Synthesis of Heterocyclic Compounds Possessing the 4*H*-Thieno[3,2-*b*]Pyrrole Moiety

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A series of novel heterocyclic combinatorial libraries containing 4*H*-thieno[3,2-*b*]pyrrole, thieno[2′,3′:4,5]-pyrrolo[1,2-*d*][1,2,4]triazine and thieno[2′,3′:4,5]pyrrolo[1,2-*a*]pyrazine heterocyclic moieties were obtained by parallel solution-phase synthesis. Key steps include different reactions of initial alkyl 4*H*-thieno[3,2-*b*]-pyrrole-5-carboxylates, such as alkylation with alkylating agents; transformation of the carboxylate group into different reactive functionalities, followed by reactions with electrophilic species; intramolecular cyclizations; and amide bond formation. Simple manual techniques for parallel reactions were coupled with easy purification procedures to give high-purity final products.

Introduction

Heterocyclic compounds containing the thieno[3,2-*b*]-pyrrole moiety in their structures attract the attention of researchers as promising and little-explored pharmacophoric scaffolds (Figure 1). The parent heterocycle **I** was synthesized in 1957 by the reductive cyclization of 3-nitro-2-thienylpyruvic acid, followed by decarboxylation of the product, namely, thieno[3,2-*b*]pyrrole-5-carboxylic acid,[1] and also by the reduction of 2*H*,3*H*-thieno[3,2-*b*]pyrrol-3-one obtained via cyclization of pyrrole-3-thioacetic acid.[2] The general synthetic approach to the substituted alkyl thieno-[3,2-*b*]pyrrole-5-carboxylates includes transformation of compounds **II** into numerous derivatives **III** under treatment of different reagents.[3−38] For example, the reported works describe synthesis of alkyl thieno[3,2-*b*]pyrrole-5-carboxylates **III** with the following substituents: 2-formyl,[11,19] 2-acetyl,[11] 2-bromo,[28] 2,6-dibromo,[11] 2,3,6-tribromo,[11] 2-nitro,[28] 2,6-dinitro,[28] 3-formyl,[19] 4-benzyl,[10] 4-(2-nitrobenzyl),[11,34] 6-dimethylaminomethyl,[11] 6-(1-piperidinylmethyl),[13] 6-cyanomethyl,[11] 6-formyl,[11,37] 2-methyl-3-acyl,[35−37] 2-methyl-3,6-diacyl,[35,37] 2-methyl-4-(2-oxopropyl),[38] and 2-methyl-4-(2-oxo-2-phenylethyl).[38] Some of the mentioned esters were then hydrolyzed to the corresponding acids, which usually served as convenient starting materials in subsequent transformations, for example, for synthesis of the corresponding amides[13,18] or decarboxylated products.[18]

Syntheses of several annulated heterocycles possessing the 4*H*-thieno[3,2-*b*]pyrrole moiety have been previously described, for example, thieno[2,3-*b*]indolizine **IV**,[39] 5,6,7,8-tetrahydro-4*H*-thieno[3′,2′:2,3]pyrrolo[4,5-*c*]pyridine **V**,[14] 8-oxo-5,6,7,8-tetrahydrothieno[2′,3′:4,5]pyrrolo[1,2-*a*]pyrazine **VI**,[38] 3*H*,4*H*,5*H*-thieno[3′,2′:2,3]pyridazin-4-ones **VII**,[11,37] and 5-oxo-6,11-dihydro-5*H*-benzo[e]thieno[2′,3′:4,5]pyrrolo-[1,2-*a*][1,4]diazepine **VIII**.[34] Among the synthesized compounds containing the thieno[3,2-*b*]pyrrole moiety, several physiologically active agents were described. For example, compound **IV** is a phospholipase A2 inhibitor that possesses antiallergy, antiasthmatic, and septic shock treatment properties.[39] Compounds **IX**[40] and **X**[41] are glycogen phosphorylase inhibitors that display antidiabetic activity.

The mentioned examples highlight the high level of interest of organic chemists to the synthesis of various derivatives of thieno[3,2-*b*]pyrroles. However, until recently, there has been no data about combinatorial libraries containing the thieno[3,2-*b*]pyrrole moiety needed for effective search of active compounds in the early stages of drug development. In this paper, we report a successful solution-phase strategy for parallel synthesis of novel combinatorial libraries, including variously substituted thieno[3,2-*b*]pyrrole heterocyclic compounds and their annulated derivatives.

