of research is so voluminous that it couldn't comprehend. Interestingly, an overview of general aspects about the structure, application and synthetic efforts for the generation of various fused 1,2-, 1,3-, 1,4-thiazepine frameworks have been disclosed.[4-9] In comparison with the regioisomeric thiazepines, a survey shows there are a limited number of published protocols accessing the thiazocines[10] and higher medium-sized *N,S*-heterocyclic systems.

The most general procedures to thiazocines implied, reactions of α,α`-dibromo-*o*-xylenes with 2-aminothiophenols using $NaHCO_3$ in DMF,[11] the ring-closing metathesis (RCM) of sulfoxide and sulfone intermediates,[12] Pd-catalyzed carbonylations of 2-(2-iodobenzylthio)benzenamines,[13] intramolecular cyclization of thioethers substrates,[14] and LDA-induced cyclizations of 3-(2-bromophenylthio)propan-1-amines.[15] Unfortunately, the work in the literature towards the synthesis of highly valuable thiazonines or higher ring systems are limited to three restricted examples. These pioneering strategies to thiazonine regioisomers included ring expansion of ω-bromoalkyl benzothiazolium salts which derived from thiazoles substrates,[16] 2,3-sigmatropic shifts of *S*-imides which originated from the reaction of chloramines-T with 2-vinylthiacycloheptane[17] and arynic condensation of substituted *S*-lactam with $NaIO_4$.[18]

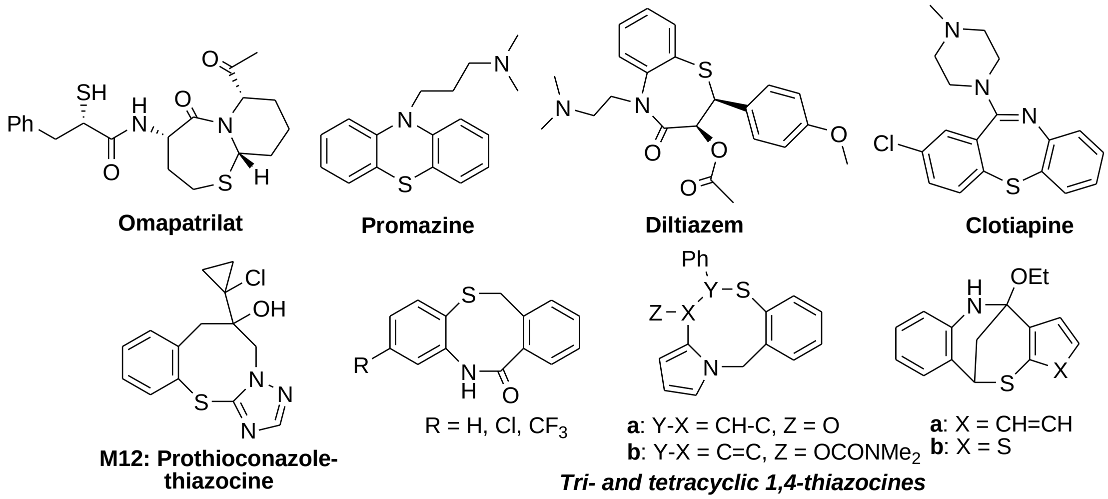


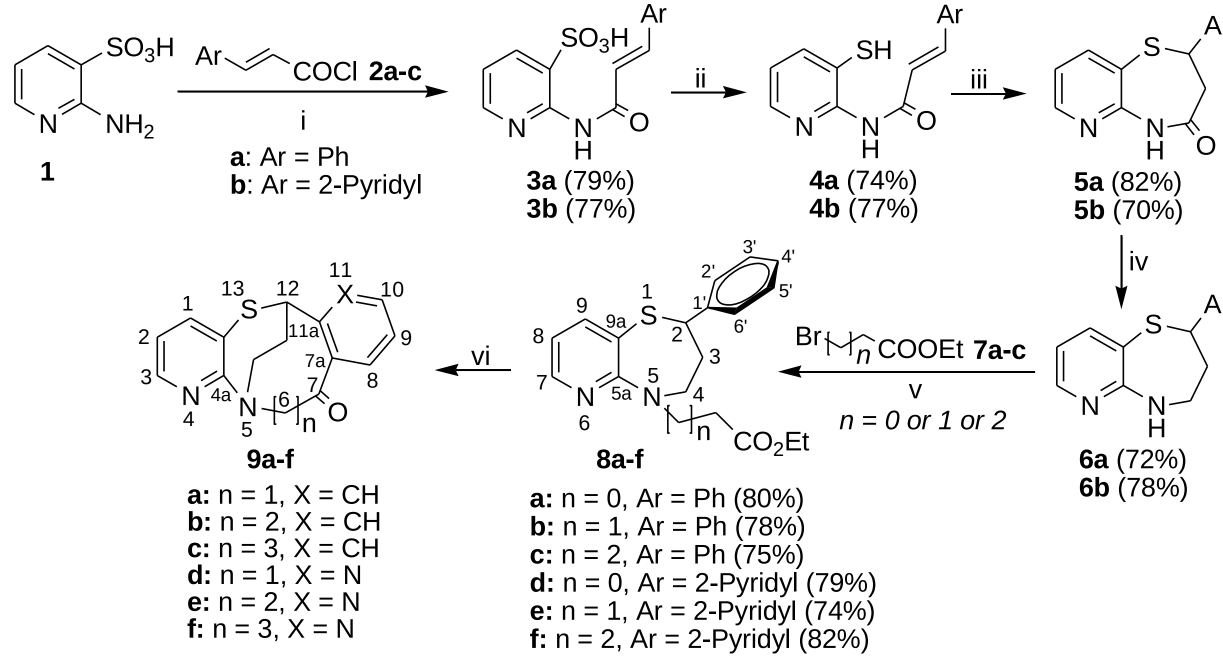
Figure 1. Examples of medium-sized *N* and *S*-heterocycles containing pharmaceutical drugs.

In view of their enticing structural complexity, interesting pharmaceutical importance and the great structural diversity of such heterocyclic systems, synthetic chemists have sought to evaluate versatile methods for the synthesis of highly functionalized bioactive cores useful in the drug research field. With these importances in mind, we sought to design a facile protocol for the attempt of accessing medium-sized *N*&*S*-heterocycles focusing on achieving molecular diversity and efficiency. In continuation of our research interests in Friedel-Crafts reactions[19-22] regarding the development of concise methods for the construction *carbo*- and heterocycles,[23-27] herein, we wish to report the concise synthesis of condensed medium-sized *N&S*-heterocyclic scaffolds (*e.g.* tetracyclic benzo-and pyrido-fused 1,4-thiazoninones, 1,4-thiazecinones and 1,4-

thiazacycloundecanones) through the Friedel-Crafts ring closures of ester precursors. To the best of our knowledge, there are no reports on the construction of these scaffolds in the literature.

Results and Discussion

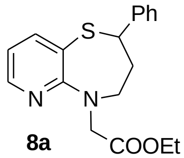
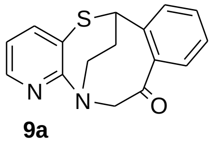
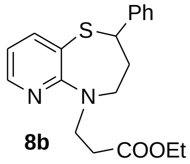
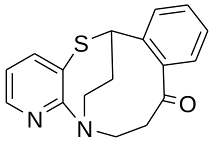
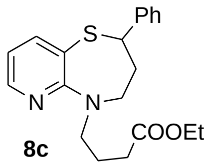
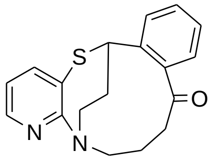
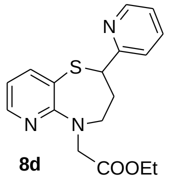
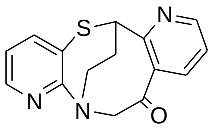
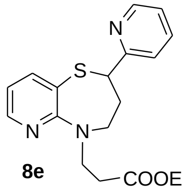
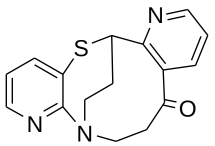
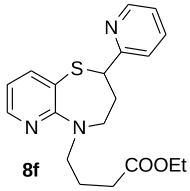
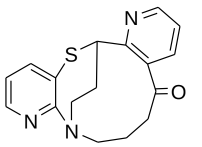
We anticipated that the most commonly used synthetic procedures utilized to access medium-sized rings are the Friedel-Crafts reactions. Our synthetic route to the tetracyclic medium-sized rings containing *N-or S-*heterocycles **9a-f** is summarized in Scheme 1. In the process, synthesis of heterocyclic ester precursors **8a-f** was planned from the model 2-aminopyridine-3-sulfonic acid (**1**). Acylations of amino-sulfonic acid **1** with cinnamoyl chloride **2a** or 3–(pyridin–2–yl)acryloyl chloride **2b**[28] in benzene under reflux condition provides amides **3a,b**. The latter amides were treated with PCl_5 and the resulting sulfonyl-chlorides were subjected to reduction with $Zn/H_2SO_4/H_2O$ following the standard procedures[29] to obtain thiols **4a,b** in moderate yields. Cyclizations of the substituted mercapto-amides **4a,b** were achieved via the thio-Michael[30] additions using Et_3N as a catalyst in dry DCM to give the substituted pyrido[3,2-b][1,4]thiazepinones **5a,b**. The resulting bicyclic thiazepinones were reduced with $LiAlH_4$ in Et_2O/THF to afford cyclic amines **6a,b** followed by *N*-alkylation with ethyl α– or β– or γ-halo-alkanoate **7a-c** in the presence of K_2CO_3 in DMF to obtain the corresponding *N*-ester precursors **8a-f** in good overall yields. The constitutions of the products without stereochemical assignments were appropriately characterized by the elemental analysis and spectroscopic analyses.



