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Article

Unusual Oxidative Dimerization in the 3-Aminothieno[2,3-*b*]pyridine-2-carboxamide Series

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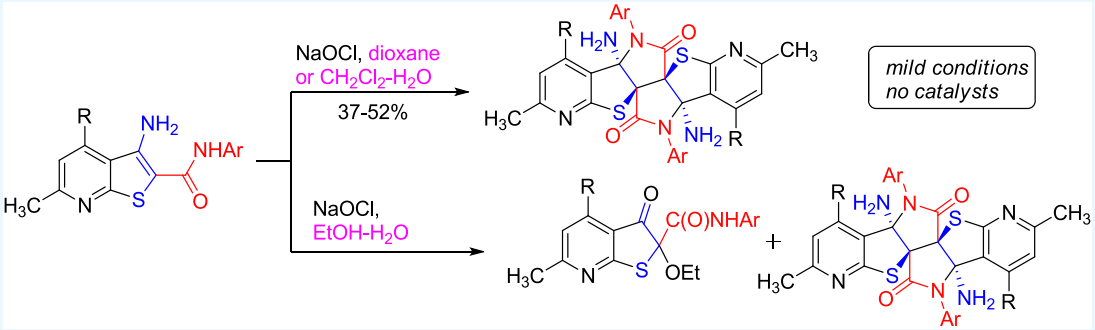

ABSTRACT: Noncatalyzed, regio- and stereoselective hypochlorite oxidation of 3-aminothieno[2,3-*b*]pyridine-2-carboxamides is presented. Unexpectedly, the oxidation proceeded by different mechanistic pathways, and different products were formed, depending on the nature of solvents used. A possible mechanism, the structure of products, kinetics and dynamics of intramolecular processes, and biological activity of products are discussed.

INTRODUCTION

Thieno[2,3-*b*]pyridines belong to a privileged class of compounds that has for a long time attracted great interest for its beneficial effects in the treatment of many diseases.[1−5] Recently, there have been a number of reports concerning the biological activity of thienopyridines. Recently, 3,6-diaminothieno[2,3-*b*]pyridines **1** were identified as selective inhibitors of the plasmodial glycogen synthase kinase-3 *Pf*GSK-3,[6−9] inhibitors of bacterial histidine kinase autophosphorylation,[10] heat shock protein Hsp90 and serine/threonine kinase B-Raf inhibitors,[11] TGF-βR1 modulators,[12] and inhibitors of infectious prion isoform PrP^{Sc} replication[13] (Figure 1). Easily available[14] thieno[2,3-*b*]quinolines **2** have been reported as phosphoinositide specific-phospholipase C-γ (PLC-γ) enzyme inhibitors[15−19] with significant antiproliferative activities against a range of human cancer cell lines[20−25] and as potent antiplatelet agents.[26] 4-Aminothienopyridine-3-carbonitriles **3** or their derivatives showed good activity against *Staphylococcus epidermidis*,[27] *Leishmania amazonensis*,[28] and Mayaro virus[29] and were also recognized as protein kinase C θ (PKCθ) inhibitors[30−32] for treatment of autoimmune and inflammatory diseases. Several thienopyridines have been developed as bone anabolic agents[33] (**4**, Figure 1), inhibitors of 15-prostaglandin dehydrogenase **5** useful for tissue regeneration,[34,35] alkaline phosphatase enhancers **6** for osteoporosis treatment,[36] hepatitis C virus inhibitors **7**,[37] anti-HIV agents **8**,[38] highly selective 5-hydroxytryptamine (5-HT)$_4$ receptor agonists and memory enhancers such as PRX-03140 (**9**),[39,40] and negative allosteric modulators of metabotropic GluR5 receptors (**10**).[41] A series of 3-amino-4-methylthieno[2,3-*b*]pyridine-2-carboxamides **11**−**14** were reported[42−53] as selective muscarinic acetylcholine receptor 4 (M_4) positive allosteric modulators that displayed *in vivo* efficacy in preclinical models of antispsychotic drug effects. Some thienopyridines are useful as insecticides,[54,55] pesticides,[56] herbicide antidotes with respect to 2,4-dichlorophenoxyacetic acid (2,4-D),[57,58] and plant growth regulators.[59] Easily acccessible[60] 3-aminothienopyridine-5-carboxylic acids **15** were identified and developed as a novel class of IKKβ inhibitors,[61] ubiquitin C-terminal hydrolase-L1 (UCH-L1) inhibitors,[62] and HIV-1 integrase inhibitors.[63]

A functionalization of substituents and a new ring addition to the thieno[2,3-*b*]pyridine core system may be used to enhance and broaden the application of compounds. Thus, biological activities exhibited by ring-fused thienopyridines include antimicrobial and antiprotozoal,[64−67] antihistaminic,[68]

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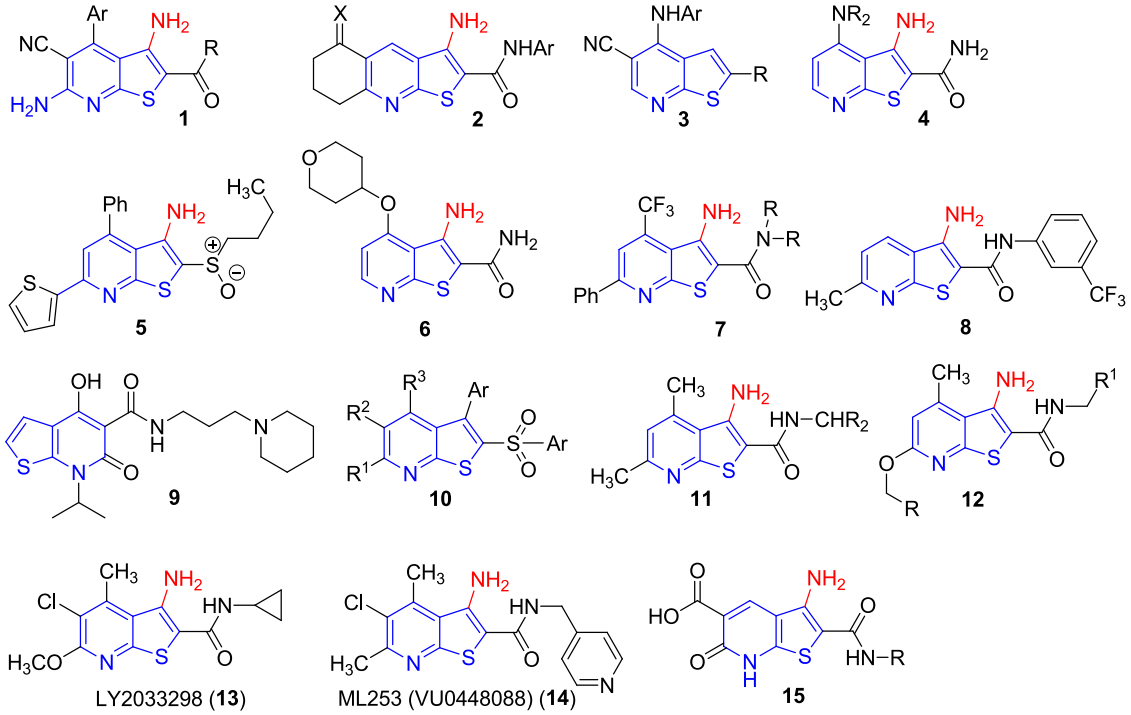

Figure 1. Biologically active thieno[2,3-*b*]pyridines.

antiproliferative/anticancer,[69−71] anti-Alzheimer,[72] anticonvulsant, and neurotropic[73−76] effects. Pyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidines were reported as phosphodiesterase type 4 inhibitors,[77] multitarget Ser/Thr kinase inhibitors,[78] Cdc7 kinase inhibitors,[79] and hepatic gluconeogenesis inhibitors.[80]

In continuation of our studies on the synthesis and biological properties of thienopyridines,[81−90] we wish now to report the synthesis and structures of new polyheterocyclic ensembles prepared by noncatalyzed oxidative dimerization of 3-aminothieno[2,3-*b*]pyridine-2-carboxamides.

In general, selective oxidation of thienopyridines with a variety of reagents can be considered as an effective route to functionalization of the bicyclic core and has been used for preparation of the corresponding N-oxides **16** and **17**,[91−96] halo derivatives **18** and **19**,[94,97] S-oxides **20**−**22**,[91,95,98,99] sulfones **23** and **24**,[95,98−100] and functionalized molecules **25**−**29** (Scheme 1).

However, a survey of the literature has revealed the lack of studies on the oxidation of easily available and biologically active 3-aminothieno[2,3-*b*]pyridines. These studies can be helpful in consideration of possible metabolic *in vivo* oxidation pathways for thienopyridine drugs.

First, we considered the oxidation of 3-aminothieno[2,3-*b*]pyridine-2-carboxamides and 2-acyl-3-aminothieno[2,3-*b*]-pyridines as the possible route toward polyheterocyclic ensembles having pyrazole or isoxazole fragments (Scheme 2).

In fact, the preparation of benz[*c*]isoxazoles by oxidation of *ortho*-aminophenyl ketones with monopersulphate was reported[101] by Bamberger and Elger as far back as in 1903. The more modern improved methods of the oxidation involve the use of oxone,[102] [bis(acetoxy)iodo]benzene,[103−105] NaOCl in ethanolic NaOH solution,[106] MCPBA,[107] and H_2O_2−AcOH[108] as oxidizing agents. 3-Indazolones[109,110] or their heteroanalogs[110,111] can be prepared by hypervalent iodine oxidation of anthranilamides or related heterocyclic *ortho*-amino carboxamides (Scheme 3). The improved procedure for the synthesis of 3-indazolones was proposed by Dai et al. and based on the use of a copper−air catalytic system for intramolecular N−N bond formation.[112] Recently, an approach to construct *N*,*N*′-diarylindazol-3-ones has been developed[113] using the tandem sequence of Chan−Evans−Lam oxidative C−N cross-coupling of anthranilamides with aryl boronic acids, followed by dimethyl sulfoxide (DMSO)/air oxidative N−N coupling.

With these points in mind, we decided to investigate the oxidation of 3-aminothieno[2,3-*b*]pyridine-2-carboxamides using a commercial bleach (aq. NaOCl) solution. To our surprise, preliminary results showed[114] that the expected pyrazole ring formation did not take place and that the reaction proceeded in a more complex way to afford unusual oxidative dimerization products.

In this paper, we wish to report the detailed studies on the new reaction and its scope and limitations, the structure, stereochemistry of products in the solid state and in a solution, the kinetics and dynamics of intramolecular processes in a solution, and the results of biological *in silico* studies.