Combinatorial Libraries of Substituted Thieno[3,2-*b*]-pyrroles. In the first part of this work, a combinatorial library of novel 4-substituted methyl thieno[3,2-*b*]pyrrole-5-carboxylates **3**{*1*−*255*} was obtained in good yields (65−85%) by parallel phase transfer (PT) alkylation reactions of carboxylates **1a**−**d** with various alkylating agents **2**{*1*−*106*} in MeCN in the presence of K_2CO_3 and 18-crown-6 as a catalyst (Scheme 1). Initial 2-substituted methyl 4*H*-thieno-[3,2-*b*]pyrrole-5-carboxylates **1a**−**d** were synthesized using a previously reported method[42] based on Knoevenagel-type condensation of the corresponding thiophene-2-carbaldehyde with ethyl azidoacetate, followed by cyclization of the resulting 2-azido-3-thien-2-ylacrylate. As alkylating agents, we used alkyl halides, α-chloroketones, benzyl chlorides and their heteroanalogues, and chloroacetamides and their analogues. Representative examples of alkylating agents are depicted in Scheme 1. Structures of all alkylating agents explored in this work are shown in the Supporting Informa-

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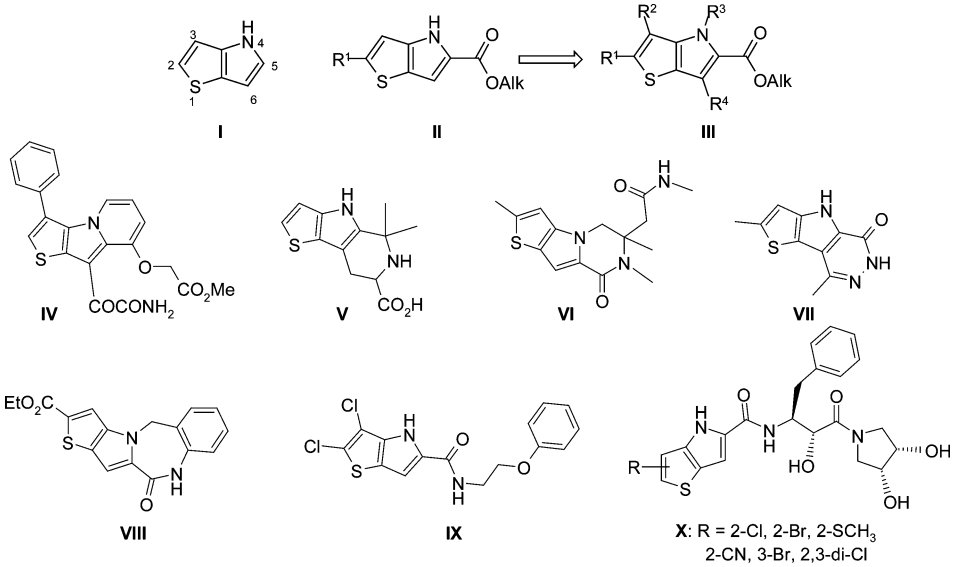
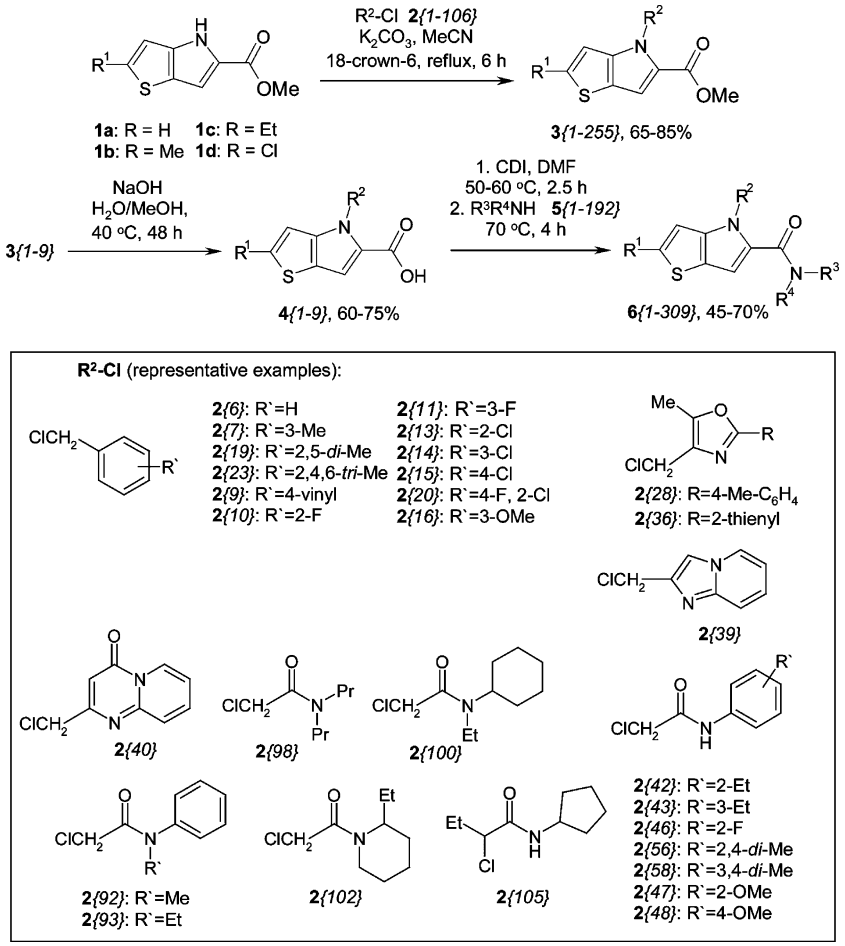