Scheme 1. Reagents and conditions: (i) cinnamoyl chloride or 3-(pyridin–2–yl)acryloyl chloride/PhH, 6 h, reflux, 77-79%, (ii) *a.* PCl_5, 70–80 °C, 3h, *b.* Zn/H_2SO_4, 3h, 40–50 °C, 74-77% (iii) Et_3N/CH_2Cl_2, 14-16 h, 40-50 °C, 70-82%, (iv) $LiAlH_4$/THF/Et_2O, reflux, 6-7 h, NaOH, 72-78%, (v) α-or β- or γ-bromoalkanoic ester (**7a-c**), K_2CO_3/DMF, 8-10 h, reflux, 74-82%, (vi) $AlCl_3/CH_3NO_2$ or TfOH-mediated cyclizations of esters (Table 1).

Cyclizations of ester precursors **8a-f** have been performed by using $AlCl_3/CH_3NO_2$ or TfOH (trifluoromethanesulfonic acid)-catalysts under different reaction conditions to provide the fused tetracyclic skeletons **9a-f** with different regiochemical outcomes (Table 1). After a search in the literature, it was found that this type of transformation is usually carried out by following the Thorpe-Ingold effect, and to test the possibility of cyclizations of suitable functionalized precursors, we decided to carry out a screening of various mild acidic catalysts and optimization of the reaction conditions. A closer look at the data cited in table 1, a few distinct observations that have a bearing on the work presented herein deserve further mention. Electrophilic inhibition problems are common with inter- and intramolecular Friedel-Crafts reactions in the preparation of heterocyclic systems.[31] It was found that the ring closure of hetero-arenes is complicated by the continued presence of heteroatoms in the substrates and cyclization step occurs at a slower rate of reaction than that with carbocyclic substrates.[32] This occurs due to the basic heteroatoms (*sp*^{3}-hybridized) presented in substrates. This property inhibited acidic catalysts due to the binding properties of the catalyst which accumulates to a build-up of positive charge on the heteroatoms of the substrate. Such effects led to no reactions occurred with less than four equivalents of mild catalysts.

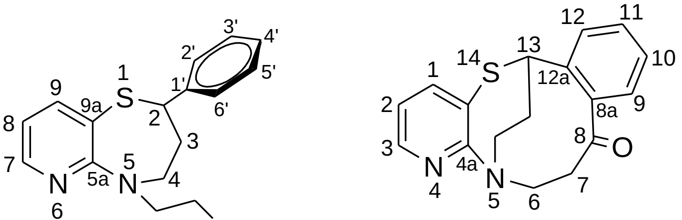
Table 1: Optimization of reaction conditions for the synthesis of **9a–f**

Entry	Ester	Conditions	Product	Yield (%)[a]
1	 **8a**	$AlCl_3/CH_3NO_2$[b], DCM[c], 15 h, rt TfOH[d], DCE[e], 8 h, 60–70 °C	 **9a**	80 74
2	 **8b**	$AlCl_3/CH_3NO_2$, DCM, 12 h, rt TfOH, DCE, 10 h, 60–70 °C	 **9b**	79 74
3	 **8c**	$AlCl_3/CH_3NO_2$, DCM, 14 h, rt TfOH, DCE, 8 h, 50–60 °C	 **9c**	80 71
4	 **8d**	$AlCl_3/CH_3NO_2$, DCM, 15 h, rt TfOH, DCE, 10 h, 60–70 °C	 **9d**	78 72
5	 **8e**	$AlCl_3/CH_3NO_2$, DCM, 18 h, rt TfOH, DCE, 7 h, 70–80 °C	 **9e**	80 70
6	 **8f**	$AlCl_3/CH_3NO_2$, DCM, 15 h, rt TfOH, DCE, 10 h, 60–70 °C	 **9f**	80 78

[a]Crude yields. [b]With $AlCl_3/CH_3NO_2$–catalyst reactant proportions were: ester (5 mmol), $AlCl_3$ (10 mmol) in CH_3NO_2 (100 mmol), solvent (10 mL). [c]Dichloromethane. [d]With TfOH–catalyst reactant proportions were: ester (10 mmol) and TfOH (3.0 equiv.), solvent (10 mL). [e]1,2–Dichloroethane

The results depicted in Table 1 suggest that the selected acidic catalysts are poorly acidic and are unable to compete effectively complexation with the heteroatoms containing substrates. Hereby, in highly strained notoriously medium rings, the intramolecular cyclizations were carried out under more drastic conditions and the extent of interaction depends on the mildness of catalyst which could possibly allow the ring-closing processes to occur with expanding functional group congruity.

On the other hand, in order to achieve medium-sized carbocycles, these take place by minimizing the transannular severity at the expense of having the unfavorable eclipsed conformations of the cyclic congeners which would surmount or partially circumvented by using more drastic conditions. As a result, these difficulties could be overwhelmed by the use of poor electrophilic catalyst. Hence, we explored the cyclization of esters **8a-f** by using more stoichiometric quantities of acidic promoters and the reactions were carried out at high temperatures for longer reaction times. At last, with our optimized reaction conditions in hand, we can ensure that the catalyst strength has proven to be a vital parameter in the cyclization process beside the activated functional group of substrate however, excellent results were obtained with poor electrophilic one.



8b **9b**

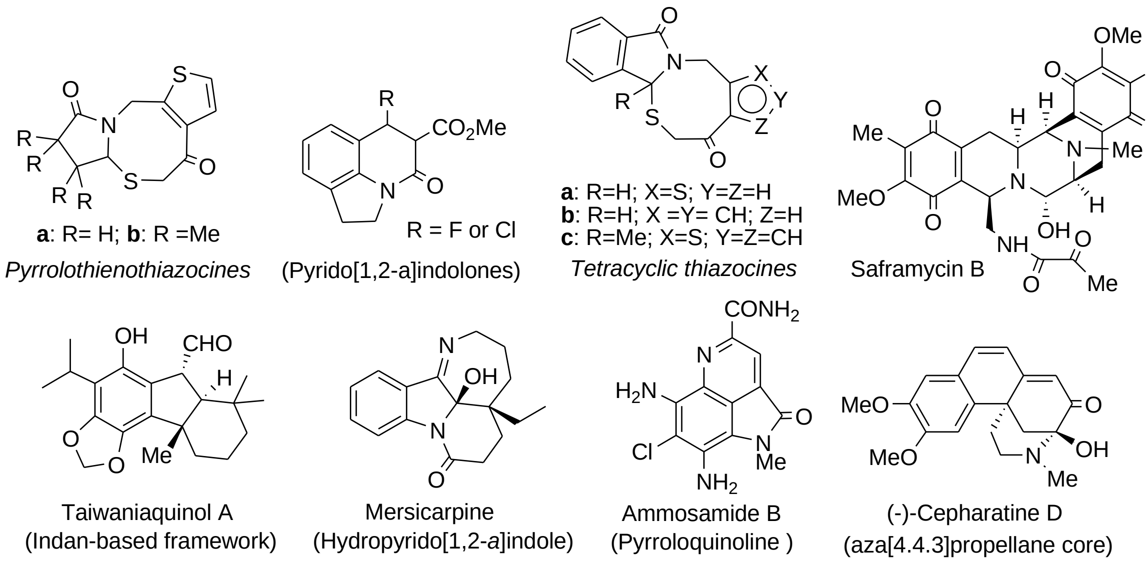
Figure 2. Structural example of tetracyclic product **9b** and its ester precursor **8b.**

Further evidence for this result was confirmed from NMR spectroscopy. A closer look at the intermediates and cyclic structures, we observed that the benzylic-carbon (C-2) has different groups attached, and so is a chiral center. Because the methylene group is next to a chiral center, its protons are diastereotopic[33] nature. These protons are chemically inequivalent and will split each other resulted in the experience of complex overlapping signals and displayed different chemical shifts. Examples are illustrated in Figure 2. Interestingly, in this orientation, one of the methylene CHs is cis to the aromatic ring, and the other is trans, therefore, they experience different chemical environments with different chemical shifts as well as they cannot be interchanged by any symmetry operation. In addition to the presence of diastereotopic protons, another constitutionally non-equivalent set of conformations (pseudo-axial and equatorial hydrogens) appeared in both precursors **8a-f** and products **9a-f**. In general, the combination of the chirality with the different conformations in medium-rings, these would lead to that the protons of the methylene group become inequivalent and presenting as more complex signals.