RESULTS AND DISCUSSION

We found that thienopyridines **30** readily undergo oxidation upon treatment with a 10-fold excess of aq. NaOCl in aqueous dioxane to afford the new products of oxidative dimerization, pyrido[3‴,2‴:4‴,5‴]thieno[2‴,3‴:4″,5″]pyrrolo[3″,4″:3′,4′]-pyrrolo-[2′,3′:4,5]thieno[2,3-*b*]pyridine-6,13-diones **31** in moderate (37−55%) yields (method A, Scheme 4 and Table 1). Somewhat better results (43−64%) were achieved when the oxidation proceeded under phase transfer catalyst (PTC) conditions in a CH_2Cl_2−water system (method B). The scope of the substrates is limited to those thienopyridine-2-carboxamides bearing mostly electron-donating groups in aryl substituents. Thus, we failed to obtain any oxidation products from thienopyridine **30l** (R = Me, Ar = 4-$NO_2C_6H_4$, Table 1, entry 12), though thienopyridines **30g** and **30h** bearing less

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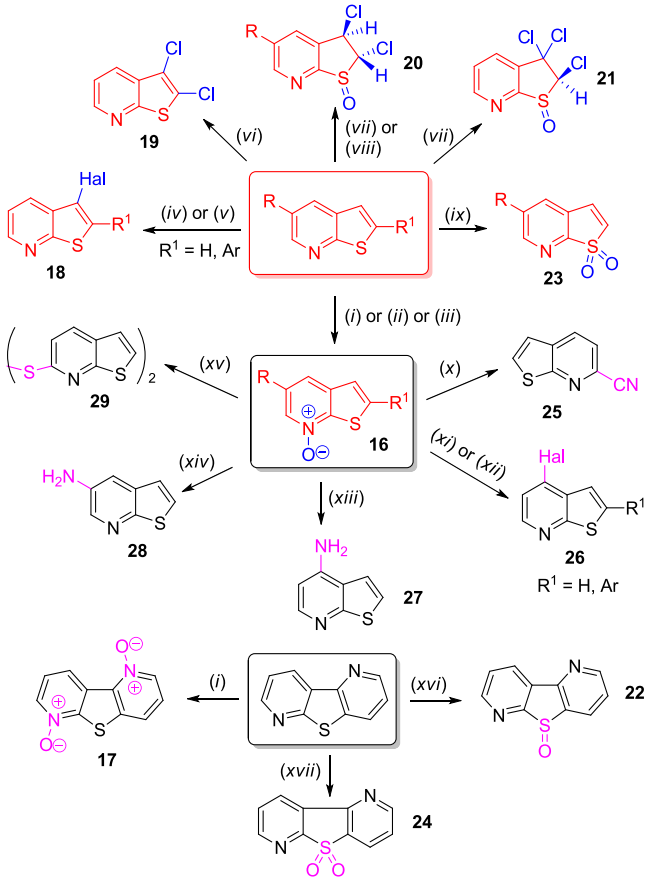
Scheme 1. Oxidation of Thieno[2,3-*b*]pyridines and the Reactions of Oxidation Products[a]

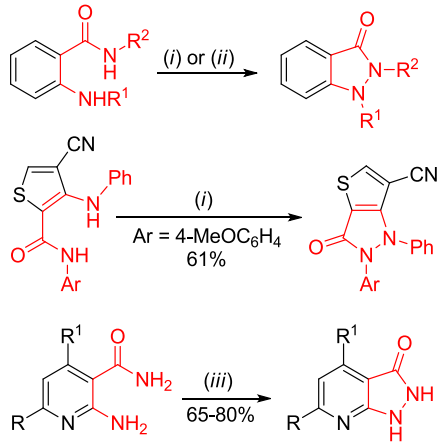


[a]R = H, Et. (i) 30% H_2O_2, and AcOH, 55 °C; (ii) *meta*-chloroperbenzoic acid (MCPBA) in $HCCl_3$ or CH_2Cl_2–EtOAc and at 0 °C; (iii) magnesium monoperoxyphthalate hexahydrate, AcOH, and 25 °C; (iv) Hal_2, Ag_2SO_4, and conc. H_2SO_4; (v) Br_2, dry Et_2O or CH_2Cl_2, and 0 °C; (vi) Cl_2, $HCCl_3$–H_2O, and reflux 3 h; (vii) Cl_2, $HCCl_3$–H_2O, 0–10 °C, and 3 h; (viii) NaOCl, conc. H_2SO_4, and tetrahydrofuran (THF)–H_2O; (ix) aqueous (aq.) NaOCl, HCl, and room temperature (r.t.); (x) $Me_2NC(O)Cl$, Me_3SiCN, and CH_3CN; (xi) $POCl_3$, $CHCl_3$, 100 °C, and 3 h; (xii) Bu_4N^+ Br^-, CH_2Cl_2, $(CF_3SO_2)_2O$, 0 °C, and 16 h; (xiii) (1) HNO_3, H_2SO_4, and 90–120 °C; (2) Fe, AcOH, and 100 °C; (xiv) (1) HNO_3, AcOH, and 120 °C; (2) Sn, HCl, and 25 °C; (xv) KSCN, CH_2Cl_2–H_2O, PhC(O)Cl, and 25 °C; (xvi) $PhICl_2$ (IBDC) and MeCN–H_2O; and (xvii) Cl_2, CCl_4–H_2O, and 0 °C.

strong withdrawing groups (Ar = 4-AcC_6H_4, 4-$CF_3C_6H_4$, Table 1, entries 7 and 8) reacted well. Surprisingly, when the reaction was conducted in aq. EtOH, a mixture of polycycles **31** (28–29%) and oxidation/solvolysis products **32** (14–15%) was obtained (method C, Scheme 4 and Table 2).

To examine whether other oxidants are suitable for preparation of polycycles **31** from thienopyridines **30**, we performed the reaction of compound **30d** (R = Me, Ar = 4-EtC_6H_4) with MCPBA and magnesium monoperoxyphthalate (MMPP) (Scheme 5). In both cases, only simple S-oxidation products **33** and **34** were isolated.

Scheme 3. Intramolecular N–N Oxidative Coupling of Anthranilamides and Related Substrates[a]



[a](i) $PhI(OC(O)CF_3)_2$ (phenyliodine bis(trifluoroacetate) (PIFA)), CH_2Cl_2, trifluoroacetic acid (TFA), 0 °C, and 45–81%; (ii) CuBr (20 mol %), DMSO, air, 120 °C, and 56–99%; and (iii) PIFA, dimethylformamide (DMF)–H_2O, r.t., and 4 h.

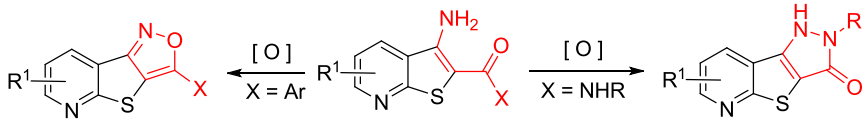
The structure of 2-ethoxy-4,6-dimethyl-*N*-(4-methylphenyl)-3-oxo-2,3-dihydrothieno[2,3-*b*]pyridine-2-carboxamide **32a** was studied in detail using NMR spectroscopy, including two-dimensional (2D) NMR heteronuclear single-quantum correlation (HSQC) and heteronuclear multiple bond correlation (HMBC) techniques (Figure 2), high-resolution mass spectrometry (HRMS), and elemental analysis.

As we can see from Figure 2, in the ^{1}H NMR spectrum, diastereotopic protons of OCH_2 appeared as two doublets of quartets with coupling constants ^2J 14.2 Hz and ^3J 6.9 Hz due to the presence of the neighboring chiral C-2 carbon atom. In the ^{1}H NMR spectrum of the related thienopyridine **32b**, two doublets of quartets of OCH_2 (^2J 14.5 Hz), as well as AB quartet of methylene protons CH_2OMe (^2J 12.8 Hz), were observed. The signals of keto carbons at δ 197.3–197.4 ppm were also observed in the ^{13}C NMR spectra of **32a** and **32b**. In the IR spectra, bands at ν 1640–1650 and 1690–1695 cm^{-1} can be assigned to the stretches of keto and amide C=O groups, respectively.

Formation of compounds **32a** and **32b** can be rationalized by the following mechanistic sequence (Scheme 6). We suggest that electrophilic chlorination occurs at the C-2 position with formation of stabilized cation **A**, followed by deprotonation, nucleophilic substitution of a chlorine atom with an ethoxide ion, and hydrolysis.

The compounds **31** are colorless, high melting crystalline solids, sparingly soluble in most organic solvents, except for acetone, CH_2Cl_2, DMF, and DMSO. The IR spectra of polycycles **31** differ from the spectra of compounds **30** and **32**.

Scheme 2. Expected Oxidation Pathways for 2-Substituted 3-Aminothieno[2,3-*b*]pyridines



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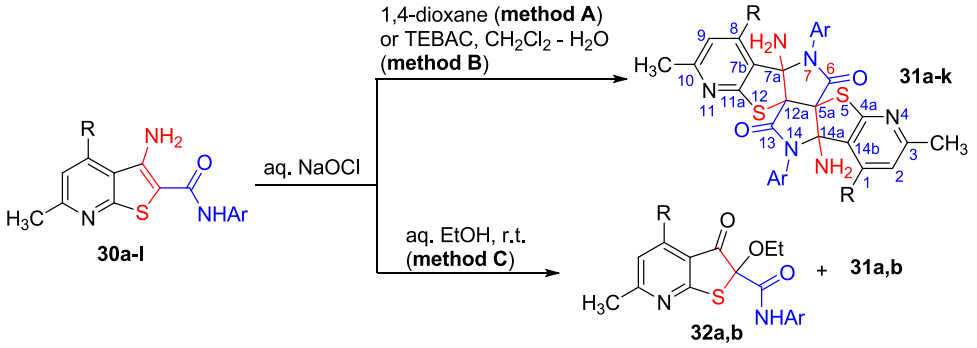
Scheme 4. Oxidation of 3-Aminothieno[2,3-*b*]pyridine-2-carboxamides with Bleach Solution under Different Conditions



Thus, the latter spectra revealed the typical absorption bands of amide carbonyls ν C=O in the region of 1630−1645 cm^{-1} while the bands at 1730−1740 cm^{-1}, which are due to five-membered lactam carbonyl stretches, were observed in the spectra of **31**.

Another interesting issue is the stereochemical features of polycyclic oxidation products. Compounds **31** exhibit four chiral centers giving rise to eight possible pairs of diastereomers. However, only one set of signals corresponding to one of the possible stereoisomeric pairs was observed in the ^{1}H and ^{13}C NMR spectra at high temperatures (80−120 °C). In the spectra of compounds **31b**, **31f**, and **31j**, which have prochiral methoxymethyl groups, the signals of diastereotopic hydrogens appeared as a pair of doublets with germinal coupling constant of 14.5−15.7 Hz.

The X-ray study of the crystal structure of compound **31c** (Figure 3) showed that products exist as a pair of (*R*,*R*,*R*,*R*)/(*S*,*S*,*S*,*S*) enantiomers only. The molecule of **31c** has a second-order symmetry axis passing through the center of the C−C bond common to both lactam rings. After recrystallization from DMSO, two solvent molecules, which are linked through hydrogen bonds to the amino groups, also filled the crystal unit cell (Figure 4). The geometry of DMSO-d_6 molecules captured in the crystal lattice showed no difference, neither in bond lengths nor in angles, with the results reported for DMSO-d_6 single crystal at 100 K.[115]

Intermolecular hydrogen bonds between **31c** and DMSO-d_6 molecules are somewhat different from each other. Thus, the intermolecular bond O(5)···H(6B) has an interatomic distance of 2.173 Å and bond angles S(3)−O(5)···H(6B) and N(6)−H(6BB)···O(5) equal to 132.4 and 157.5°, respectively. The bond O(6)···H(5A) has a length of 2.139 Å, and the angles S(4)−O(6)···H(5A) and N(5)−H(5A)···O(6) were found to be 157.6 and 125.9°, respectively.

The main stereochemical and structural features of molecule **31c** are the following.