Figure 1. Substituted and annulated thieno[3,2-*b*]pyrroles reported in the literature.

Scheme 1. Synthesis of Combinatorial Library of Thieno[3,2-*b*]Pyrrole-5-carboxamides and Representative Examples of Alkylating Agents Explored in This Work



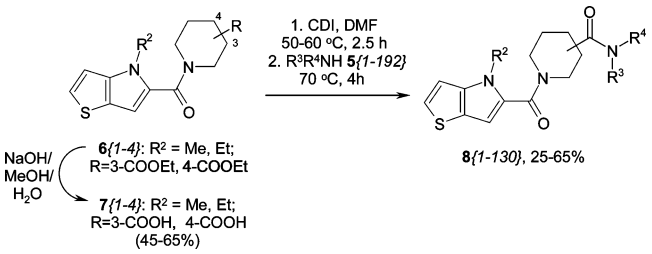
tion. Conversion of nine arbitrarily selected esters **3**{*1*−*9*} to corresponding acids **4**{*1*−*9*} (Table 1) was achieved through alkaline hydrolysis in a methanol−water mixture in 60−75% yield.

The obtained acids were used for the synthesis of a large combinatorial library of the corresponding thieno[3,2-*b*]-pyrrole-5-carboxamides **6**{*1*−*309*}. The latter were obtained by the reaction of acids **4**{*1*−*9*} with primary and secondary amines **5**{*1*−*192*} via CDI-mediated (CDI, *N*,*N*′-carbonyldiimidazole) activation of the carboxylate group. We evaluated a total of 65 aliphatic and aromatic amines, such as substituted anilines and benzylamines, heteroarylamines, cyclic and acyclic aliphatic amines, and oxygen- and nitrogen-containing compounds. Unhindered aliphatic amines consistently underwent rapid conversion into the desired products and provided the highest yield and purity of amides

Table 1. R^1,R^2 Substituents and Yields of Compounds **4**{*1*−*9*}

no.	R^1	R^2	yield, %
4{*1*}	H	Me	60
4{*2*}	H	Et	57
4{*3*}	H	4-Me-C_6H_4-CH_2	75
4{*4*}	H	4-F-C_6H_4-CH_2	73
4{*5*}	H	4-Cl-C_6H_4-CH_2	70
4{*6*}	Me	Me	65
4{*7*}	Et	Me	62
4{*8*}	Cl	Me	67
4{*9*}	Cl	Et	64

Scheme 2. Synthesis of 1-(4*H*-Thieno[3,2-*b*]pyrrole-5-carbonyl)piperidinecarboxamide Combinatorial Library