Although the main aim of the research is exclusively directed towards the synthesis of polyheterocycles, herein we do our efforts to identify the configuration of intermediates and cyclic products by Interpretation of NMR spectra. For example, the direct inspection of the ^1H NMR spectrum of compounds **8b** and **9b** displayed complex signals for both for the protons of CH_2-group adjacent to the stereogenic center and bridged pseudo-axial and equatorial protons. Moreover, the neighboring environment of the bridged *N*-CH_2 group is very unsymmetrical due to the ring conformations. The expected downfield shifting signal for pseudo-equatorial could be explained in terms of shielding effect exerted by the magnetic anisotropic effect generated by heteroatoms of both carbonyl group or *N&S*-heteroatoms of the tetracyclic structures. Thus, the ^{1}H NMR spectrum of **8b** exhibited three triplet signals at δ 1.15, 2.51 and 3.41 ppm related to CH_3, $C^{\alpha}H_2$ and $C^{\beta}H_2$ groups and one quartet signal appeared at δ 4.10 ppm is assigned to the ester-CH_2 group. Two doublets of doublet doublets signals at 3.66 and 3.54 ppm were suggested to that one of these protons is pseudo-axial, while the other is pseudo-equatorial (C^4Ha and C^4Hb) respectively. The most downfield doublet of doublets signal appears at δ 4.20 ppm is assigned to the chiral-C^2H group. The complex and shielded diastereotopic (C^3Ha and C^3Hb) protons of the CH_2-group showed as a doublet of doublets of doublets of doublets (dddd) at upfield chemical shifts near δ 1.75 ppm with four higher vicinal coupling constants than the other proton. This was ascribed to the equatorial-H3a. While the other proton (axial-H3b) appeared as downfield chemical shifts near δ 2.02 ppm with the same multiplicity (dddd) and low vicinal couplings.

In comparison with the ester **8b**, the ^{1}H NMR spectrum for compound **9b** showed that the most upfield with a multiplicity of doublet of doublets of doublets of doublets at δ 2.62 ppm is assigned to the bridged axial-Ha. While the downfield bridged equatorial-Hb signals appeared at δ 2.66 ppm with the same multiplicity (dddd). Complex multiple signals appeared in the regions δ 2.89-3.10, 3.69-3.59 and 3.58-3.69 ppm are assigned to C^7H_2CO, N-C^6H_2 and *bridged-NCH₂* groups, respectively. These upfield shifts could be explicated by shielding due to the magnetic anisotropic effect created by a heteroatom or the carbonyl group. The ^{13}C-NMR spectrum of compound **9b** became rather simple showed the splitting patterns corresponding to four upfield signals at δ 31.6, 35.2, 47.1 and 49.5 (2C) ppm represents C-7, ethano-bridged carbon $C^{13}\underline{CH_2}$, C-13, ethano-bridged carbon N^5-$\underline{CH_2}$ and C-6, respectively.

Based on literature precedents on Friedel-Crafts reactions,[19] the result highlights the utility of cyclization procedures lies in the mildness of selected catalysts, operated conditions and functional group compatibility in order to bring ring closure thoroughly. An insight into the carbocation-type mechanism[34] to account for the conversions of esters **8a-f** into fused tetracyclic ketones **9a-f** is realized on the creation of acyl–carbocation by loss of ethanol molecule upon treatment of ester with acidic catalysts. The resulting acyl–carbocation underwent intramolecular acylations into substituted tetracyclic ketones in overall good yields. Concurrent with these studies, it is worthy to highlight the versatility and synthetic tolerance of Friedel–Crafts reactions in the development of a catalytic version regarding the production of several natural products, pharmaceuticals and bioactive skeletons (Figure 3).[35-38] Many comprehensive reviews and books addressing detailed descriptions of applications, orientations, mechanisms and outcomes of Friedel-Crafts reactions which highlighted scattered examples for the synthesis of *homo*-and *hetero*-polynuclear aromatic systems are reported.[39-42]



Pyrrolothienothiazocines (Pyrido[1,2-a]indolones) *Tetracyclic thiazocines* Saframycin B

Taiwaniaquinol A (Indan-based framework) Mersicarpine (Hydropyrido[1,2-*a*]indole) Ammosamide B (Pyrroloquinoline) (-)-Cepharatine D (aza[4.4.3]propellane core)

Figure 3. Examples of condensed heterocycles synthesized by Friedel–Crafts processes.

Lately, the reactions have strong upsurge utilities for acylations and alkylations of highly reactive electron–rich arenes (thiophene, indole, quinoline) constituting the main synthetic step in the synthesis of heterocycles of various ring sizes such as thiazocines,[43] pyrrolothienothiazocines[44] and benzodiazocines.[45] In general, syntheses of medium-sized heterocycles via classical cyclization strategies are often entropically less favored by enthalpic and transannular barriers (Figure 3).[46] The discovery of Friedel–Crafts processes have revolutionized in the area of medium-ring synthesis, in the main, the reaction was considered as one of the macrocyclization approaches (*e.g.* carbocyclizations, macrolactonizations and macrolactamizations) applied for the constructions of macromolecule frameworks. Literally, medium-ring rings have a large number of conformations with low energy barriers as well as commonly occurring transannular interactions (non-bonded repulsions). This leads to a considerable amount of Pitzer, Prelog and Baeyer strains.[47] The significant cyclization progress in this direction is combined by a relatively small entropic strain in the transition state. To avoid these transannular interactions implied in the synthesis of medium-sized heterocycles, this takes place at the cost of minimized these penalties which could surmount or partially circumvented by using low strength catalysts.[48]

Conclusions

In summary, we provided an efficient and concise approach to constructing functionalized benzo- and pyrido-fused 1,4-thiazonines, 1,4-thiazecines and 1,4-thiazacycloundecanes using $AlCl_3/CH_3NO_2$ and TfOH–mediated cyclizations of the heterocyclic carboxylic esters under a mild condition. Substituted pyrido[3,2-b][1,4]thiazepinone intermediates were synthesized in three linear steps with good yields. Our success with this reaction sequence demonstrating the versatility and the wide variability of Friedel–Crafts reactions in the synthesis of condensed heterocycles from readily available starting materials.

Experimental Section

General. Commercially available reagents were used without further purification unless otherwise stated; solvents were dried by standard procedures. Melting points were taken on a digital Gallenkamp capillary melting point apparatus and are uncorrected. Infrared (IR) spectra were obtained on a Perkin-Elmer 1600 FT-IR spectrophotometer using KBr wafer and thin-film techniques (ν cm^{-1}) and are in cm^{-1}. The ^{1}H NMR and ^{13}C NMR spectra were recorded on JEOL LA 400 MHz FT-NMR (400 MHz for ^{1}H NMR, 100 MHz for ^{13}C NMR) using CDCl$_3$ solvent with tetramethylsilane (Me$_4$Si, TMS) as an internal standard. Chemical shifts are given in parts per million (δ), and the coupling constants (*J*) are given in Hertz (Hz), respectively. Elemental analyses were carried out by a GmbH Vario EL III, 2400, CHNOS-elemental analyzer. The progress of reactions was accomplished by thin-layer chromatography (TLC) analysis on precoated silica plates (Silufol, UV-254 TLC, aluminum sheets) and plates were visualized with UV light (at 254 and/or 360 nm). Flash column chromatography was performed on silica gel (230–400 mesh). Preparation of 3–(pyridin–2–yl)acryloyl chloride **2b** was prepared by heating a mixture of 3-(pyridin-2-yl)acrylic acid, mp 225 °C, *dec.* (Lit.[16] mp 233–236°C) [16] with PCl$_5$ in benzene for 2 h at a water bath.