(1) All four five-membered rings are almost planar (the average deviation of atoms from planes does not exceed 0.1 Å), and pyridine rings lie in the planes of thiophene fragments. Four five-membered cycles form a folded structure in which the atoms common for two [C(6) and C(14)] and three [C(8) and C(16)] cycles almost have no distortions of bond angles, and the interatomic distances are close to the standard C_{sp^3}−C_{sp^3} bond lengths.

(2) The angle between the central planes of lactam rings (Figure 5) C(16)−C(8)−N(1)−C(7)−C(8) (plane 1) and C(16)−C(8)−C(14)−N(2)−C(15) (plane 2) is equal to 125.8°, and the adjacent planes of thiophene rings S(1)−C(1)−C(5)−C(6)−C(16) (plane 3) and C(8)−C(14)−C(13)−C(9)−S(2) (plane 4) form angles close to 115° with lactam cycles (angles between planes 1−3 and 2−4 are equal to 114.7 and 115.2°, respectively). With regard to the folded system of five-membered rings, the amino groups are located on one side and both sulfur atoms on the other side in pseudoaxial positions, while carbonyl occupied pseudoequatorial positions.

(3) The C−NH_2 bonds are almost parallel to each other; the amino groups are linked by intramolecular hydrogen bonds with the interatomic distances H···N(6) and N(5)−N(6) equal to 2.620 and 3.008 Å and the angle N(5)−H···N(6), 150.0°. The arrangement of amino groups on one side of the rigid central tetracyclic structure allows one to assume the properties of proton sponges[116,117] for compounds **31** and favors the preparation of more complex supramolecular structures.

(4) In the crystal, the aryl substituents are rotated by 108.0 and 64.8° out of the plane of lactam rings [cycles C(17)···C(22) and C(23)···C(28)]. We believe that such preferred non-coplanar orientation is typical for all para-substituted aryls (compounds **31a**−**h**). As a result, the *ortho*-hydrogen atoms of aryl substituents are in different chemical environments. Thus, hydrogen atoms H(15) and H(24), which are located on the same side of the central core with amino groups, are at an almost equal distance from nitrogens of amino groups and carbonyl oxygens: the interatomic distances H(15)···O(2), H(15)···N(6), H(24)···O(1), and H(24)···N(5) are equal to 2.931, 3.297, 3.276, and 3.297 Å, respectively.

This atomic neighborhood would result in deformation of the electron shells of H(15) and H(24); therefore, their signals in the ^{1}H NMR spectra are expected to be shifted to the weaker field. In contrast, the distances H(22)−pyridine ring N(4) and H(27)−pyridine ring N(3) were found to be ∼3.5 Å and due to the shielding effect of aromatic pyridine rings, the signals of *ortho*-hydrogens H(22) and H(27) should be shifted to the anomalously stronger fields. In fact, these shielding/deshielding effects of aryl *ortho*-hydrogen atoms were indeed observed in the ^{1}H NMR spectra recorded at −40 °C (Figure 6), when the rotation around the N−C(Ar) bond was almost negligible.

As we can see from Figure 6, four signals from four nonequivalent hydrogens of para-substituted benzene ring are observed in the downfield region of low-temperature NMR

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Table 1. Reaction Scope, Yields, and Conditions

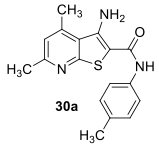
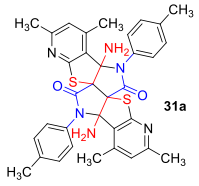
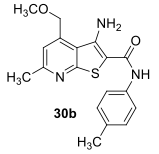
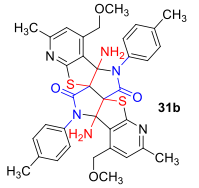
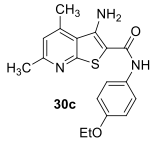
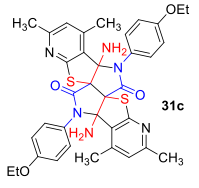
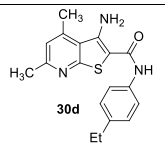
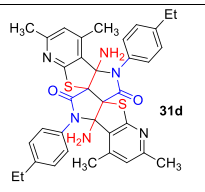
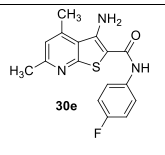
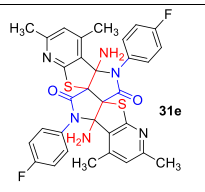
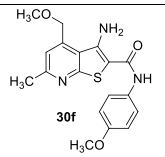
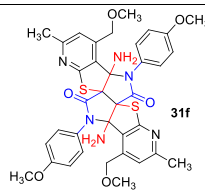
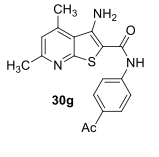
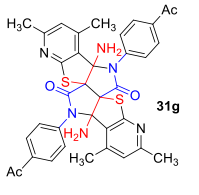
Entry	Starting compound	Product(s)	Conditions and yields	
			Method A (NaOCl, aq. dioxane, r.t.), %	**Method B** (NaOCl, $Et_3N^+CH_2Ph\ Cl^-$ (TEBAC), CH_2Cl_2 –H_2O),%
1	 **30a**	 **31a**	46	52
2	 **30b**	 **31b**	37	43
3	 **30c**	 **31c**	43	50
4	 **30d**	 **31d**	52	61
5	 **30e**	 **31e**	52	60
6	 **30f**	 **31f**	42	53
7	 **30g**	 **31g**	–	64

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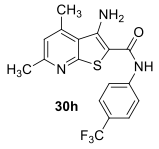
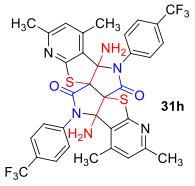
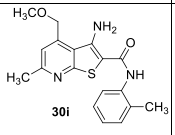
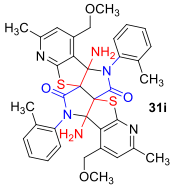
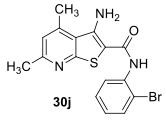
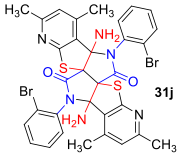
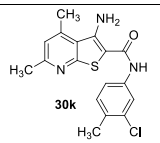
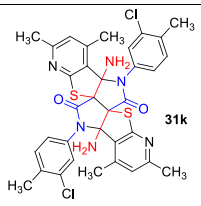
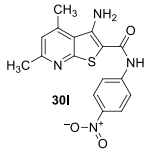
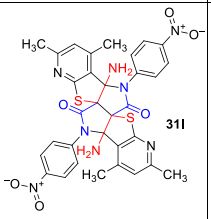
Table 1. continued

Entry	Starting compound	Product(s)	Conditions and yields	
			Method A (NaOCl, aq. dioxane, r.t.), %	**Method B** (NaOCl, $Et_3N^+CH_2Ph\ Cl^-$ (TEBAC), CH_2Cl_2 –H_2O),%
8	 **30h**	 **31h**	–	62
9	 **30i**	 **31i**	47	58
10	 **30j**	 **31j**	–	51
11	 **30k**	 **31k**	55	63
12	 **30l**	 **31l**	0	0

spectra of polycycles **31e** and **31f**, and the sharp singlets at δ 6.7 and 7.0 ppm belong to pyridine protons. According to the correlated spectroscopy (COSY) experiment, the signals at δ 6.3−6.5 and 7.4−7.6 ppm should be assigned to aryl H-2′ and H-6′ protons, and the signals at δ 6.3−6.5 and 7.4−7.6 ppm should be attributed to H-3′ and H-5′ atoms, respectively.

Hence, one may conclude that at low temperatures (≤−40 °C), the intramolecular rotation of the aryl fragment along the N−Ar bond is slow and it may be assumed that the molecular geometry in cold solutions is essentially similar to that in crystals. Upon heating of solutions of compounds **31**, the ^{1}H NMR spectra revealed time evolution of signals, and final coalescence takes place near room temperature (Figure 6).

The kinetic and activation parameters of rotamerization were estimated by analysis of NMR line shapes of aryl H-2′,6′ and H-3′,5′ signals in the ^{1}H NMR spectra of **31e** and **31f** recorded in deuteroacetone upon cooling.

It is noteworthy that the spectral lines in the ^{1}H NMR spectrum of **31e** tend to broaden, and the spectrum was poorly resolved due to the partial spontaneous crystallization at below −40 °C. Therefore, for the theoretical modeling of NMR spectra, we used the chemical shifts of the indicated protons at −40 °C as reference values. The multiplets of H-3′,5′ atoms, which appeared as doublets of doublets collapsed to triplets due to spin−spin coupling to fluorine atom and H-2′,6′ atoms, are well resolved, and the spectral picture at −40 °C is closer to the spectrum in the absence of exchange than to the state of intermediate exchange (Figure 6). The line width at half maximum of the reference signals was taken equal to 2.8 Hz similar to **31f**, and spin−spin coupling constants were accepted as those reported for 4-fluoroaniline.[118] Theoretical spectra (Figure 6, red lines) were simulated by variation of rate constants for the exchange of reference proton signals in the aryl rings, and these theoretical spectra were compared with

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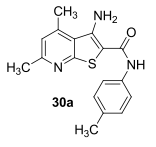
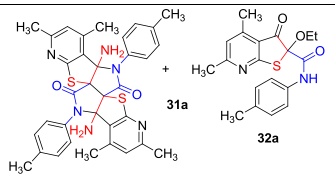
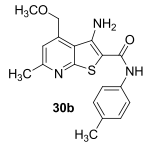
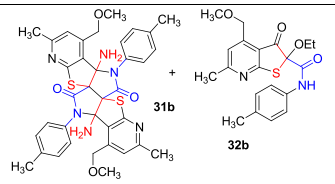
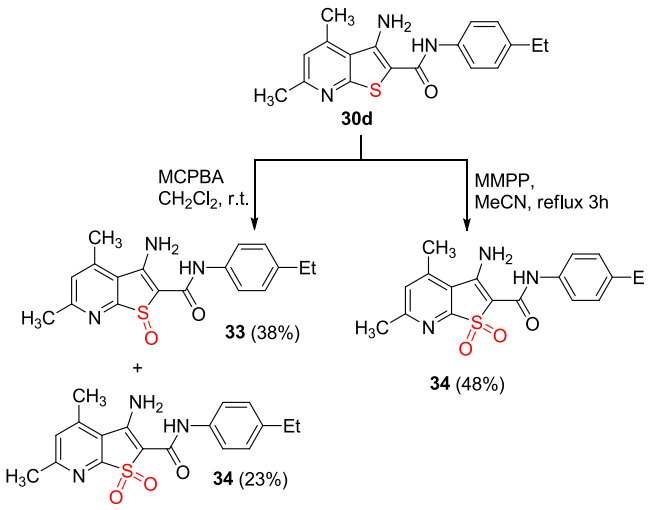
Table 2. Results of Oxidation of Thienopyridines 30a and 30b with NaOCl in EtOH[a]

Entry	Starting compound	Products	Yields
1			**31a** (28%) **32a** (15%)
2			**31b** (29%) **32b** (14%)

[a]Conditions: aq. NaOCl, EtOH, r.t., and 6−9 h.