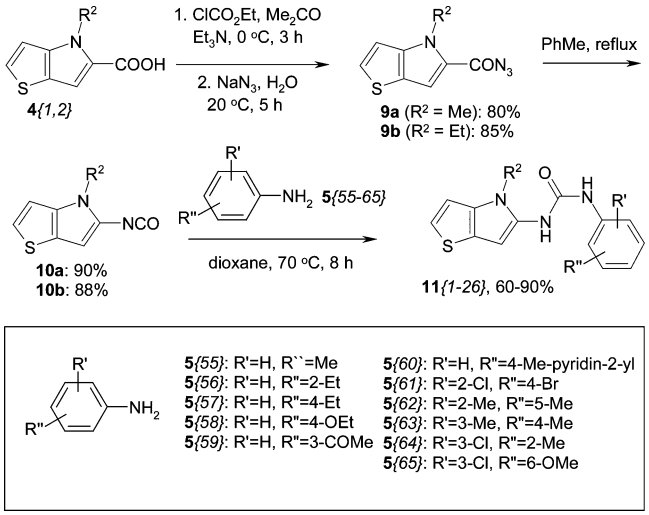
in the described transformations. Sterically hindered alkylamines, anilines, and their heterocyclic analogs reacted more slowly and required elevated temperature and increased time for the complete conversion of the initial reactants. Structures of all amines explored in this work are given in the Supporting Information.

The reaction workup was straightforward and compatible with the high-throughput operation mode. The reaction mixtures (solvent $CHCl_3$) were successively washed in the reaction vials with aqueous solution of $NaHCO_3$. Then the organic layers were removed from the vials, filtered, and evaporated to dryness in vacuo. The obtained crude residues were triturated with diethyl ether, and the formed precipitates were collected and dried. According to LC/MS data, the purity of the obtained compounds was >95%. If necessary, the products could be recrystallized from hexane. The yields of isolated amides **6**{*1*−*309*} ranged from 45 to 70%.

Additional complexity of the obtained thieno[3,2-*b*]pyrrole-5-carboxamide scaffold can be introduced with the use of bifunctional amines (Scheme 2). Thus, acids **4**{*1,2*} by interacting with 3-piperidinecarboxylate and 4-piperidinecarboxylate could be easily converted to four corresponding ethyl 1-(4*H*-thieno[3,2-*b*]pyrrole-5-carbonyl)piperidine carboxylates **6**{*1*−*4*}, from which acids **7**{*1*−*4*} were prepared by alkaline hydrolysis in a methanol-water mixture. Acids **7**{*1*−*4*} in parallel reactions with amines **5**{*1*−*192*} were transformed in 25−65% yield into a combinatorial library of carboxamides **8**{*1*−*130*} via a CDI-promoted coupling. For esters **6**{*1*−*4*} and acids **7**{*1*−*4*}, characteristic signals from protons of the piperidine cycle were seen in the upfield range of $\delta \sim 1.5-4.3$ ppm.

Interaction of 4*H*-thieno[3,2-*b*]pyrrole-5-carboxylic acids **4**{*1,2*} and NaN_3 afforded acylazides **9a**,**b** which were transformed into the corresponding isocyanates **10a**,**b** (Scheme 3) in toluene solution under reflux (yield 88−90%). The subsequent parallel reactions of isocyanates **10a**,**b** with anilines **5**{*55*−*65*} in dioxane at 70 °C led to a combinatorial

Scheme 3. Synthesis of 1-Aryl-3-(4*H*-thieno-[3,2-*b*]pyrrol-5-yl)urea Combinatorial Library