General procedure for synthesis of arylamides 3a,b

A solution of acid chloride (cinnamoyl chloride **2a** or 3–(pyridin–2–yl)acryloyl chloride **2b** (35 mmol) in benzene (20 mL) was added dropwise with stirring to a solution of amino-acid **1** (30 mmol) in dry benzene (40 mL) containing a catalytic amount of pyridine (0.5 mL). The mixture was stirred at room temperature for 2 h and then refluxed in a steam bath for 4 h. The solvent was then concentrated in *vacuo* and the resulting deposit solid on standing was filtered to afford the crude amides. Purifications, yields and spectral data are given in the following:

2-(Cinnamamido)pyridine-3-sulfonic acid (3a). White crystals; 79%, mp 145-148 ºC (acetone); IR (KBr) ν_{max} 3253, 3070, 1662, 1600, 1570, 1443, 1340, 1213, 1160, 979 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$, δ, ppm): 5.91 (1H, s, NH), 6.76 (1H, d, *J* 15.7 Hz, =CH), 7.06 (1H, dd, *J* 7.1, 5.2 Hz), 7.44 (1H, tt, *J* 7.2, 1.6 Hz), 7.38 (2H, dddd, *J* 8.1, 7.2, 2.0, 0.5 Hz), 7.52 (2H, dddd, *J* 8.1, 2.4, 1.6, 0.5 Hz), 7.67 (1H, d, *J* 15.7 Hz, =CH), 7.93 (1H, dd, *J* 7.1, 1.9 Hz), 8.26 (1H, dd, *J* 5.2, 1.9 Hz), 10.15 (1H, s, OH); ^{13}C NMR (100 MHz, CDCl$_3$, δ, ppm): 116.9, 117.1, 119.6, 127.3 (2C), 128.7 (2C), 128.9, 134.0, 137.2, 140.8, 145.8, 150.2, 163.9. Anal. Calcd. for $C_{14}H_{12}N_2O_4S$ (304); C, 55.26; H, 3.94; N, 9.21; S, 10.52. Found; C, 55.41; H, 4.17; N, 9.11; S, 10.40%.

2-((*E*)-3-(pyridin-2-yl)acrylamido)pyridine-3-sulfonic acid (3b). Yellow plates; 77%; mp 192 ºC *dec.* (AcOEt); IR (KBr) ν_{max} 3290, 3077, 2940, 1670, 1605, 1480, 1450, 1355, 1215, 980 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$, δ, ppm): 6.20 (1H, s, NH), 6.88 (1H, d, *J* 15.8 Hz, =CH), 7.06 (1H, dd, *J* 7.1, 5.2 Hz), 7.49 (1H, d, *J* 15.8 Hz, =CH), 7.55 (1H, ddd, *J* 7.4, 4.7, 1.4 Hz), 7.72 (1H, ddd, *J* 7.7, 1.4, 0.5 Hz), 7.85-7.96 (2H, 7.93 (1H, dd, *J* 7.1, 1.9 Hz), 7.88 (1H, ddd, *J* 7.7, 7.4, 1.9 Hz), 8.26 (1H, dd, *J* 5.2, 1.9 Hz), 8.73 (1H, ddd, *J* 4.7, 1.9, 0.5 Hz), 9.85 (1H, s, OH); ^{13}C NMR (100 MHz, CDCl$_3$, δ, ppm): 116.9, 117.1, 120.8, 122.4, 123.3 , 123.3 , 136.6, 137.2, 145.8, 149.5, 150.2, 155.3, 163.9. Anal. Calcd. for $C_{13}H_{11}N_3O_4S$ (305); C, 51.14; H, 3.60; N, 13.77; S, 10.49. Found; C, 51.08; H, 3.75; N, 13.91; S, 10.27%.

General procedure for conversion of sulfonic acids 3a,b to mercapto-derivatives 4a,b

A mixture of compound **3a** or **3b** (25 mmol) and PCl$_5$ (50 mmol) was heated to reflux for 3 h in a water bath and then the sulfonyl chloride was decanted and used in the next step without further purification. To the resulted acid chloride, was added water (30 mL) and zinc dust (20 mmol) and the mixture was heated to 40-50 °C for 5 min. While keeping the temperature at 50-60 °C, zinc dust (40 mmol) added in one portion followed by gradually addition of H_2SO_4 (80 mmol, 93%) during a period of one 30 min. After the addition was completed, the water-bath was removed and the mixture was stirred at room temperature for 3 h (monitored by TLC, AcOEt/hexane, 1:1). The reaction mixture was diluted with water (100 mL) and extracted with $CHCl_3$ (3×40 mL). The combined organic layer was separated, washed with water, dried over $MgSO_4$, filtered and concentrated in *vacuo*. The residue was purified by flash column chromatography to provide the product **4a,b**. Purifications, specified yields and spectral data are given in the following:

(*E*)-*N*-(3-Mercaptopyridin-2-yl)cinnamamide (4a). Yellow needles, 74%, mp 160-63 °C (AcOEt); IR (KBr) ν_{max} 3281, 3040, 2933, 2545, 1672, 1600, 1460, 1347, 970 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 4.05 (1H, s, -SH), 5.94 (1H, s, NH), 6.69 (1H, dd, *J* 7.4, 4.5 Hz), 6.77 (1H, d, *J* 15.7 Hz, =CH), 7.38 (2H, dddd, *J* 8.1, 7.2, 2.0, 0.5 Hz), 7.44 (1H, tt, *J* 7.2, 1.6 Hz), 7.51 (2H, dddd, *J* 8.1, 2.4, 1.6, 0.5 Hz), 7.62 (1H, d, *J* 15.7 Hz, =CH), 7.69 (1H, dd, *J* 7.4, 1.9 Hz), 8.04 (1H, dd, *J* 4.5, 1.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 119.6, 122.2, 127.3 (2C), 127.4, 128.7 (2C), 128.9, 134.0, 134.4, 140.8, 148.3, 153.9, 163.9. Anal. Calcd. for $C_{14}H_{12}N_2OS$ (256); C, 65.62; H, 4.68; N, 10.93; S, 12.50. Found; C, 65.60; H, 4.72; N, 11.08; S, 12.39%.

(*E*)-*N*-(3-Mercaptopyridin-2-yl)-3-(pyridin-2-yl)acrylamide (4b): Yellow plates, 77%, mp 182-85 °C (AcOEt); IR (KBr) ν_{max} 3320, 3066, 2976, 2550, 1665, 1605, 1485, 1362, 990 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 4.46 (1H, s, -SH), 5.52 (1H, s, NH), 6.69 (1H, dd, *J* 7.4, 4.5 Hz), 6.87 (1H, d, *J* 15.6 Hz, =CH), 7.50 (1H, d, *J* 15.6 Hz, =CH), 7.54 (1H, ddd, *J* 7.4, 4.7, 1.4 Hz), 7.69 (1H, dd, *J* 7.4, 1.9 Hz), 7.71 (1H, ddd, *J* 7.7, 1.4, 0.5 Hz), 7.89 (1H, ddd, *J* 7.7, 7.4, 1.9 Hz), 8.04 (1H, dd, *J* 4.5, 1.9 Hz), 8.73 (1H, ddd, *J* 4.7, 1.9, 0.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 120.8, 122.2, 122.4, 123.3, 123.3, 127.4, 134.4, 136.6, 148.3, 149.5, 153.9, 155.3, 163.9. Anal. Calcd. for $C_{13}H_{11}N_3OS$ (257); C, 60.70; H, 4.28; N, 16.34; S, 12.45. Found; C, 60.55; H, 4.20; N, 16.52; S, 12.40%.

General procedure for the synthesis of thiazepinones via thiol-Michael reaction

To a stirred solution of **4a** or **4b** (20 mmol) in dry DCM (15 mL) was added dropwise Et_3N (1 mL) during a period of 10 min while the temperature was kept between 40-50 °C. The mixture was stirred at the same temperature for 14-16h, while the progress of the reaction was monitored by TLC (hexane:EtOAc, 3:1). Upon completion of the reaction, the content was quenched by the addition of aq. HCl solution (10 mL, 20%) and the organic material was extracted with AcOEt (3×30 mL). The combined organic layer was washed with water, dried over Na_2SO_4, filtered and concentrated in *vacuo*. The residue was purified by flash chromatography (basic alumina, AcOEt/hexane, 2:1) to afford the bicyclic products. Purifications, yields and spectral data are given in the following:

2,3-Dihydro-2-phenylpyrido[3,2-*b*][1,4]thiazepin-4(5*H*)-one (5a). White crystals; 82%, mp 135-37 ºC (benzene); IR (KBr) ν_{max} 3280, 3062, 1660, 1600, 1585, 1460, 1445, 1380, 1220, 979 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 2.79 (1H, dd, *J* 16.9, 9.8 Hz, C^{3}Ha), 3.03 (1H, dd, *J* 16.9, 1.6 Hz, C^{3}Hb), 4.63 (1H, dd, *J* 9.8, 1.6 Hz, C^{2}H), 6.65 (1H, dd, *J* 7.1, 4.5 Hz), 7.11 (2H, dddd, *J* 7.6, 1.5, 1.3, 0.5 Hz), 7.20 (1H, tt, *J* 7.7, 1.5 Hz), 7.32 (2H, dddd, *J* 7.7, 7.6, 1.9, 0.5 Hz), 8.06 (1H, dd, *J* 7.1, 1.6 Hz), 8.35 (1H, dd, *J* 4.5, 1.6 Hz), 9.92 (1H, s, NH); ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 41.5, 53.1, 122.2, 126.7 (2C), 127.4, 128.5 (2C), 128.9, 134.4, 141.3, 148.3, 153.9, 170.6. Anal. Calcd. for $C_{14}H_{12}N_2OS$ (256); C, 65.62; H, 4.68; N, 10.93; S, 12.50. Found; C, 65.54; H, 4.60; N, 10.74; S, 12.62%.