Scheme 5. Reactions of 3-Aminothieno[2,3-*b*]pyridine-2-carboxamides with MCPBA and MMPP



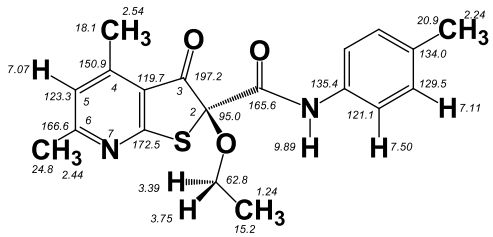


Figure 2. Chemical shifts in the ^{1}H and ^{13}C NMR spectra of **32a** (DMSO-d_6, 25 °C).

temperature-dependent experimental spectra. The calculated activation energy values $\Delta G^{\ddagger}$, ΔH, and ΔS for intramolecular degenerate rotation in the molecules of compounds **31e** and **31f** are given in Figure 7.

The computer simulation of ^{1}H NMR spectra and calculation of exchange rate constants were performed using gNMR 5.0.6.0 software package.[119] First, a series of temperature-dependent experimental ^{1}H NMR spectra were exported to Galactic (*.spc) files using JEOL Delta 5.3 software (https://nmrsupport.jeol.com/) for further conversion into gNMR compatible.spg files using the gCVT program (included in the gNMR package). Next, for the spectrum recorded in the absence of exchange, the line shapes of the reference proton signals were theoretically modeled. Then, by program-driven varying of the chemical shifts, the width at half maximum and the spin−spin coupling constant (if any) line shapes were optimized using the least-squares method with the line shapes experimentally observed in.spg files.

The spectra, calculated with a fixed difference between chemical shifts of the reference signals, fixed width at half maximum, and coupling constants, were correlated with a series of other experimental temperature-dependent spectra by varying the exchange rate constant. As a result, the rate constants were determined for each spectrum at the corresponding temperature (see Figure 7), and the changes in Gibbs free energies ($\Delta G^{\ddagger}$) were calculated for each rate constant using the Arrhenius equation. The enthalpy ($\Delta H^{\ddagger}$) and entropy ($\Delta S^{\ddagger}$) of activation were calculated by treating the dependence of $\Delta G^{\ddagger}$ *vs* temperature using least-squares linearization with a correlation coefficient of at least 0.99 (see Figure 7). According to our estimates based on the known data,[120] we assume that error of the exchange rate constant k determination does not exceed 5%. This gives an estimated error for $\Delta G^{\ddagger}$, 0.04 kcal/mol (0.15 kJ/mol); $\Delta H^{\ddagger}$, 0.19 kcal/mol (0.8 kJ/mol); and $\Delta S^{\ddagger}$, 0.23 cal/(mol·K) (0.96 J/(mol·K)).

The very close values of the activation parameters determined for compounds **31e** and **31f** allowed us to suggest a small influence of a substituent in the para-position on the activation barrier. The rather high differences between the rate constants are supposedly associated with the weight of the substituent(s) in the aromatic ring, since more heavy molecular fragments are prone to slower rotation.

The conformational analysis of the X-ray-determined structure of **31c** revealed that upon rotation along the N−Ar bond and when the bonds C(17)−C(18) and N(2)−C(15) are eclipsed, the interatomic distances H(18)···N(6) and H(18)···O(2) are reduced to 1.7 and 1.9 Å, respectively. In both cases, the distances are longer than the sum of van der Waals radii of the atoms; therefore, one may conclude that carbonyl and amino groups are nearly equal with regard to steric restrictions of free rotation of aryl substituents.

When the temperature of DMSO-d_6 solutions of compounds **31** was further increased from room temperature to 120−140

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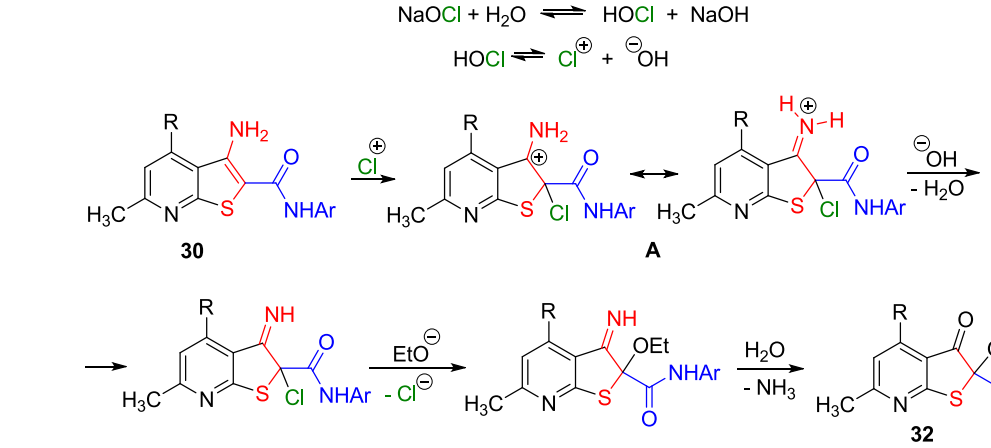
Scheme 6. Plausible Mechanism for Formation of Thienopyridines 32



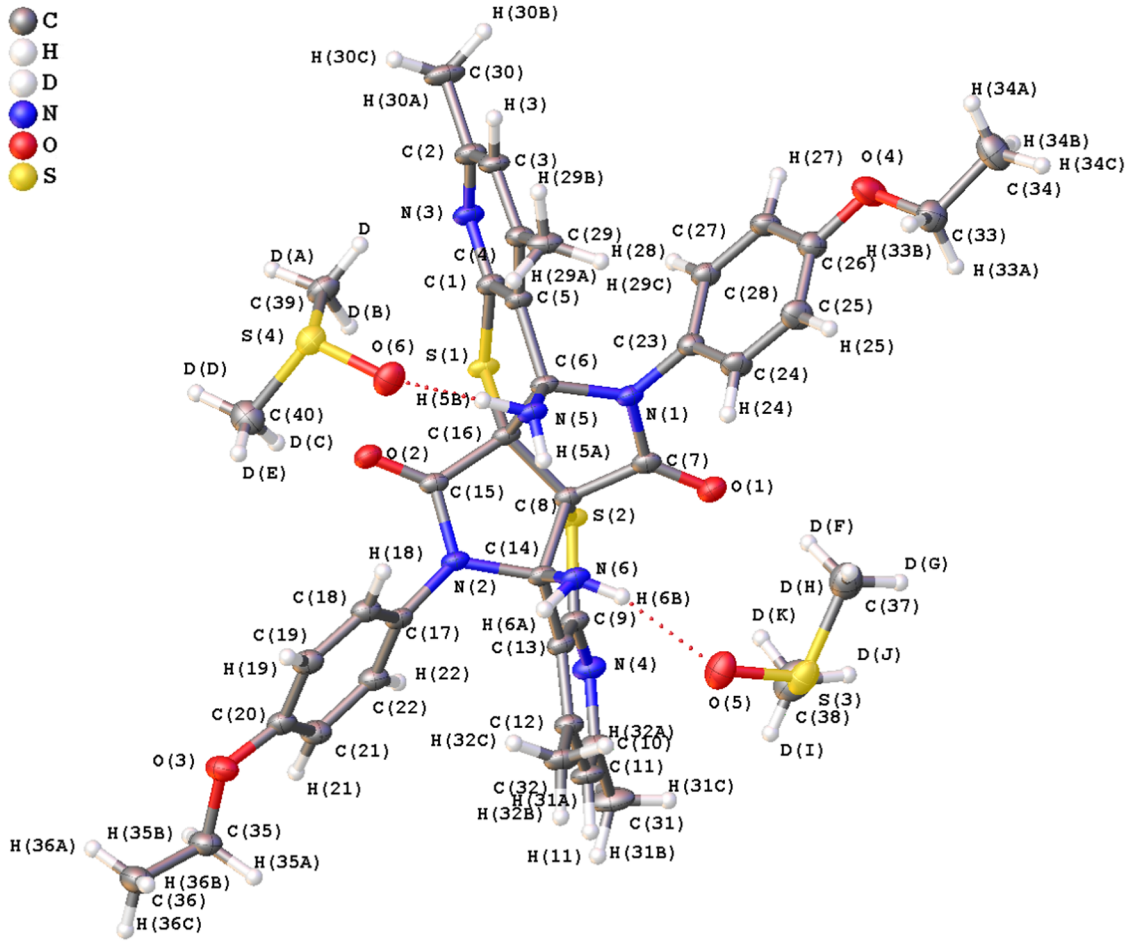


Figure 3. General view of the molecule of compound **31c** (as solvate with two molecules of DMSO-d_6) with atom numbering (by X-ray data).

°C, the signals of *ortho*- and *meta*-hydrogens in ^{1}H NMR spectra collapsed to two doublets typical for para-disubstituted aromatics. These high-temperature spectra are given in the Supporting Information, and the full assignment of the signals using 2D HSQC and HMBC experiments was also performed at 120−140 °C.

In the case of ortho-substituted aryl derivatives **31i** and **31j**, free rotation along N−Ar is absent and the ^{1}H NMR spectra revealed no significant changes (excluding the usual temperature-dependent small chemical shifts) at any temperature from −40 to +120 °C. Only a typical ABCD-pattern of ortho-substituted aromatics was observed in the ^{1}H NMR spectra of **31i** and **31j**; in addition, two methyl groups of both *ortho*-tolyl substituents appeared as one singlet in the NMR spectrum of **316i**. In other words, both N−Ar substituents in the molecules of **31i** and **31j** are located symmetrically with respect to the central heterocyclic core. Furthermore, nuclear Overhauser enhancement spectroscopy (NOESY) experiments showed no correlation peaks between methyl and amino hydrogens, allowing one to suggest that CH_3 and NH_2 groups in **31i** are

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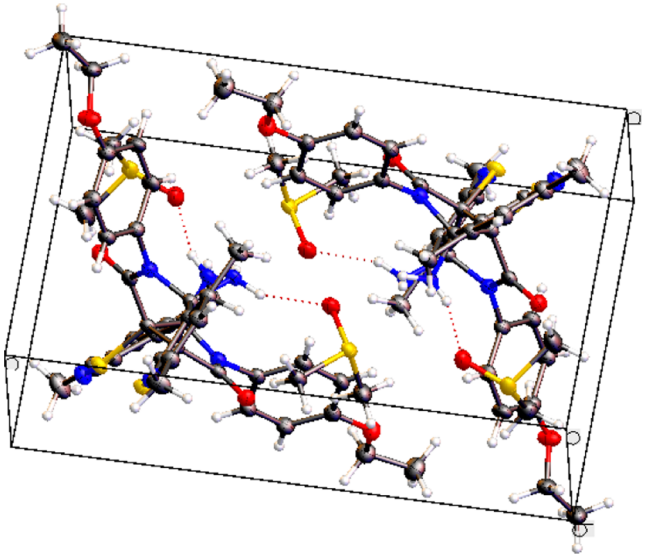

Figure 4. Crystal packing of the (*R*,*R*,*R*,*R*)/(*S*,*S*,*S*,*S*)-pair and four DMSO-d_6 molecules in the unit cell of racemic compound **31c**.