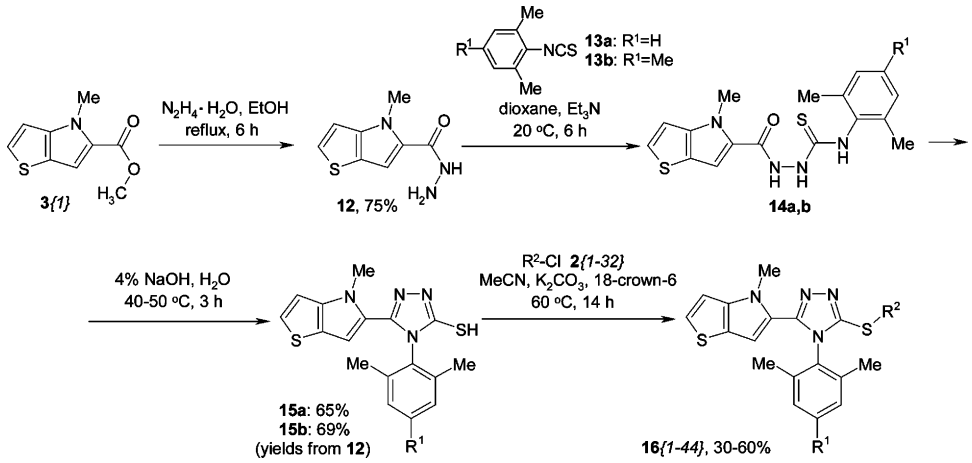
library of 1-aryl-3-(4*H*-thieno[3,2-*b*]pyrrol-5-yl)ureas **11**{*1*−*26*} with yields ranging from 60 to 90%. As in most transformations reported in this paper, products **11**{*1*−*26*} containing different substituents were isolated in good yields and purity (>95% as evidenced from LC/MS analysis) using simple procedures, such as filtration of precipitates from the reaction mixtures.

The synthetic route to another library of novel 4-methyl-5-(5-sulfanyl-4-aryl-4*H*-[1,2,4]triazol-3-yl)-4*H*-thieno[3,2-*b*]-pyrroles **6**{*1*−*44*} is depicted in Scheme 4. At the first step, methyl ester **3**{*1*} was converted into hydrazide **12** upon the treatment with $N_2H_4 \cdot H_2O$ in ethanol under reflux. Reaction of the resulting hydrazide **12** with isothiocyanates **13a**,**b** in 1,4-dioxane in the presence of Et_3N led to thioureas **14a**,**b**. Upon the treatment with aqueous alkali, compounds **14a**,**b** were effectively converted to [1,2,4]triazole-3-thiols **15a**,**b**. Similar approaches to the synthesis of 5-heteroaryl-4-phenyl-4*H*-1,2,4-triazole-3-thiols were reported.[43] Compounds **15a**,**b** were alkylated under conditions of phase-transfer catalysis (PTC) by various benzyl chlorides **2**{*1*−*15*}, their heteroanalogues **2**{*16*−*19*}, and chloroacetylamides **2**{*20*−*32*} (see Scheme 1) in MeCN in the presence of K_2CO_3 and catalytic amounts of 18-crown-6. As a result, the corresponding 5-sulfanyl derivatives **16**{*1*−*44*} were obtained in 30−60% yields. As expected, ^{1}H−NMR spectra of compounds **15a**,**b** contain a downfield signal of SH proton ($\delta \sim 14$ ppm) that disappears in the spectra of S-alkylated products **16**{*1*−*44*}.

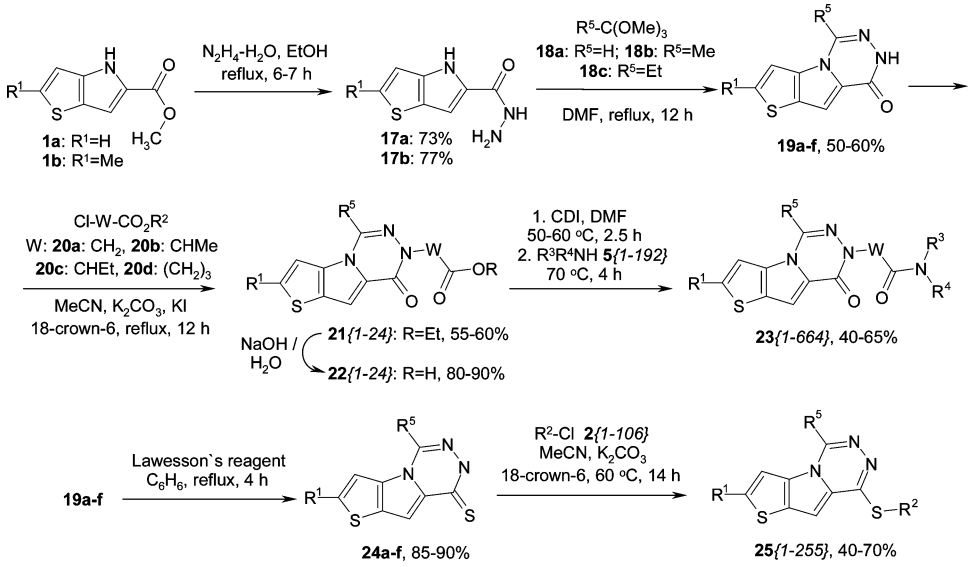
The described 4*H*-thieno[3,2-*b*]pyrroles were isolated from reaction mixtures as precipitates, and according to LC/MS data, they had purity > 95%. In cases when purity of the solids was <95%, they were recrystallized from ethanol. Structures and purity of all compounds were established using ^{1}H NMR and LC/MS analyses. The spectral data gave satisfactory results consistent with suggested molecular structures.