2,3-Dihydro-2-(pyridin-2-yl)pyrido[3,2-*b*][1,4]thiazepin-4(5*H*)-one (5b). White crystal; 70%, mp 140-42 ºC (AcOEt); IR (KBr) 3345, 3047, 2945, 1670, 1600, 1592, 1447, 1346, 1245 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 2.86 (1H, dd, *J* 17.6, 9.8 Hz, C^{3}Ha), 3.01 (1H, dd, *J* 17.6, 1.6 Hz, C^{3}Hb), 4.61 (1H, dd, *J* 9.8, 1.6 Hz, C^{2}H), 6.65 (1H, dd, *J* 7.1, 4.5 Hz), 7.21 (1H, ddd, *J* 7.4, 5.1, 1.4 Hz), 7.30 (1H, ddd, *J* 7.9, 1.4, 0.6 Hz), 7.64 (1H, ddd, *J* 7.9, 7.4, 1.9 Hz), 8.06 (1H, dd, *J* 7.1, 1.6 Hz), 8.35 (1H, dd, *J* 4.5, 1.6 Hz), 8.52 (1H, ddd, *J* 5.1, 1.9, 0.6 Hz), 9.52 (1H, s, NH); ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 41.5, 49.3, 122.0, 122.2, 123.3, 127.4, 134.4, 136.7, 148.3, 149.0, 152.0, 153.9, 170.6. Anal. Calcd. for $C_{13}H_{11}N_3OS$ (257); C, 60.70; H, 4.28; N, 16.34; S, 12.45. Found; C, 60.74; H, 4.39; N, 16.54; S, 12.29%.

General procedure for the reduction of thiazepinones 5a,b

To an ice-cold stirred suspension of $LiAlH_4$ (15 mmol) in ether (40 mL), a solution of thiazepinones **5a** or **5b** (10 mmol) in THF (35 mL) was added dropwise over a period of 20 min. The mixture was stirred at room temperature for 6-7 h. After cooling, the mixture was carefully decomposed by the sequential addition of cold water (5 mL) and aqueous NaOH solution (20 mL, 10%) with efficient stirring. After filtration and triturating the precipitate with AcOEt, the precipitate was discarded and the filtrate was then extracted with AcOEt (3×30 mL). The combined organic phase was washed with water, $NaHCO_3$ (20 mL, 5%), and dried over anhydrous $MgSO_4$. The solvent was distilled off to afford the target product. Purification of the product by flash column chromatography (basic alumina, EtOAc/hexane, 1/1) gave pure bicyclic amines **5a,b** whose analytical, physical and spectroscopic data were as follows:

2,3,4,5-Tetrahydro-2-phenylpyrido[3,2-*b*][1,4]thiazepine (6a). Pale yellow crystals; 72%; mp 133-36 ºC (acetone); IR (KBr) ν_{max} 3420, 3060, 2944, 1600, 1585, 1445, 1380, 1272, 757 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 1.89 (1H, dddd, *J* 14.3, 10.2, 10.0, 2.2 Hz, C^{3}Ha), 2.11 (1H, dddd, *J* 14.3, 3.8, 2.0, 1.7 Hz, C^{3}Hb), 3.54 (ddd, *J* 14.4, 10.2, 2.0 Hz, C^{4}Ha), 3.52 (ddd, *J* 14.4, 3.8, 2.2 Hz, C^{4}Hb), 4.24 (1H, dd, *J* 10.0, 1.7 Hz, C^{2}H), 6.72 (1H, dd, *J* 8.0, 4.6 Hz), 7.19 (1H, tt, *J* 7.7, 1.3 Hz), 7.25-7.40 (4H,m), 7.71 (1H, dd, *J* 8.0, 1.9 Hz), 8.12 (1H, dd, *J* 4.6, 1.9 Hz), 10.05 (1H, s, NH); ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 31.6, 43.0, 47.1, 122.2, 126.7 (2C), 127.4, 128.5 (2C), 128.9, 134.4, 137.6, 148.3, 153.9. Anal. Calcd. for $C_{14}H_{14}N_2S$ (242); C, 69.42; H, 5.78; N, 11.57; S, 13.22. Found; C, 69.35; H, 5.91; N, 11.44; S, 13.36%.

2,3,4,5-Tetrahydro-2-(pyridin-2-yl)pyrido[3,2-*b*][1,4]thiazepine (6b). Yellow crystals; 78%, mp 155-58 ºC (benzene); IR (KBr) ν_{max} 3385, 3062, 2950, 1605, 1590, 1445, 1365, 1280, 1130, 796 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 1.94 (dddd, *J* 14.3, 10.2, 10.0, 2.2 Hz, C^{3}Ha), 2.06 (dddd, *J* 14.3, 3.8, 2.0, 1.7 Hz, C^{3}Hb), 3.50 (ddd, *J* 14.4, 10.2, 2.0 Hz, C^{4}Ha), 3.53 (ddd, *J* 14.4, 3.8, 2.2 Hz, C^{4}Hb), 4.46 (1H, dd, *J* 10.0, 1.7 Hz, C^{2}H), 6.72 (1H, dd, *J* 8.0, 4.6 Hz), 7.21 (1H, ddd, *J* 7.4, 5.1, 1.2 Hz), 7.29 (1H, ddd, *J* 7.6, 1.2, 0.5 Hz), 7.63 (1H, ddd, *J* 7.6, 7.4, 1.9 Hz), 7.71 (1H, dd, *J* 8.0, 1.9 Hz), 8.12 (1H, dd, *J* 4.6, 1.9 Hz), 8.52 (1H, ddd, *J* 5.1, 1.9, 0.5 Hz), 10.13 (1H, s, NH); ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 31.6, 43.0, 49.3, 122.0, 122.2, 123.3, 127.4, 134.4, 136.7, 148.3, 149.0, 152.0, 153.9. Anal. Calcd. for $C_{13}H_{13}N_3S$ (243); C, 64.19; H, 5.34; N, 17.28; S, 13.16. Found; C, 64.15; H, 5.42; N, 17.35; S, 13.04%.

General procedure for the synthesis of heterocyclic esters 8a-f

Haloesters **7a-c** (ethyl 2–bromoacetate **7a** or ethyl 3–bromopropanoate **7b** or ethyl 4-bromobutanoate **7c**) (20 mmol) was added dropwise in 20 min to a suspension of bicyclic amine **6a** or **6b** (15 mmol) and K_2CO_3 (40 mmol) in DMF (30 mL) with efficient stirring at room temperature. The reaction mixture was then refluxed for 8–10 h. The progress of the reaction was monitored by TLC (AcOEt/hexane, 1/3). After completion of the reaction, the solvent was removed in *vacuo* and the residue was diluted with water (100 mL) and extracted with AcOEt (3×40 mL). The combined organic layer was washed with water, dried over $MgSO_4$, filtered and concentrated. The residue was purified by a flash chromatography column to afford the expected crude ester **8a–f**. Purifications, yields and spectral data are given in the following:

Ethyl 2-(3,4-dihydro-2-phenylpyrido[3,2-*b*][1,4]thiazepin-5(2*H*)-yl)acetate (8a). Yellow crystals; 80%, mp 130-33 ºC (acetone); IR (KBr) ν_{max} 3050, 2946, 1735, 1605, 1585, 1440, 1379, 1230, 780 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 1.16 (3H, t, *J* 7.1 Hz, CH_3), 1.76 (1H, dddd, *J* 13.8, 10.1, 10.1, 1.9 Hz, C^{3}Ha), 2.04 (1H, dddd, *J* 13.8, 4.3, 1.9, 1.8 Hz, C^{3}Hb), 3.69 (2H, s, C$^\alpha$H$_2$), 3.64 (1H, ddd, *J* 16.1, 4.3, 1.9 Hz, C^{4}Ha), 3.79 (1H, ddd, *J* 16.1, 10.1, 1.8 Hz, C^4Hb), 4.14 (2H, q, *J* 7.1 Hz, CH_2), 4.20 (1H, dd, *J* 10.1, 1.9 Hz, C^2H), 6.73 (1H, dd, *J* 8.0, 4.6 Hz), 7.25 (1H, tt, *J* 7.7, 1.3 Hz), 7.28 (2H, dddd, *J* 7.8, 1.3, 1.2, 0.5 Hz), 7.36 (2H, tdd, *J* 7.7, 1.9, 0.5 Hz), 7.71 (1H, dd, *J* 8.0, 1.9 Hz), 8.05 (1H, dd, *J* 4.6, 1.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 14.1, 31.6, 47.1, 49.5, 51.9, 61.6, 122.2, 126.7 (2C), 127.4, 128.5 (2C), 128.9, 134.4, 137.6, 148.3, 153.9, 168.4. Anal. Calcd. for $C_{18}H_{20}N_2O_2S$ (328); C, 65.85; H, 6.09; N, 8.53; S, 9.75. Found; C, 65.64; H, 6.22; N, 8.59; S, 9.82%.