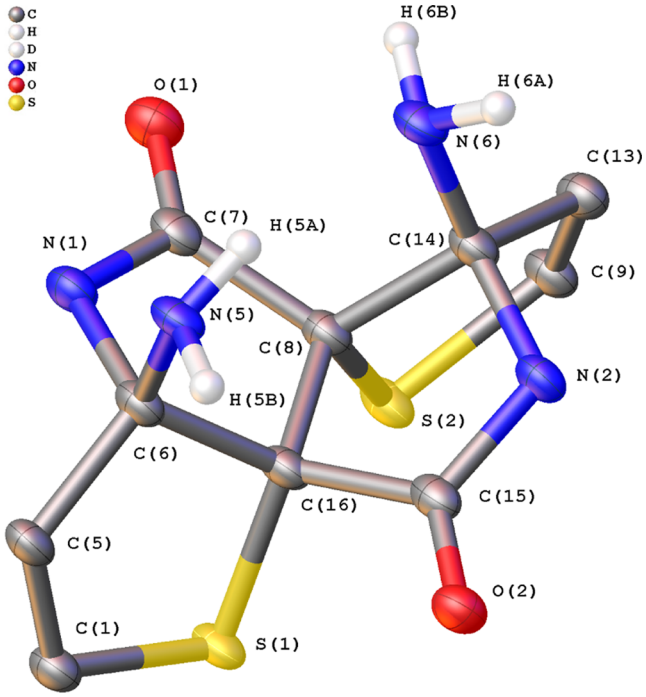

Figure 5. Central fragment of molecule **31c** (by X-ray).

located in anti positions to each other. We believe that 2-bromophenyl and amino groups in **31j** are arranged in the same way. Hindered rotation along the N−Ar bond was also observed in the NMR spectrum of **31k** bearing 3,4-disubstituted aryls, and a variable temperature study showed the same evolution of signals as was observed for compounds **31a**−**h**. The molecular ions of compounds **31** are rather unstable under electron ionization (EI) conditions. The mass spectra revealed the fragment ions $[M - 2Ar{-}N{=}C{=}O]^+$ and $[Ar{-}N{=}C{=}O]^+$, which are typical for all compounds **31**.

Mechanism of Formation of Compounds 31. Evidently, the reaction of thienopyridines **30** with the bleach proceeds as a kind of oxidative dimerization, with a cleavage of N−H and C(2)=C(3) bonds and formation of three new σ-bonds (Figure 8). It is noteworthy that neither pyridine nitrogen nor sulfur atoms are involved in the oxidation.

We suggest two possible mechanistic pathways for the oxidative dimerization of thienopyridines **30**. The first plausible mechanism (#1) is shown in Scheme 7. We suppose that the specificity of the new unusual oxidative dimerization is determined by the presence of HOCl (or Cl^+) that appeared due to the hydrolysis of NaOCl in aqueous solution. In the first step, Cl^+ or free HOCl reacts as the electrophile with thienopyridine **30** to afford resonance-stabilized cation **A**. We also suggest that a parallel process of alkaline-promoted deprotonation of amide with the formation of anion **B** occurs. The reaction between **A** and **B** leads to formation of a new intramolecular C−N bond; next, the carbocation-initiated multistep cascade process occurs, affording polycycles **31**.

Another possible mechanism (#2) is depicted in Scheme 8. Bleach (or HOCl that appeared due to hydrolysis) might act as a single electron transfer (SET) oxidant to produce cation-radical species **35**. Their dimerization leads to dications **36**, which undergo double intramolecular heterocyclization to afford polycycles **31**. However, both proposed mechanisms are disputable and require further diligent studies.

***In Silico* Biological Studies.** The prediction of targeted biological activity of new compounds **31** was performed using the unique QSAR package "Microcosm BioS"[121] by the method of maximum similarity with the reference structures. As reference compounds, we used the set of compounds that were previously studied for various types of targeted biological activity. As target proteins, we selected acetylcholinesterase; proto-oncogene tyrosine-protein kinase (Src), disintegrin and metalloproteinase domain-containing protein 10 (ADAM10), ADAM17, FXN frataxin, and neurokinin 1 receptor. For compounds **31a**, **31b**, **31d**, **31f**, **31i**, and **31k**, the indices of the expected biological activity of the tested structures for targets such as acetylcholinesterase and proto-oncogene tyrosine-protein kinase (Src) were equal to 2. Therefore, these structures can be considered promising candidates for docking studies and biological tests *in vitro* and *in vivo*.

According to the Microcosm BioS prediction, compounds **31a**, **31b**, **31d**−**f**, and **31i**−**k** are of interest as possible inhibitors of acetylcholinesterase, *i.e.*, by reducing the biological activity of AChE and increasing the level of acetylcholine in the brain, and can be used for the treatment of Alzheimer's disease (AD). In addition, compounds **31b**, **31f**, and **31i** are likely to have inhibitory effects against proto-oncogene tyrosine-protein kinase (Src). The results of the *in silico* studies are given in the Supporting Information.

CONCLUSIONS

In summary, we have developed new oxidative dimerization of 3-aminothieno[2,3-*b*]pyridine-2-carboxamides upon treatment with commercial bleach leading to the formation of the unusual polyheterocyclic ensembles. The reaction proceeds in a highly stereoselective manner to give only one (*R*,*R*,*R*,*R*/*S*,*S*,*S*,*S*) out of the eight possible enantiomeric pairs. The preliminary results of *in silico* experiments indicate that the new compounds are promising candidates for further studies to identify new inhibitors of acetylcholinesterase and proto-oncogene tyrosine-protein kinase (Src). The studies on the biological activity of compounds are currently underway. The unique stereochemistry and the cis-arrangement of two amino groups make the molecules suitable for use as a good platform for supramolecular architectures.

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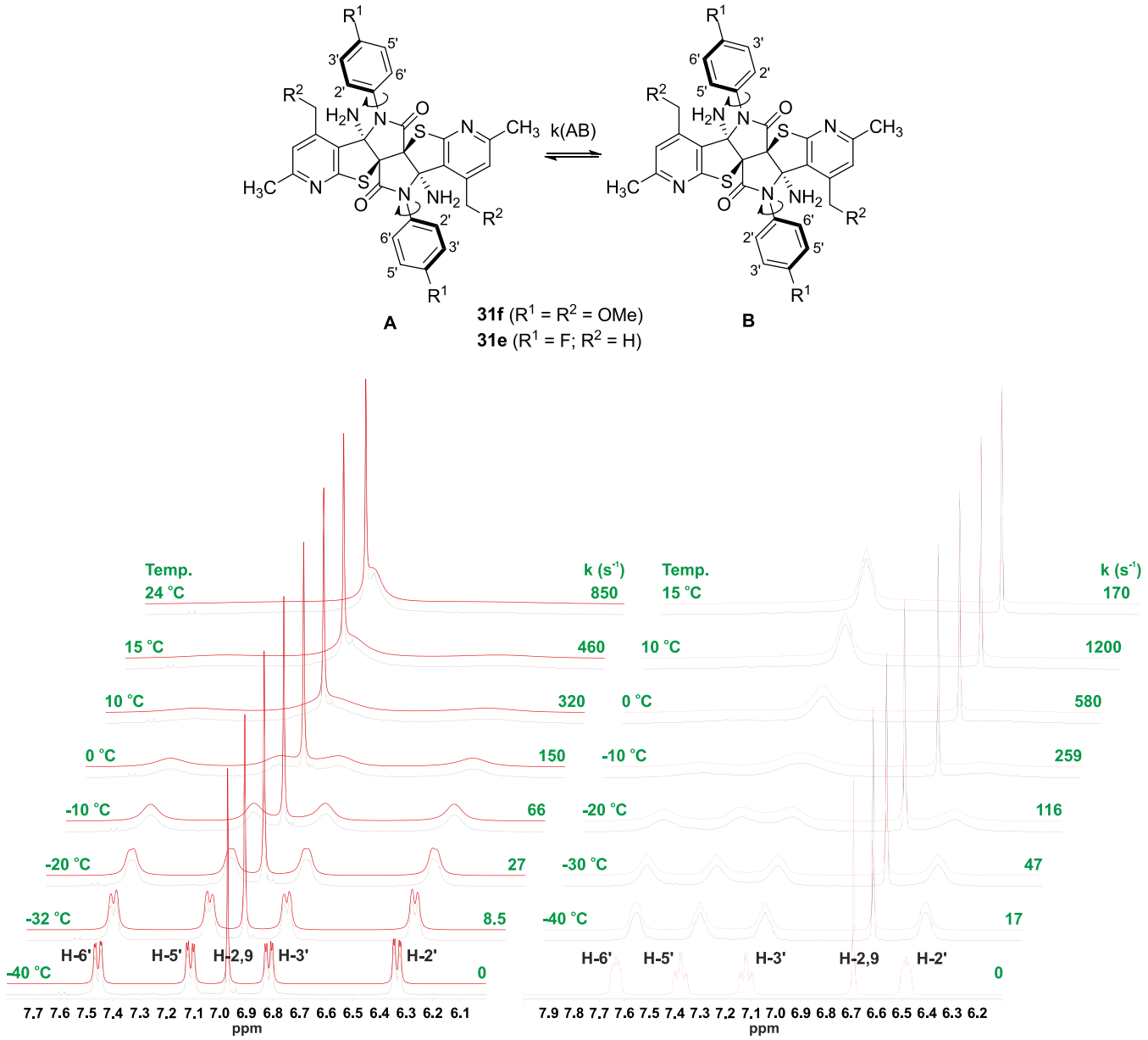

Figure 6. Evolution of ^{1}H NMR signals (acetone-d_6) of compounds **31f** (left) and **31e** (right) upon changing the temperature from −40 to +24 °C (the downfield region of spectra is presented; black lines, experimental; red lines, theoretical; *k*, rate constant for the degenerate rotation of aryl substituent around the exocyclic Ar−N bond; and **A** and **B**, different rotamers of compounds **31e** and **31f**, respectively).

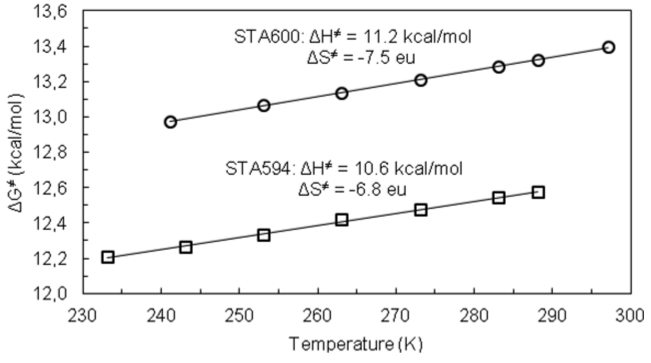

Figure 7. Changes in Gibbs free energies ($\Delta G^{\ddagger}$) at the temperature-dependent rotamerization of compounds **31f** (up) and **31e** (down).

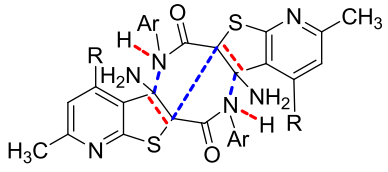

Figure 8. Cleavage and formation of bonds in the bleach-based oxidation reaction of thienopyridines **30**. Breaking bonds are shown in red and forming bonds in blue bold dashed lines.