Combinatorial Libraries of Annulated Thieno[3,2-*b*]-pyrroles. Annulated thieno[3,2-*b*]pyrroles are interesting yet poorly explored heterocyclic systems with promising pharmacological potential.[39−41] It can be suggested that development of efficient synthetic approaches to the related combinatorial scaffolds will provide valuable materials for

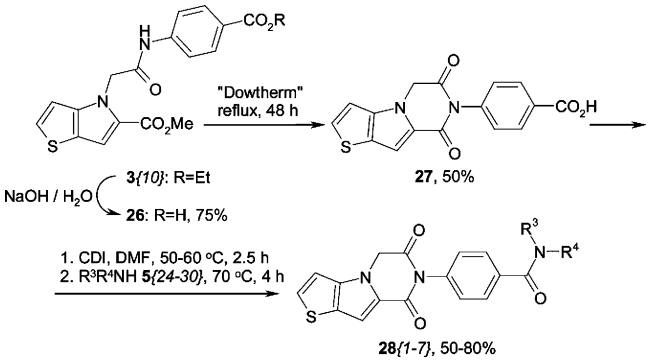
Scheme 4. Synthesis of 4-Methyl-5-(5-sulfanyl-4-aryl-4*H*-[1,2,4]triazol-3-yl)-4*H*-thieno[3,2-*b*]pyrrole Combinatorial Library



Scheme 5. Synthesis of Thieno[2′,3′:4,5]pyrrolo[1,2-*d*][1,2,4]triazine Derivatives



Scheme 6. Synthesis of 4-(5,7-Dioxo-4,5-dihydro-7*H*-thieno[2′,3′:4,5]pyrrolo[1,2-*a*]pyrazin-6-yl)benzoic Acid and Its Amides



pharmaceutical discovery. In this work, we have developed effective solution chemistry approaches to a wide series of variously substituted thieno[2′,3′:4,5]pyrrolo[1,2-*d*] [1,2,4]-triazines (Scheme 5) and 4,5,6,7-tetrahydrothieno[2′,3′:4,5]-pyrrolo[1,2-*a*]pyrazines (Scheme 6).

At the first step, methyl esters **1a**,**b** were converted into the corresponding hydrazides **17a**,**b** upon the treatment with $N_2H_4 \cdot H_2O$ in ethanol under reflux. The conversion of the initial esters can be effectively monitored by disappearance of a characteristic methoxy group singlet (δ 3.73−3.81 ppm) in the ^{1}H NMR spectra. The interaction of orthoethers **18a**−**c** with hydrazides **17a**,**b** in DMF under reflux afforded a series of novel 6*H*-thieno[2′,3′:4,5]pyrrolo[1,2-*d*][1,2,4]triazin-7-ones **19a**−**f**. A similar approach to the synthesis of 6*H*-furo-[2′,3′:4,5]pyrrolo[1,2-*d*] [1,2,4]triazin-7-ones has been described.[44] Compounds **19a**−**f** were then alkylated with α-chloroalkylcarboxylic acid ethyl esters **20a**−**c** or γ-chlorobutyric acid ethyl ester **20d** in MeCN under reflux in the presence of K_2CO_3, KI, and 18-crown-6. The reaction led to the corresponding N^6-alkylated derivatives **21**{*1*−*24*}, and this observation is in agreement with previous data on alkylation of pyrrolo[1,2-*d*]1,2,4triazin-1(2H)-ones.[45] As a result of alkylation, the NH proton is not further observed at $\delta \sim 11.5$ ppm, but there appear the signals of substituents. For example, the characteristic protons of NCH_2 and NCH fragments are seen at $\delta \sim 4.7$ and 5.4 ppm, respectively. Esters **21**{*1*−*24*} were then hydrolyzed by aqueous alkali. Upon the hydrolysis, along with the disappearance of ethoxy group protons in ^{1}H NMR spectra, a signal from an OH group sometimes can be found downfield ($\delta \sim 12$ ppm). More often, this signal is not identified because of exchange processes with water protons of the solvent. The resulting