Ethyl 3-(3,4-dihydro-2-phenylpyrido[3,2-*b*][1,4]thiazepin-5(2*H*)-yl)propanoate (8b). Peal yellow needles; 78%, mp 118-20 ºC (benzene); IR (KBr) ν_{max} 3051, 2962, 1740, 1600, 1590, 1445, 1390, 1274, 781 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 1.15 (3H, t, *J* 7.1 Hz, CH_3), 1.75 (1H, dddd, *J* 14.2, 10.1, 10.1, 1.9 Hz, C^3Ha), 2.02 (1H, dddd, *J* 14.2, 4.3, 1.9, 1.8 Hz, C^3Hb), 2.51 (2H, t, *J* 6.7 Hz, $C^{\alpha}H_2$), 3.41 (2H, t, *J* 6.7 Hz, $C^{\beta}H_2$), 3.66 (1H, ddd, *J* 14.1, 10.1, 1.8 Hz, C^4Ha), 3.54 (1H, ddd, *J* 14.1, 4.3, 1.9 Hz, C^4Hb), 4.10 (2H, q, *J* 7.1 Hz, CH_2), 4.20 (1H, dd, *J* 10.1, 1.9 Hz, C^2H), 6.72 (1H, dd, *J* 8.0, 4.6 Hz), 7.25 (1H, tt, *J* 7.7, 1.3 Hz), 7.28 (2H, dddd, *J* 7.8, 1.3, 1.2, 0.5 Hz), 7.36 (2H, tdd, *J* 7.7, 1.9, 0.5 Hz), 7.71 (1H, dd, *J* 8.0, 1.9 Hz), 8.11 (1H, dd, *J* 4.6, 1.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 14.1, 31.6, 32.4, 47.1, 49.5 (2C), 60.6, 122.2, 126.7 (2C), 127.4, 128.5 (2C), 128.9, 134.4, 137.6, 148.3, 153.9, 172.3. Anal. Calcd. for $C_{19}H_{22}N_2O_2S$ (342); C, 66.66; H, 6.43; N, 8.18; S, 9.35. Found; C, 66.61; H, 6.59; N, 8.03; S, 9.39%.

Ethyl 4-(3,4-dihydro-2-phenylpyrido[3,2-*b*][1,4]thiazepin-5(2*H*)-yl)butanoate (8c). White crystals; 75%, mp 129-31 ºC (ethanol); IR (KBr) ν_{max} 3036, 2953, 1735, 1600, 1585, 1445, 1359, 1280, 770 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 1.15 (3H, t, *J* 7.1 Hz, CH_3), 1.75 (1H, dddd, *J* 14.2, 10.1, 10.1, 1.9 Hz, C^3Ha), 1.89 (2H, tt, *J* 7.4, 2.7 Hz, $C^{\beta}H_2$), 2.02 (1H, dddd, *J* 14.2, 4.3, 1.9, 1.8 Hz, C^3Hb), 2.33 (2H, t, *J* 7.4 Hz, $C^{\alpha}H_2$), 3.07 (2H, t, *J* 2.7 Hz, $C^{\gamma}H_2$), 3.44 (1H, ddd, *J* 13.6, 4.3, 1.9 Hz, C^4Ha), 3.67 (1H, ddd, *J* 13.6, 10.1, 1.8 Hz, C^4Hb), 4.10 (2H, q, *J* 7.1 Hz, CH_2), 4.20 (1H, dd, *J* 10.1, 1.9 Hz, C^2H), 6.72 (1H, dd, *J* 8.0, 4.6 Hz), 7.25 (1H, tt, *J* 7.7, 1.3 Hz), 7.28 (2H, dddd, *J* 7.8, 1.3, 1.2, 0.5 Hz), 7.36 (2H, tdd, *J* 7.7, 1.9, 0.5 Hz), 7.71 (1H, dd, *J* 8.0, 1.9 Hz), 8.11 (1H, dd, *J* 4.6, 1.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 14.1, 25.5, 30.7, 31.6, 47.1, 49.5 (2C), 60.6, 122.2, 126.7 (2C), 127.4, 128.5 (2C), 128.9, 134.4, 137.6, 148.3, 153.9, 172.4. Anal. Calcd. for $C_{20}H_{24}N_2O_2S$ (356); C, 67.41; H, 6.74; N, 7.86; S, 8.98. Found; C, 67.62; H, 6.61; N, 7.80; S, 9.16%.

Ethyl 2-(3,4-dihydro-2-(pyridin-2-yl)pyrido[3,2-*b*][1,4]thiazepin-5(2*H*)-yl)acetate (8d). Yellow crystals; 79%, mp 150-53 ºC (AcOEt); IR (KBr) ν_{max} 3060, 2935, 1742, 1610, 1590, 1445, 1366, 1130, 790 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 1.15 (3H, t, *J* 7.1 Hz, CH_3), 1.83 (1H, dddd, *J* 14.2, 10.1, 10.1, 1.9 Hz, C^3Ha), 2.10 (1H, dddd, *J* 14.2, 4.3, 1.9, 1.8 Hz, C^3Hb), 3.69 (2H, s, $C^{\alpha}H_2$), 3.68 (1H, ddd, *J* 16.2, 4.3, 1.9 Hz, C^4Ha), 3.79 (1H, ddd, *J* 16.2, 10.1, 1.8 Hz, C^4Hb), 4.14 (2H, q, *J* 7.1 Hz, CH_2), 4.44 (1H, dd, *J* 10.1, 1.9 Hz, C^2H), 6.73 (1H, dd, *J* 8.0, 4.6 Hz), 7.21 (1H, ddd, *J* 7.4, 5.1, 1.2 Hz), 7.29 (1H, ddd, *J* 7.9, 1.2, 0.5 Hz), 7.63 (1H, ddd, *J* 7.9, 7.4, 1.9 Hz), 7.71 (1H, dd, *J* 8.0, 1.9 Hz), 8.05 (1H, dd, *J* 4.6, 1.9 Hz), 8.52 (1H, ddd, *J* 5.1, 1.9, 0.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 14.1, 31.6, 49.3, 49.5, 51.9, 61.6, 122.0, 122.2, 123.3, 127.4, 134.4, 136.7, 148.3, 149.0, 152.0, 153.9, 168.4. Anal. Calcd. for $C_{17}H_{19}N_3O_2S$ (329); C, 62.00; H, 5.77; N, 12.76; S, 9.72. Found; C, 61.86; H, 5.64; N, 12.91; S, 9.84%.

Ethyl 3-(3,4-dihydro-2-(pyridin-2-yl)pyrido[3,2-*b*][1,4]thiazepin-5(2*H*)-yl)propanoate (8e). White crystals; 74%, mp 142-45 ºC (benzene); IR (KBr) ν_{max} 3072, 2961, 1740, 1600, 1590, 1440, 1396, 1275, 775 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 1.15 (3H, t, *J* 7.1 Hz, CH_3), 1.85 (1H, dddd, *J* 14.2, 10.1, 10.1, 1.9 Hz, C^3Ha), 2.08 (1H, dddd, *J* 14.2, 4.3, 1.9, 1.8 Hz, C^3Hb), 2.51 (2H, t, *J* 6.7 Hz, $C^{\alpha}H_2$), 3.41 (2H, t, *J* 6.7 Hz, $C^{\beta}H_2$), 3.63 (1H, ddd, *J* 14.6, 4.3, 1.9 Hz, C^4Ha), 3.66 (1H, ddd, *J* 14.6, 10.1, 1.8 Hz, C^4Hb), 4.10 (2H, q, *J* 7.1 Hz, CH_2), 4.44 (1H, dd, *J* 10.1, 1.9 Hz, C^2H), 6.72 (1H, dd, *J* 8.0, 4.6 Hz), 7.21 (1H, ddd, *J* 7.4, 5.1, 1.2 Hz), 7.29 (1H, ddd, *J* 7.9, 1.2, 0.5 Hz), 7.71 (1H, dd, *J* 8.0, 1.9 Hz), 7.63 (1H, ddd, *J* 7.9, 7.4, 1.9 Hz), 8.11 (1H, dd, *J* 4.6, 1.9 Hz), 8.52 (1H, ddd, *J* 5.1, 1.9, 0.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 14.1, 31.6, 32.4, 49.3, 49.5 (2C), 60.6, 122.0, 122.2, 123.3, 127.4, 134.4, 136.7, 148.3, 149.0, 152.0, 153.9, 172.3. Anal. Calcd. for $C_{18}H_{21}N_3O_2S$ (343); C, 62.97; H, 6.12; N, 12.24; S, 9.32. Found; C, 63.05; H, 6.19; N, 12.11; S, 9.38%.