EXPERIMENTAL SECTION

IR spectra were obtained using a Fourier transform infrared (FTIR) PerkinElmer Spectrum Two instrument in attenuated total reflection (ATR) mode. ^{1}H and ^{13}C NMR spectra were recorded on an Agilent 400/54 spectrometer (400 and 100

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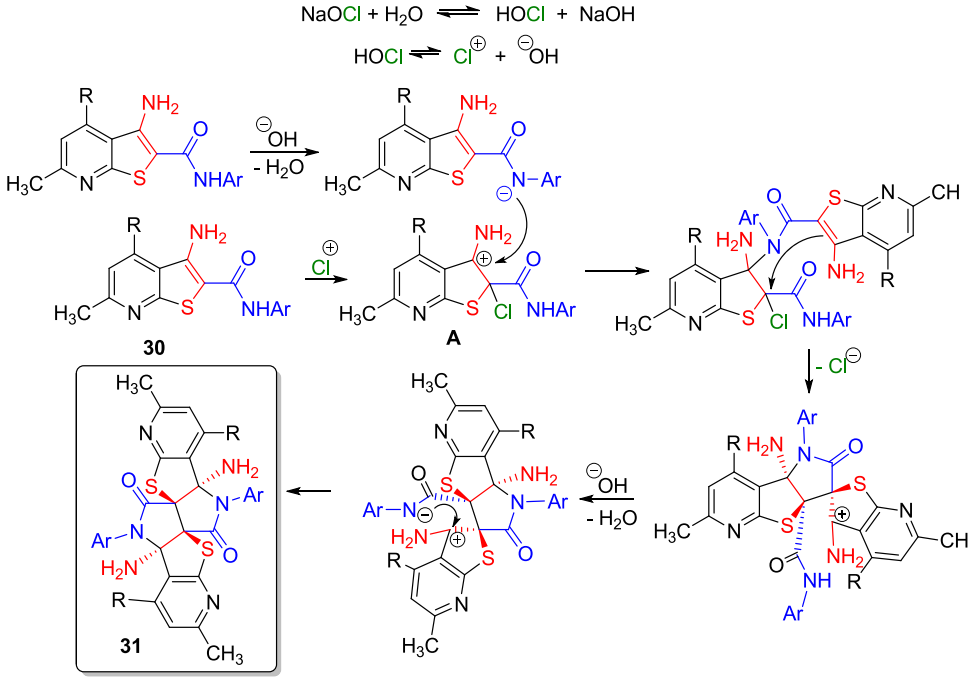
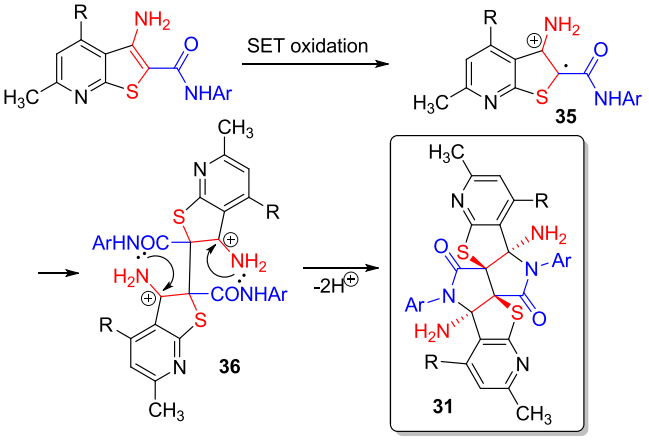
Scheme 7. Plausible Mechanism #1 for Formation of Polycycles 31



Scheme 8. Plausible Mechanism #2 for Formation of Polycycles 31



MHz, respectively) in DMSO-d_6 or $CDCl_3$ using tetramethylsilane (TMS) or residual solvent peaks as internal standards. COSY, $^1H-^{13}C$ HSQC, and $^1H-^{13}C$ HMBC spectra were obtained using an Agilent 400/54 spectrometer. Low-temperature ^1H NMR spectra were recorded on a JEOL JNM-ESA spectrometer (400 MHz) in acetone-d_6 using TMS as an internal standard. Mass spectra were recorded on a Varian CH-6 mass spectrometer with direct sample injection at 50−180 °C, using the ionization method, EI. Elemental analysis was performed on a Hewlett Packard HP-185B CHN-analyzer. Melting points were determined on a Stuart SMO 30 apparatus.

Single crystals $C_{40}H_{36}D_{12}N_6O_6S_4$ of compound **31c** (as solvate with DMSO-d_6) were grown from DMSO-d_6. A suitable crystal was selected and studied on a SuperNova, Dual, Cu at zero, AtlasS2 diffractometer. The crystal was kept at 100.00(10) K during data collection. Using Olex2,[122] the structure was solved with the ShelXT structure solution program[123] using Intrinsic Phasing and refined with the ShelXL refinement package[124] using least-squares minimization. The X-ray crystal structure of **31c** has been deposited at the Cambridge Crystallographic Data Centre (CCDC 1816549). High-resolution mass spectra were obtained using a Bruker Maxis spectrometer (electrospray ionization-time-of-flight (ESI-TOF), MeCN solution, using $HCO_2Na-HCO_2H$ for calibration).

Crystal Data for $C_{40}H_{36}D_{12}N_6O_6S_4$ (M = 849.16 g/mol). Triclinic, space group $P\bar{1}$ (no. 2), a = 11.0531(3) Å, b = 12.6868(3) Å, c = 16.6049(5) Å, α = 75.757(2)°, β = 83.114(2)°, γ = 66.615(3)°, V = 2070.87(11) Å^3, Z = 2, T = 100.00(10) K, μ(Cu Kα) = 2.547 mm^{-1}, D_{calc} = 1.362 g/cm^3, 30 796 reflections measured (7.778 ≤ 2θ ≤ 148.988°), and 8458 unique (R_{int} = 0.0517, R_{sigma} = 0.0366), which were used in all calculations. The final R_1 was 0.0502 (I > 2σ(I)), and wR_2 was 0.1363 (all data).

General Procedure for the Synthesis of 3-Amino-*N*-arylthieno[2,3-*b*]pyridine-2-carboxamides 30a−l. To a mixture of 4,6-dimethyl-2-thioxo-1,2-dihydropyridine-3-carbonitrile[125,126] or 4-(methoxymethyl)-6-methyl-2-thioxo-1,2-dihydropyridine-3-carbonitrile[127] (20 mmol) and 10% aq. KOH solution (11.2 mL, 20 mmol) in DMF (20 mL), the corresponding *N*-aryl-2-chloroacetamide (20 mmol) was added. The resulting mixture was stirred for 30−40 min at r.t. (the formation of a white precipitate of the S-alkylation product may be observed). Then, another portion of 10% aq. KOH solution (11.2 mL, 20 mmol) was added, and the mixture was stirred for 0.5−1 h until a precipitate was formed. The yellow solid was filtered off, washed with cold aqueous ethanol, and dried to give 3-aminothieno[2,3-*b*]pyridine-2-carboxamides **30a−l** in 67−84% yield. The products were sufficiently pure and were used in the next step without further purification. Full details of the preparation and the spectral data of **30a−l** are given in the Supporting Information. Some representative examples are given below.

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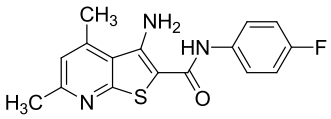
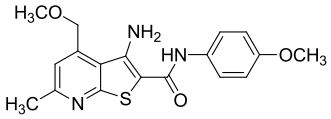
*3-Amino-N-(4-fluorophenyl)-4,6-dimethylthieno[2,3-b]-pyridine-2-carboxamide (**30e**).*



Compound **30e** was prepared according to the general procedure in 83% yield as yellow crystals, mp 208−209 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ, 9.45 (CONH), 7.59 (dd, J_{H-H} = 9.5 Hz, J_{H-F} = 5.2 Hz, 2H, H-2 and H-6 Ar), 7.11 (dd, J_{H-H} = 9.5 Hz, J_{H-F} = 9.5 Hz, 2H, H-3 and H-5 Ph), 7.01 (s, 1H, H-5), 6.88 (s, 2H, NH_2), 2.69 (s, 3H, CH_3-4), 2.47 (s, 3H, CH_3-6); ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.7 (C═O), 159.6 (C-7a), 159.3 (C-6), 159.0 (d, J_{C-F} = 240.0 Hz, C-4 Ar), 149.6 (C-3), 145.3 (C-4), 135.3 (d, J_{C-F} = 2.8 Hz, C-1 Ar), 123.9 (d, J_{C-F} = 8.0 Hz, 2C, C-2 and C-6 Ar), 123.2 (C-3a), 122.5 (C-5), 115.5 (d, J_{C-F} = 22.5 Hz, 2C, C-3 and C-5 Ar), 96.7 (C-2), 24.2 (CH_3-6), 20.1 (CH_3-4); MS, *m*/*z* (*I*, %): 315 (57, M), 257 (88), 256 (57), 177 (45), 111 (100), 95 (34), 41 (22). Found, C 61.05, H 4.38, N 13. $C_{16}H_{14}FN_3OS$. M 315. Calcd: C 60.94, H 4.47, N 13.32. HRMS (ESI) calcd for $C_{16}H_{15}FN_2OS$ $(M + H)^+$: 316.0914; found: 316.0910.

*3-Amino-4-(methoxymethyl)-6-methyl-N-(4-methoxyphenyl)thieno[2,3-b]pyridine-2-carboxamide (**30f**).*



Compound **30f** was prepared according to the general procedure in 69% yield as pale yellow crystals, mp 169−171 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ, 9.37 (CONH), 7.54 (d, *J* = 8.9 Hz, 2H, H-2 and H-6 Ar), 7.21 (s, 1H, H-5), 7.02 (s, 2H, NH_2), 6.88 (d, *J* = 8.9 Hz, 2H, H-3 and H-5 Ar), 4.82 (s, 2H, CH_2O), 3.72 (s, 3H, CH_3OAr), 3.37 (s, 3H, $\mathbf{CH_3}OCH_2$), 2.55 (s, 3H, CH_3-6); ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.3 (C═O), 159.7 (C-6), 159.6 (C-7a), 156.0 (C-4 Ar), 148.3 (C-3), 143.5 (C-4), 132.2 (C-1 Ar), 123.6 (2C, C-2 and C-6 Ar), 122.9 (C-3a), 120.6 (C-5), 114.0 (2C, C-3 and C-5 Ar), 98.1 (C-2), 71.9 (CH_2O), 58.1 ($\mathbf{CH_3}OCH_2$), 55.6 (CH_3OAr), 24.5 (CH_3-6); MS, *m*/*z* (*I*, %): 357 (42, M), 326 (31), 235 (45), 234 (33), 205 (12), 176 (32), 123 (100), 95 (41), 80 (22), 43 (13). Found, C 60.35, H 5.50, N 11.94. $C_{18}H_{19}N_3O_3S$. M 357.43. Calcd, C 60.49, H 5.36, N 11.76. HRMS (ESI) calcd for $C_{18}H_{19}N_3NaO_3S$ $(M + Na)^+$: 380.1050; found: 380.1039.

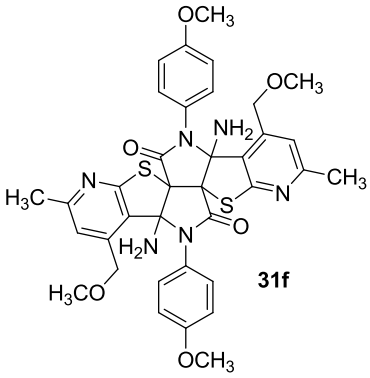
General Procedures for the Oxidation of Thienopyridines 30 with NaOCl. *Method A.* A solution of the corresponding thienopyridine **30a−f**, **30i**, and **30k** (2.0 mmol) in 1,4-dioxane (20 mL) was treated with aq. 10% NaOCl (5 mL). The solution was stirred at r.t. for 3−8 h until no starting compound was detected using thin-layer chromatography (TLC). Then, the mixture was treated with cold water (100 mL) and stirred until the formation of precipitate stopped. The solid was filtered off, washed with cold water (2 × 10 mL), and air-dried. The crude product was purified by flash chromatography (silica gel, pethroleum ether−EtOAc 30−100%) to afford compounds **31a−f**, **30i**, and **30k** as colorless crystals and white or beige powders in 37−55% yield.