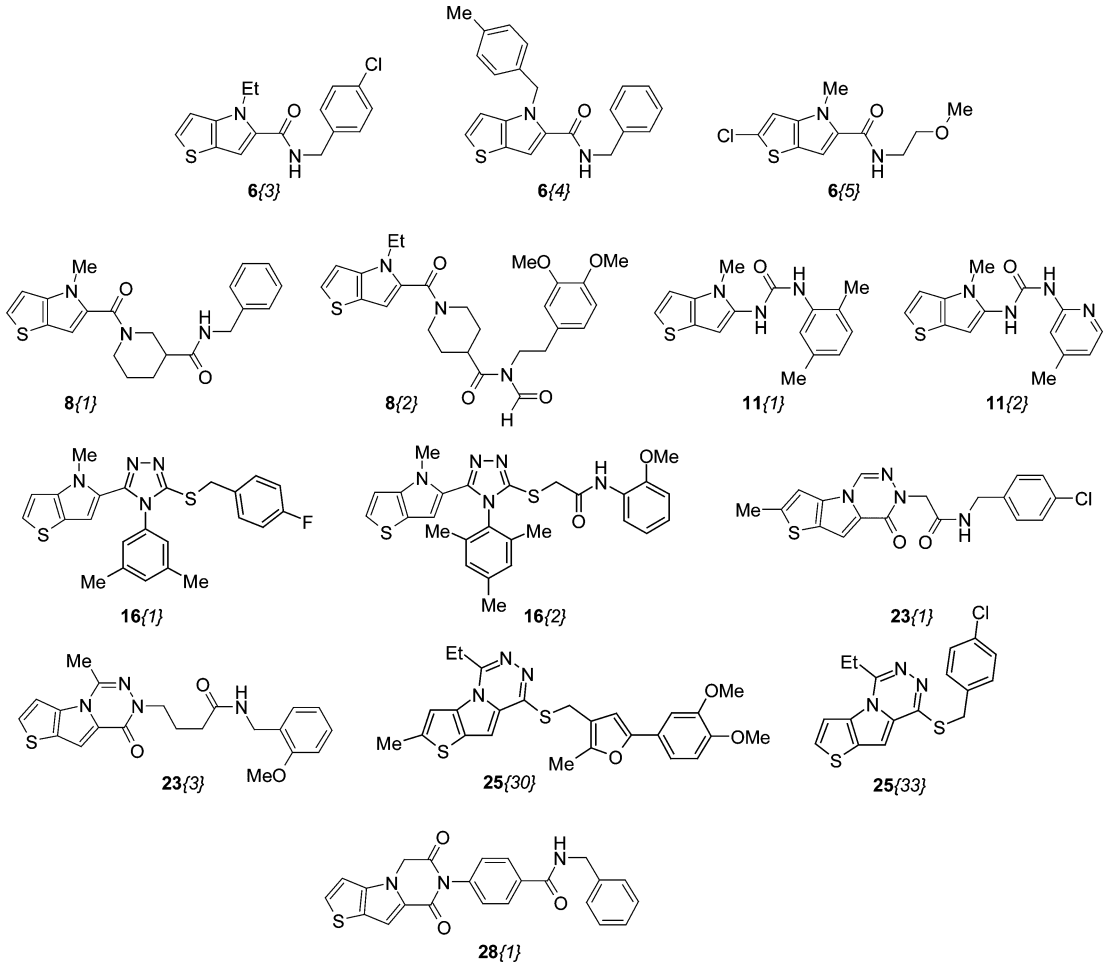


Figure 2. Examples of compounds synthesized in this work.

acids **22**{*1*−*24*} were converted into the corresponding carboxamides **23**{*1*−*664*} via CDI-promoted coupling with various amines **5**{*1*−*192*} in DMF at 70 °C. The yields of final amides **23**{*1*−*664*} varied from 40 to 65%.