Ethyl 4-(3,4-dihydro-2-(pyridin-2-yl)pyrido[3,2-*b*][1,4]thiazepin-5(2*H*)-yl)butanoate (8f). Yellow crystals; 82%, mp 138-40 ºC (acetone); IR (KBr) ν_{max} 3057, 2940, 1745, 1600, 1590, 1490, 1445, 1365, 1189, 795 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 1.15 (3H, t, *J* 7.1 Hz, CH_3), 1.89 (2H, tt, *J* 7.4, 2.7 Hz, $C^{\beta}H_2$), 1.82 (1H, dddd, *J* 14.2, 10.1, 10.1, 1.9 Hz, C^3Ha), 2.07 (1H, dddd, *J* 14.2, 4.3, 1.9, 1.8 Hz, C^3Hb), 2.33 (2H, t, *J* 7.4 Hz, $C^{\alpha}H_2$), 3.07 (2H, t, *J* 2.7 Hz, $C^{\gamma}H_2$), 3.59 (1H, ddd, *J* 14.2, 4.3, 1.9 Hz, C^4Ha), 3.64 (1H, ddd, *J* 14.2, 10.1, 1.8 Hz, C^4Hb), 4.10 (2H, q, *J* 7.1 Hz, CH_2), 4.44 (1H, dd, *J* 10.1, 1.9 Hz, C^2H), 6.72 (1H, dd, *J* 8.0, 4.6 Hz), 7.21 (1H, ddd, *J* 7.4, 5.1, 1.2 Hz), 7.29 (1H, ddd, *J* 7.9, 1.2, 0.5 Hz), 7.63 (1H, ddd, *J* 7.9, 7.4, 1.9 Hz), 7.71 (1H, dd, *J* 8.0, 1.9 Hz), 8.11 (1H, dd, *J* 4.6, 1.9 Hz), 8.52 (1H, ddd, *J* 5.1, 1.9, 0.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 14.1, 25.5, 30.7, 31.6, 49.3, 49.5 (2C), 60.6, 122.0, 122.2, 123.3, 127.4, 134.4, 136.7, 148.3, 149.0, 152.0, 153.9, 172.4. Anal. Calcd. for $C_{19}H_{23}N_3O_2S$ (357); C, 63.86; H, 6.44; N, 11.76; S, 8.96. Found; C, 63.85; H, 6.29; N, 11.70; S, 9.17%.

General Procedure for $AlCl_3/CH_3NO_2$–mediated ring closures

A solution of required ester precursor **8a**–**f** (2 mmol) in DCM (10 mL) was added dropwise with constant stirring over 10–15 min to a solution of $AlCl_3/CH_3NO_2$-complex (prepared by addition of $AlCl_3$ (10 mmol) to CH_3NO_2 (100 mmol)). The reaction mixture was stirred for a certain time at the required temperature (Table 1). After completion, the reaction was quenched by the addition of ice–cold HCl solution (20 mL, 10%) and was extracted with ether (2×30 mL). The combined organic phase was washed with Na_2CO_3 (30 mL, 10%), washed with water and dried over anhydrous Na_2SO_4. The solvent was evaporated in *vacuo* to afford the products **9a-f**.

General Procedure for TfOH–mediated ring closures

TfOH (5.0 equiv.) was added dropwise to a solution of the indicated ester **9a–f** (30 mmol) in dry dichloroethane (15 mL) at 0 °C. The mixture was stirred at the required temperature for a certain time as shown in Table 1. The mixture was quenched with saturated aqueous $NaHCO_3$ solution (40 ml, 30%) and the product was extracted with ether (3×25 mL). The combined organic layer was worked up by washing with water, dried over anhydrous $MgSO_4$, filtered and the solvent was concentrated *in vacuo* to afford the products **9a-f**.

In all procedures, the progress of the cyclization reactions was monitored by TLC (hexane/AcOEt, 4:1). All crude cyclic products (Table 1) were initially purified by flash chromatography through a short column of basic alumina (eluent: EtOAc/hexane, 1:3). Further purifications of compounds were carried out by crystallization to give extract purified compounds **9a-f**. Yields and spectral data of resulting products are given in the following.

6,11,12-Trihydro-13*H*-6,13-ethanobenzo[7,8][1,4]thiazonino[3,2-*b*]pyridin-11-one (9a). White crystals; 85%; mp 152-55 °C (acetone); IR (KBr) ν_{max} 3040, 2938, 1695, 1605, 1585, 1475, 1440, 1386, 1270, 1130, 960 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 2.47 (1H, dddd, *J* 14.8, 3.1, 2.6, 2.3 Hz, *bridged-CHa*), 2.57 (1H, ddt, *J* 14.8, 9.9, 4.2 Hz, *bridged-CHb*), 3.45 (1H, ddd, *J* 14.1, 9.9, 3.1 Hz, *bridged-NCHa*), 3.74 (1H, ddd, *J* 14.1, 4.2, 2.3 Hz, *bridged-NCHb*), 4.88 (1H, *app*-d, *J* 16.9 Hz, N-CH^{12}CO), 4.88 (1H, dd, *J* 4.2, 2.6 Hz, C^6H), 4.83 (1H, *app*-d, *J* 16.9 Hz, N-CH^{12}CO), 6.72 (1H, dd, *J* 7.9, 4.6 Hz), 7.17 (1H, ddd, *J* 8.0, 1.3, 0.4 Hz), 7.37 (1H, ddd, *J* 7.8, 7.5, 1.3 Hz), 7.49 (1H, ddd, *J* 8.0, 7.5, 1.3 Hz), 7.52 (1H, dd, *J* 7.9, 1.9 Hz), 7.84 (1H, ddd, *J* 7.8, 1.3, 0.4 Hz), 8.01 (1H, dd, *J* 4.6, 1.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 31.6, 47.1, 49.5, 54.4, 122.2, 125.8, 126.3, 127.4, 129.2, 132.3, 133.1, 134.4, 140.6, 148.3, 153.9, 191.6. Anal. Calcd. for $C_{16}H_{14}N_2OS$ (282); C, 68.08; H, 4.96; N, 9.92; S, 11.34. Found; C, 67.92; H, 4.95; N, 10.08; S, 11.40%.

6,7,13-Trihydro-5*H*-5,13-ethanobenzo[8,9][1,4]thiazecino[3,2-*b*]pyridin-8-one (9b). Yellowish plates; 82%; mp 142-45 ºC (acetone); IR (KBr) ν_{max} 3037, 2960, 1705, 1570, 1470, 1380, 1252, 1170, 767 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$, δ, ppm): 2.62 (1H, dddd, *J* 14.2, 6.8, 2.4, 1.7 Hz, *bridged-CHa*), 2.66 (1H, dddd, *J* 14.2, 7.3, 7.1, 3.4 Hz, *bridged-CHb*), 2.89 (1H, ddd, *J* 14.4, 7.3, 5.0 Hz, CH^{7}CO), 3.10 (1H, ddd, *J* 14.4, 5.9, 3.5 Hz, CH^{7}CO), 3.58 (1H, ddd, *J* 13.7, 7.3, 1.7 Hz, *bridged-NCHa*), 3.69 (1H, ddd, *J* 15.1, 7.3, 5.9 Hz, *bridged-NCHb*), 3.69 (1H, ddd, *J* 15.1, 5.0, 3.5 Hz, N-CH^6), 3.59 (1H, ddd, *J* 13.7, 7.1, 6.8 Hz, N-CH^6), 5.60 (1H, dd, *J* 3.4, 2.4 Hz, C^{13}H), 7.09 (1H, dd, *J* 7.5, 4.7 Hz), 7.16 (1H, ddd, *J* 8.2, 1.4, 0.5 Hz), 7.45-7.55 (2H,m), 7.68 (1H, ddd, *J* 8.7, 7.7, 1.4 Hz), 7.76 (1H, ddd, *J* 8.7, 1.2, 0.5 Hz), 7.98 (1H, dd, *J* 4.7, 1.9 Hz); ^{13}C NMR (100 MHz, CDCl$_3$, δ, ppm): 31.6, 35.2, 47.1, 49.5 (2C), 122.2, 125.8, 126.3, 127.4, 129.2, 132.3, 133.1, 134.4, 140.6, 148.3, 153.9, 199.2. Anal. Calcd. for $C_{17}H_{16}N_2OS$ (296); C, 68.91; H, 5.40; N, 9.45; S, 10.81. Found; C, 68.94; H, 5.36; N, 9.52; S, 10.67%.