Method B. A mixture of thienopyridine **30a−k** (2 mmol), CH_2Cl_2 (40 mL), 10% aq. NaOCl (8 mL), and benzyltriethylammonium chloride (TEBAC) (30 mg) was stirred at r.t. for 4−10 h until full conversion of the thienopyridine (as monitored using TLC). The organic layer was separated; the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic phases were washed with water (2 × 10 mL), dried over Na_2SO_4, and concentrated under reduced pressure to 1/4 of the volume. The residue was treated with hexane and left to stand for crystallization to give the desired products **31a−k** in 43−64% yields.

Method C. A mixture of thienopyridine **30a**, **30b** (2 mmol), EtOH (80 mL), and 10% aq. NaOCl (5 mL) was stirred at r.t. for 6−9 h until no starting compound was detected using TLC. The mixture was poured into cold water (100 mL) and stirred until formation of the precipitate stopped. The solid was filtered off, washed with cold water (2 × 10 mL), and air-dried. The crude product was separated by flash chromatography on a Biotage KP-Sil column (50 g) using a gradient of 10−30% EtOAc in CH_2Cl_2 as the mobile phase to give compounds **31a** and **31b** and **32a** and **32b**.

Full details of the preparation and the spectral data of **31a−k** and **32a** and **32b** are given in the Supporting Information. Some representative examples are given below.

(5a*R*,7a*R*,12a*R*,14a*R*/5a*S*,7a*S*,12a*S*,14a*S*)-7a,14a-Diamino-1,8-bis(methoxymethyl)-7,14-bis(4-methoxyphenyl)-3,10-dimethyl-7,7a,14,14a-tetrahydro-6*H*,13*H*-pyrido[3‴,2‴:4‴,5‴]thieno[2‴,3‴:4″,5″]pyrrolo-[3″,4″:3′,4′]pyrrolo[2′,3′:4,5]thieno[2,3-*b*]pyridine-6,13-dione (31f).



31f

Compound **31f** was prepared according to the general procedure in 42% (method A) and 53% (method B) yields as a beige solid, mp 203−205 °C (from EtOAc). ^{1}H NMR (400 MHz, DMSO-d_6, 120 °C) δ 6.95 (d, ^3J = 8.0 Hz, 4H, 2 × H-3 and 2 × H-5 Ar), 6.94 (s, 2H, H-2, H-10), 6.88 (d, ^3J = 8.0 Hz, 4H, 2 × H-2 and 2 × H-5 Ar), 4.32 (d, ^2J = 14.9 Hz, 2H, 2 × CH_2O), 3.79 (s, 6H, 2 × CH_3OAr), 3.43 (br s, 4H, 2 × NH_2), 3.07 (d, ^2J = 14.9 Hz, 2H, 2 × CH_2O), 2.68 (s, 6H, 2 × CH_2OCH_3), 2.43 (s, 6H, CH_3-3 and CH_3-10).

^{13}C NMR (100 MHz, DMSO-d_6, 120 °C) δ 168.9 (2C, C-6 and C-13), 161.9 (2C, C-4a and C-11a), 160.7 (2C, C-3 and C-10), 160.6 (2C, 2 × C-4 Ar), 148.8 (2C, C-1 and C-8), 132.0 (2C, 2 × C-1 Ar), 128.0 (4C, 2 × C-2 and 2 × C-6 Ar), 125.0 (2C, C-7b and C-14b), 118.1 (2C, C-2 and C-9), 115.2 (4C, 2 × C-3 and 2 × C-5 Ar), 88.0 (2C, C-5a and C-12a), 72.0 (2C, C-7a and C-14a), 69.5 (2C, 2 × CH_2OCH_3), 56.0 (2C, 2 × CH_2OCH_3), 24.3 (2C, CH_3-3 and CH_3-10).

HRMS (ESI) calcd for $C_{36}H_{36}N_6NaO_6S_2$ $(M + Na)^+$: 735.2041; found: 375.2035. MS, EI, 70 eV, *m*/*z* (*I*, %): 484 (13), 414 [M − 2ArN═C═O] (12), 365 (22), 149 [ArN═C═O] (70), 121 [ArN═C═O − 28] (100), 107 (21), 62 (27), 43 (47).

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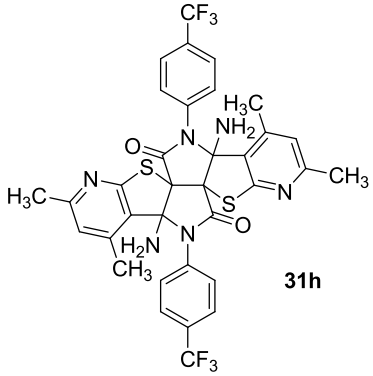
Found: C 60.81, H 4.94, N 11.67. $C_{36}H_{36}N_6O_6S_2$. M 712.84. Calcd: C 60.66, H 5.09, N 11.79%.

(5a*R*,7a*R*,12a*R*,14a*R*/5a*S*,7a*S*,12a*S*,14a*S*)-7a,14a-Diamino-1,3,8,10-tetramethyl-7,14-bis[4-(trifluoromethyl)-phenyl]-7,7a,14,14a-tetrahydro-6*H*,13*H*-pyrido-[3‴,2‴:4‴,5‴]thieno[2‴,3‴:4″,5″]pyrrolo-[3″,4″:3′,4′]-pyrrolo[2′,3′:4,5]thieno[2,3-*b*]pyridine-6,13-dione (31h).

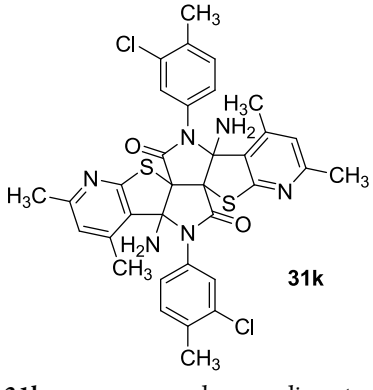


31h

Compound **31h** was prepared by method B in 62% yield as a white powder, mp 213−215 °C (from CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, ^3J = 8.3 Hz, 4H, 2 × H-3 and 2 × H-5 Ar), 7.13 (m, 4H, 2 × H-2 and 2 × H-6 Ar), 6.52 (s, 2H, H-2, H-9), 3.07 (s, 4H, 2 × NH_2), 2.44 (s, 6H, CH_3-3 and CH_3-10), 1.43 (s, 6H, CH_3-1 and CH_3-8); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.2 (2C, C-6 and C-13),162.6 (2C, C-4 and C-11a), 146.5 (2C, C-1 and C-8), 161.0 (2C, C-3 and C-10), 137.9 (4C, q, $^4J_{C-F}$ = 1.4 Hz, C-2 and C-6 Ar), 131.9 (2C, q, $^2J_{C-F}$ = 32.8, 2 × C-4 Ar), 131.1 (2C, 2 × C-1 Ar), 126.7 (4C, q, $^3J_{C-F}$ = 3.8 Hz, 2 × C-3 and 2 × C-5 Ar), 124.6 (2C, C-7b and 14b), 123.6 (2C, q, $^1J_{C-F}$ = 273.0 Hz, 2 × CF_3), 122.9 (2C, C-2 and C-9), 88.5 (2C, C-7a and 14a), 71.9 (2C, C-5a and 12a), 23.7 (2C, CH_3-3 and CH_3-10), 17.7 (2C, CH_3-1 and CH_3-8); HRMS (ESI) calcd for $C_{34}H_{27}F_6N_6O_2S_2$ $(M + H)^+$: 729.1536; found: 729.1533.

Found: C 56.14, H 3.51, N 11.45. $C_{34}H_{28}F_6N_6O_2S_2$. M 728.731. Calcd: C 56.04, H 3.60, N 11.5%.

(5a*R*,7a*R*,12a*R*,14a*R*/5a*S*,7a*S*,12a*S*,14a*S*)-7a,14a-Diamino-7,14-bis(3-chloro-4-methylphenyl)-1,3,8,10-tetramethyl-7,7a,14,14a-tetrahydro-6*H*,13*H*-pyrido-[3‴,2‴:4‴,5‴]thieno[2‴,3‴:4″,5″]pyrrolo[3″,4″:3′,4′]-pyrrolo[2′,3′:4,5]thieno[2,3-*b*]pyridine-6,13-dione (31k).



31k

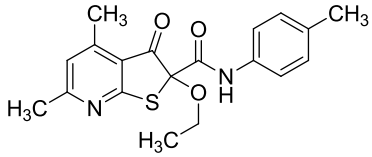
Compound **31k** was prepared according to the general procedure in 55% (method A) and 63% (method B) yields as a beige solid, mp 262−264 °C (from CH_2Cl_2). ^{1}H NMR (400 MHz, DMSO-d_6, 90 °C) δ 7.34 (d, ^3J = 8.1 Hz, 2H, 2 × H-5 Ar), 7.16 (s, 2H, 2 × H-2 Ar), 6.71 (d, ^3J = 8.1 Hz, 2H, 2 × H-6 Ar), 6.67 (s, 2H, H-2 and H-10), 3.60 (s, 4H, 2 × NH_2), 2.37 (s, 6H, CH_3-3 and CH_3-10), 2.36 (s, 6H, 2 × CH_3-Ph), 1.57 (s, 6H, CH_3-1 and CH_3-8).

^{13}C NMR (100 MHz, DMSO-d_6, 80 °C) δ 168.8 (2C, C-6 and C-13), 161.8 (2C, C-4a and C-11a), 160.1 (2C, C-3 and C-10), 148.2 (2C, C-1 and C-8), 137.2 (2C, 2 × C-4 Ar), 134.3 (2C, 2 × C-1 Ar), 133.8 (2C, 2 × C-3 Ar), 131.8 (2C, 2 × C-5 Ar), 131.4 (2C, 2 × C-2 Ar), 129.5 (2C, 2 × C-8 Ar), 126.1 (2C, C-7b and C-14b), 123.0 (2C, C-2 and C-9), 89.2 (2C, C-5a and C-12a), 72.6 (2C, C-7a and C-14a), 23.6 (2C, CH_3-3 and CH_3-10), 19.5 (2C, 2 × CH_3-4 Ar), 17.9 (2C, CH_3-1 and CH_3-8); HRMS (ESI) calcd for $C_{34}H_{31}Cl_2N_6O_2S_2$ $(M + H)^+$: 689.1322; found: 689.1333.

MS, EI, 70 eV, *m*/*z* (*I*, %): 398 (8), 396 (22), 354 [M − 2 ArN═C═O] (43), 326 (22), 169 (24), 167 (60), 141 (89), 139 (100), 91 (37), 43 (51).

Found: C, 59.18, H 4.49, N 12.27. $C_{34}H_{30}Cl_2N_6O_2S_2$. M 689.68. Calcd: C, 59.21, H 4.38, N 12.19%.