6,12,13,14-Tetrahydro-15*H*-6,15-ethanobenzo[9,10]pyrido[3,2-*b*][1,4]thiazacycloundecan-11-one (9c.White crystals; 78%; mp 172-74 ºC (ethanol); IR (KBr) ν_{max} 3050, 2965, 1704, 1600, 1580, 1480, 1350, 1273, 1140, 777 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$, δ, ppm): 1.91 (1H, ddddd, *J* 13.3, 7.1, 3.5, 1.6, 1.4 Hz, C^{13}Ha), 2.03 (1H, ddddd, *J* 13.3, 10.1, 8.0, 4.6, 1.8 Hz, C^{13}Hb), 2.15 (1H, dddd, *J* 14.3, 9.1, 6.0, 4.5 Hz, *bridged-CHa*), 2.44 (1H, dddd, *J* 14.3, 6.7, 4.1, 2.3 Hz, *bridged-CHb*), 2.60 (1H, ddd, *J* 15.5, 7.1, 1.8 Hz, C^{12}Ha), 2.74 (1H, ddd, *J* 15.5, 8.0, 1.4 Hz, C^{12}Hb), 3.47 (1H, ddd, *J* 14.6, 9.1, 4.1 Hz, *bridged-NCHa*), 3.54 (1H, ddd, *J* 14.6, 4.5, 2.3 Hz, *bridged-NCHb*), 3.50 (1H, ddd, *J* 14.1, 4.6, 1.6 Hz, C^{14}Ha), 3.68 (1H, ddd, *J* 14.1, 10.1, 3.5 Hz, C^{14}Hb), 5.08 (1H, dd, *J* 6.7, 6.0 Hz, C^{6}H), 6.71 (1H, dd, *J* 7.9, 4.6 Hz), 7.15 (1H, ddd, *J* 8.0, 1.2, 0.5 Hz), 7.42-7.52 (2H, m), 7.68 (1H, ddd, *J* 7.9, 7.6, 1.2 Hz), 7.82 (1H, ddd, *J* 7.9, 1.3, 0.5 Hz), 7.99 (1H, dd, *J* 4.6, 1.9 Hz); ^{13}C NMR (100 MHz, CDCl$_3$, δ, ppm): 21.8, 31.6, 35.3, 47.1, 49.5 (2C), 122.2, 125.8, 126.3, 127.4, 129.2, 132.3, 133.1, 134.4, 140.6, 148.3, 153.9, 206.8. Anal. Calcd. for $C_{18}H_{18}N_2OS$ (310); C, 69.67; H, 5.80; N, 9.03; S, 10.32. Found; C, 69.80; H, 5.94; N, 8.85; S, 10.20%.

6,11,12-Trihydro-13*H*-6,13-ethanopyrido[3',2':7,8][1,4]thiazonino[3,2-*b*]pyridin-11-one (9d). Yellow crystals; 80%; mp 194 *dec.* ºC (acetone); IR (KBr) ν_{max} 3082, 2928, 1700, 1580, 1485, 1440, 1366, 1140, 795 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$, δ, ppm): 2.43 (1H, dddd, *J* 14.2, 3.0, 2.6, 2.4 Hz, *bridged-CHa*), 2.51 (1H, ddt, *J* 14.2, 10.0, 4.1 Hz, *bridged-CHb*), 3.46 (1H, ddd, *J* 15.7, 10.0, 3.0 Hz, *bridged-NCHa*), 3.62 (1H, ddd, *J* 15.7, 4.1, 2.4 Hz, *bridged-NCHb*), 4.74 (1H, *app*-d, *J* 16.9 Hz, N-CH^{12}CO), 4.90 (1H, *app*-d, *J* 16.9 Hz, N-CH^{12}CO), 5.30 (1H, dd, *J* 4.1, 2.6 Hz, C^{6}H), 6.72 (1H, dd, *J* 7.9, 4.6 Hz), 7.25 (1H, dd, *J* 7.8, 4.6 Hz), 7.52 (1H, dd, *J* 7.9, 1.9 Hz), 7.88 (1H, dd, *J* 7.8, 1.9 Hz), 8.00 (1H, dd, *J* 4.6, 1.9 Hz), 8.78 (1H, dd, *J* 4.6, 1.9 Hz); ^{13}C NMR (100 MHz, CDCl$_3$, δ, ppm): 31.6, 49.3, 49.5, 54.4, 122.2, 126.7, 127.4, 128.2, 134.4, 134.7, 148.3,149.0, 152.0, 153.9, 191.6. Anal. Calcd. for $C_{15}H_{13}N_3OS$ (283); C, 63.60; H, 4.59; N, 14.84; S, 11.30. Found; C, 63.65; H, 4.63; N, 14.80; S, 11.15%.

5,6,7,14-Tetrahydro-8*H*-8,14-ethanopyrido[3',2':8,9][1,4]thiazecino[3,2-*b*]pyridin-5-one (9e). Yellow crystals; 84%; mp 158-61 ºC (acetone); IR (KBr) ν_{max} 3052, 2934, 1685, 1580, 1485, 1355, 1245, 1120, 785 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$, δ, ppm): 2.64 (1H, dddd, *J* 14.3, 7.0, 2.3, 1.8 Hz, *bridged-CHa*), 2.72 (1H, dddd, *J* 14.3, 7.4, 6.8, 3.5 Hz, *bridged-CHa*), 2.95 (1H, ddd, *J* 14.3, 7.3, 4.8 Hz, CH^{6}CO), 3.11 (1H, ddd, *J* 14.3, 5.8, 3.7 Hz, CH^{6}CO), 3.69 (1H, ddd, *J* 15.1, 4.8, 3.7 Hz, *bridged-NCHa*), 3.65 (1H, ddd, *J* 13.8, 7.0, 6.8 Hz, *bridged-NCHb*), 3.66 (1H, ddd, *J* 13.8, 7.4, 1.8 Hz, N-CH^7), 3.76 (1H, ddd, *J* 15.1, 7.3, 5.8 Hz, N-CH^7), 5.75 (1H, dd, *J* 3.5, 2.3 Hz, C^{14}H), 6.72 (1H, dd, *J* 7.9, 4.6 Hz), 7.25 (1H, dd, *J* 7.8, 4.6 Hz), 7.50 (1H, dd, *J* 7.9, 1.9 Hz), 7.99 (1H, dd, *J* 4.6, 1.9 Hz), 8.20 (1H, dd, *J* 7.8, 1.9 Hz), 8.44 (1H, dd, *J* 4.6, 1.9 Hz); ^{13}C NMR (100 MHz, CDCl$_3$, δ, ppm): 31.6, 35.2, 49.3, 49.5 (2C), 122.2, 126.7, 127.4, 128.2, 134.4, 134.7, 148.3, 149.0, 152.0, 153.9, 199.2. Anal. Calcd. for $C_{16}H_{15}N_3OS$ (297); C, 64.64; H, 5.05; N, 14.14; S, 10.77. Found; C, 64.81; H, 5.19; N, 14.02; S, 10.90%.

6,12,13,14-Tetrahydro-15*H*-6,15-ethanodipyrido[3,2-*b*:3',2'-*i*][1,4]thiazacycloundecan-11-one (9f). White crystals; 83%; mp 168-71 ºC (benzene); IR (KBr) ν_{max} 3044, 2920, 1700, 1610, 1472, 1440, 1361, 1280, 779 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$, δ, ppm): 1.93 (1H, ddddd, *J* 13.3, 7.2, 3.4, 1.7, 1.5 Hz, C^{13}Ha), 2.02 (1H, dddd, *J* 14.2, 9.2, 6.1, 4.5 Hz, *bridged-CHa*), 2.04 (1H, ddddd, *J* 13.3, 10.2, 7.7, 4.5, 1.8 Hz, C^{13}Hb), 2.42 (1H, dddd, *J*

14.2, 6.6, 4.1, 2.3 Hz, *bridged-CHb*), 2.65 (1H, ddd, *J* 15.5, 7.2, 1.8 Hz, $C^{12}Ha$), 2.82 (1H, ddd, *J* 15.5, 7.7, 1.5 Hz, $C^{12}Hb$), 3.48 (1H, ddd, *J* 14.6, 9.2, 4.1 Hz, *bridged-NCHa*), 3.51 (1H, ddd, *J* 14.1, 4.5, 1.7 Hz, *bridged-NCHb*), 3.53 (1H, ddd, *J* 14.6, 4.5, 2.3 Hz, $C^{14}Ha$), 3.68 (1H, ddd, *J* 14.1, 10.2, 3.4 Hz, $C^{14}Hb$), 5.40 (1H, dd, *J* 6.6, 6.1 Hz, C^6H), 6.70 (1H, dd, *J* 7.9, 4.6 Hz), 7.04 (1H, dd, *J* 7.9, 4.6 Hz), 7.48 (1H, dd, *J* 7.9, 1.9 Hz), 7.89 (1H, dd, *J* 7.9, 1.9 Hz), 8.00 (1H, dd, *J* 4.6, 1.9 Hz), 8.51 (1H, dd, *J* 4.6, 1.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 21.8, , 31.6, 35.3, 49.3, 49.5 (2C), 122.2, 126.7, 127.4, 128.2, 134.4, 134.7, 148.3, 149.0, 152.0, 153.9, 199.2. Anal. Calcd. for $C_{17}H_{17}N_3OS$ (311); C, 65.59; H, 5.46; N, 13.50; S, 10.28. Found; C, 65.50; H, 5.41; N, 13.66; S, 10.47%.

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