2-Ethoxy-4,6-dimethyl-*N*-(4-methylphenyl)-3-oxo-2,3-dihydrothieno[2,3-*b*]pyridine-2-carboxamide (32a).

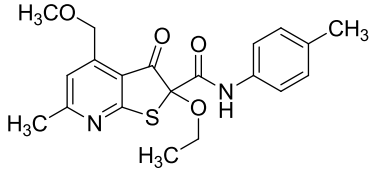


Compound **32a** was prepared according to the method C in 15% yield as a white powder, mp 98−99 °C (from EtOAc). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.89 (s, 1H, CONH), 7.50 (d, ^3J = 8.4 Hz, 2H, H-2 and H-6 Ar), 7.1 (d, ^3J = 8.4 Hz, 2H, H-3 and H-5 Ar), 7.07 (s, 1H, H-5), 3.75 (dq, *J* = 6.9 Hz, *J* = 14.2 Hz, 1H, $CH_3C\underline{H}_2O$), 3.39 (dq, *J* = 6.9, 14.2 Hz, 1H, $CH_3C\underline{H}_2O$), 2.54 (s, 3H, CH_3-4), 2.44 (s, 3H, CH_3-6), 2.24 (s, 3H, CH_3−Ar), 1.24 (t, ^3J = 6.9 Hz, 3H, $\underline{CH}_3CH_2O$); ^{13}C NMR (100 MHz, DMSO-d_6) δ 197.3 (C═O ketone), 172.5 (C-7a), 166.6 (C-6), 165.6 (C(O)NH), 150.9 (C-4), 135.4 (C-1 Ar), 134.9 (C-4 Ar), 129.5 (2C, C-3 and C-5 Ar), 123.3 (C-5), 121.1 (2C, C-2 and C-6 Ar), 119.7 (C-3a), 95.0 (C-2), 62.6 ($CH_3\underline{C}H_2O$), 24.8 (CH_3-6), 20.9 (CH_3-Ar), 18.1 (CH_3-4), 15.3 ($\underline{C}H_3CH_2O$).

MS, EI, 70 eV, *m*/*z* (*I*, %): 356 [M^+] (14), 223 [M − C_2H_4−C_7H_7N] (76), 194 [223 − CHO] (100), 166 [194 − C═O], 106 [C_7H_8N] (17), 91 [C_7H_7] (10).

Found: C, 64.02; H, 5.66; N, 7.86. $C_{19}H_{20}N_2O_3S$. M 356. Calcd: C, 64.13; H, 5.47; N, 7.71%.

2-Ethoxy-4-(methoxymethyl)-6-methyl-*N*-(4-methylphenyl)-3-oxo-2,3-dihydrothieno[2,3-*b*]pyridine-2-carboxamide (32b).



Compound **32b** was prepared according to the method C in 14% yield as a white powder, mp 111−113 °C (from EtOAc). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.91 (s, 1H, CONH), 7.52 (d, ^3J = 8.4 Hz, 2H, H-2 and H-6 Ar), 7.11 (s, 1H, H-5), 7.09 (d, ^3J = 8.4 Hz, 2H, H-3 and H-5 Ar), 4.29 (d, ^2J = 12.8 Hz,

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1H, $CH_3OC\underline{H}_2$), 3.78 (dq, ^3J = 7.0 Hz, ^2J = 14.5 Hz, 1H, $CH_3C\underline{H}_2O$), 3.37 (dq, ^3J = 7.0 Hz, ^2J = 14.5 Hz, 1H, $CH_3C\underline{H}_2O$), 3.05 (d, ^2J = 12.8 Hz, 1H, $CH_3OC\underline{H}_2$), 3.01 (s, 1H, CH_3O), 2.46 (s, 3H, CH_3-6), 2.22 (s, 3H, CH_3−Ar), 1.24 (t, J = 7.0 Hz, 3H, $C\underline{H}_3CH_2O$).

^{13}C NMR (100 MHz, DMSO-d_6) δ 197.4 (C═O ketone), 172.7 (C-7a), 166.5 (C-6), 165.5 (C(O)NH), 151.1 (C-4), 135.4 (C-1 Ar), 133.9 (C-4 Ar), 129.7 (2C, C-3 and C-5 Ar), 123.3 (C-5), 121.2 (2C, C-2 and C-6 Ar), 119.8 (C-3a), 94.8 (C-2), 69.5 (CH_2O), 62.6 ($CH_3\underline{C}H_2O$), 58.2 (CH_3O), 24.9 (CH_3-6), 21.0 (CH_3−Ar), 15.3 ($\underline{C}H_3CH_2O$).

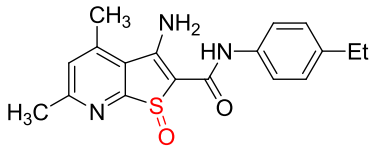
MS, EI, 70 eV, m/z (I, %): 386 [M^+] (11), 358 [$M - C_2H_4$] (24), 355 [$M - CH_3O$] (12), 280 [$M - C_7H_7N$] (100), 106 [C_7H_8N] (17), 91 [C_7H_7] (10).

Found: C, 62.05; H, 5.86; N, 7.28. $C_{20}H_{22}N_2O_4S$. M 386. Calcd: C, 62.16; H, 5.74; N, 7.25%.

Oxidation of Thienopyridine 30d with MCPBA. *meta*-Chloroperbenzoic acid (MCPBA) (740 mg, 3 mmol, 70%) in dry CH_2C1_2 (10 mL) was added to a magnetically stirred solution of 3-amino-*N*-(4-ethylphenyl)-4,6-dimethylthieno-[2,3-*b*]pyridine-2-carboxamide **30d** (650 mg, 2 mmol) in dry CH_2Cl_2 (50 mL). The reaction was kept at r.t. and monitored occasionally using TLC. After the reaction was complete, aqueous 0.2 M NaOH was added to the reaction mixture, and the aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layer was washed with brine (3 × 40 mL), dried (Na_2SO_4), and concentrated. The residue was subjected to column chromatography on silica gel (hexane/acetone = 1:2) to afford sulfoxide **33** and sulfone **34** in 38 and 23% yields, respectively.

Oxidation of Thienopyridine 30d with MMPP. A mixture of magnesium monoperoxyphthalate (MMPP) (2.48 g, 4 mmol) and 3-amino-*N*-(4-ethylphenyl)-4,6-dimethylthieno[2,3-*b*]pyridine-2-carboxamide **30d** (650 mg, 2 mmol) in dry CH_3CN (40 mL) was refluxed for 3 h. After the reaction was complete (TLC), the mixture was poured into cold water (120 mL). The resulting precipitate was filtered off, air-dried, and purified by column chromatography (SiO_2, CH_2Cl_2/acetone = 15:2) to give pure 3-amino-*N*-(4-ethylphenyl)-4,6-dimethylthieno[2,3-*b*]pyridine-2-carboxamide 1,1-dioxide **34** in 48% yield.

3-Amino-*N*-(4-ethylphenyl)-4,6-dimethylthieno[2,3-*b*]pyridine-2-carboxamide 1-Oxide (33).



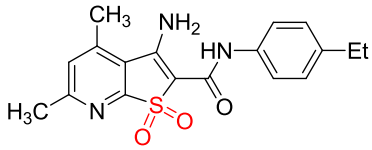
Compound **33** was prepared by oxidation of **30d** with MCPBA in 38% yield as pale yellow crystals, mp 288−289 °C. ^{1}H NMR (400 MHz, DMSO-d_6, 80 °C) δ 9.06 (s, 1H, CONH), 8.25 (br s, 2H, NH_2), 7.51 (d, ^3J = 8.6 Hz, 2H, H-2 and H-5 Ar), 7.36 (s, 1H, H-5), 7.12 (d, ^3J = 8.6, 2H, H-3 and H-5 Ar), 2.65 (s, 3H, CH_3-4), 2.55 (s, 3H, CH_3-6), 2.54 (q, ^3J = 7.5 Hz, 2H, $C\underline{H}_2CH_3$), 1.12 (t, ^3J = 7.5 Hz, 3H, $CH_2C\underline{H}_3$).

^{13}C NMR (100 MHz, DMSO-d_6, 80 °C) δ 165.4 (C-7a), 164.7 (C═O), 162.0 (C-6), 158.5 (C-3), 146.1 (C-4), 139.4 (C-4 Ar), 136.7 (C-1 Ar), 128.7 (C-5), 128.1 (2C, C-3 and C-5 Ar), 123.1 (C-3a), 121.5 (2C, C-2 and C-6 Ar), 101.9 (C-2), 28.1 ($C\underline{H}_2CH_3$), 24.0 (CH_3-6), 19.9 (CH_3-4), 16.1 ($CH_2C\underline{H}_3$).

MS, EI, 70 eV, m/z (I, %): 341 [M^+] (34), 325 (16), 225 (100), 205 (11), 177 (34), 147 (68), 105 (71), 93 (18).

Found: C, 63,17; H, 5.73; N, 12.48. $C_{18}H_{19}N_3O_2S$. M 341.429. C, 63.32; H, 5.61; N, 12.31%.

3-Amino-*N*-(4-ethylphenyl)-4,6-dimethylthieno[2,3-*b*]pyridine-2-carboxamide 1,1-Dioxide (34).



Compound **34** was prepared according to the abovementioned procedures in 23 (by oxidation with MCPBA) and 48% yields (by oxidation with MMPP) as pale yellow crystals; mp > 275 °C (sublimation). ^{1}H NMR (400 MHz, DMSO-d_6, 80 °C) δ 8.31 (br s, 2H, NH_2), 7.99 (s, 1H, CONH), 7.46 (s, 1H, H-5), 7.45 (d, ^3J = 8.2 Hz, 2H, H-2 and H-5 Ar), 7.17 (d, ^3J = 8.2 Hz, 2H, H-3 and H-5 Ar), 2.71 (s, 3H, CH_3-4), 2.59 (s, 3H, CH_3-6), 2.58 (q, ^3J = 7.7 Hz, 2H, $C\underline{H}_2CH_3$), 1.17 (t, ^3J = 7.7 Hz, 3H, $CH_2C\underline{H}_3$).

^{13}C NMR (100 MHz, DMSO-d_6, 80 °C) δ 163.6 (C-6), 161.4 (C-7a), 161.4 (C═O), 155.3 (C-3), 146.8 (C-4), 140.3 (C-4 Ar), 135.7 (C-1 Ar), 130.2 (C-5), 128.4 (2C, C-3 and C-5 Ar), 121.4 (2C, C-2 and C-6 Ar), 118.5 (C-3a), 96.4 (C-2), 28.0 ($C\underline{H}_2CH_3$), 23.9 (CH_3-6), 20.3 (CH_3-4), 15.7 ($CH_2C\underline{H}_3$).

MS, EI, 70 eV, m/z (I, %): 357 [M^+] (11), 341 (22), 237 (45), 225 (60), 205 (100), 177 (14), 147 (48), 105 (77), 93 (23).

Found: C, 60.57; H, 5.23; N, 11.88. $C_{18}H_{19}N_3O_3S$. M 357.428. Calcd: C, 60.49; H, 5.36; N, 11.76%.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.1c00341.

Additional experimental data; copies of ^{1}H, ^{13}C NMR, 2D HSQC, and HMBC NMR spectra; and HRMS and X-ray data of the synthesized compounds (PDF)

Crystallographic data file (CIF)

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Notes
The authors declare no competing financial interest.

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