As an alternative synthetic route, compounds **19a**−**f** could be efficiently converted into the corresponding thiones **24a**−**f** upon treatment with Lawesson's reagent in refluxing benzene (yield 85−90%) (Scheme 5). This transformation was accompanied by a strong downfield shift of ^{1}H NMR signals of NH proton from $\delta \sim 11.5$ ppm to ∼13−13.5 ppm. We have found that thiones **24a**−**f** are useful precursors for synthesis of the corresponding 7-sulfanylthieno[2′,3′:4,5]-pyrrolo[1,2-*d*] [1,2,4]triazines **25**{*1*−*255*}. This combinatorial library was produced by alkylation of thiones **24a**−**f** under PT conditions with various alkylating agents **2**{*1*−*106*} (see the Supporting Information). The reaction proceeded in MeCN in the presence of K_2CO_3 and 18-crown-6 under elevated temperature and furnished the desired products **25**{*1*−*255*} in 40−70% yield. The observed difference in the direction of alkylation of 1,2,4-triazin-6-ones **19a**−**f** and the corresponding thiones **24a**−**f** can be explained by different tautomeric forms in which these compounds exist under the described conditions.

In the last part of this work, we have demonstrated that some members of the combinatorial library **3**{*1*−*255*} can be useful precursors for the synthesis of a combinatorial library of novel 4,5,6,7-tetrahydrothieno[2′,3′:4,5]pyrrolo-[1,2-*a*]pyrazines (Scheme 6). For assembly of this heterocyclic scaffold, we used a synthetic method based on intramolecular cyclization. Conversion of compound **3**{*10*} to diacid **26** was achieved in good yield via hydrolysis in aqueous NaOH. The thermal cyclization of **26** (Dowtherm, 48 h) led to 4-(5,7-dioxo-4,5-dihydro-7*H*-thieno[2′,3′:4,5]-pyrrolo[1,2-*a*]pyrazin-6-yl)benzoic acid **27** in 50% yield. In a similar manner, assembly of the piperazine-2,6-dione cycle was achieved using thermal cyclization of 1-(2-amino-2-oxoethyl)-5-oxopyrrolidine-2-carboxamide.[46] Upon the CDI-promoted reaction with a series of benzylamines **5**{*24*−*30*}, acid **27** was finally converted into a small library of the corresponding carboxamides **28**{*1*−*7*} (yield 50−80%). To the best of our knowledge, compounds **27** and **28**{*1*−*7*} are the first representatives of 4,5,6,7-tetrahydrothieno[2′,3′:4,5]-pyrrolo[1,2-*a*]pyrazines described in the literature.

In summary, the parallel synthesis of diverse libraries of annulated 4*H*-thieno[3,2-*b*]pyrroles resulted in solid final products isolated in moderate to good the yields with purity more than 95% (after the standard workup of the reaction mixture described in the experimental section, some samples can contain up to 10% residual solvent, which is not detected by the LC/MS detection method). The ^{1}H NMR spectra and mass spectral data obtained on an LC/MS instrument were in agreement with the suggested structures.

Some arbitrary examples of compounds representing the combinatorial libraries synthesized in this work are shown in Figure 2.

Conclusion

An efficient synthetic route was developed for the parallel synthesis of novel 4*H*-thieno[3,2-*b*]pyrrole, thieno[2′,3′:4,5]-pyrrolo[1,2-*d*] [1,2,4]triazine, and thieno[2′,3′:4,5]pyrrolo-[1,2-*a*]pyrazine combinatorial libraries in solution. In all investigated reactions, the corresponding libraries were generated with low levels of impurities using simple crystallization from the reaction mixtures. The developed methods use readily available starting materials in mild reactions that display a relatively high substituent tolerance and, therefore, are suited for rapid synthesis of diverse libraries. In this work, novel substituted derivatives of 4*H*-thieno[3,2-*b*]pyrrole, 6*H*-thieno[2′,3′:4,5]pyrrolo[1,2-*d*] [1,2,4]triazin-7-one, 6*H*-thieno-[2′,3′:4,5]pyrrolo[1,2-*d*] [1,2,4]triazin-7-thione, and thieno-[2′,3′:4,5]pyrrolo[1,2-*a*]pyrazine were produced, which are useful building blocks for combinatorial synthesis and interesting objects for biological screening for various pharmacological activities. Product yields varied according to reactant structures, but in most cases, the desired products were obtained in moderate to good yields. One disadvantage of the described strategy is that it requires relatively lengthy synthesis, leading to templates for the library-generation steps. Biological evaluation of these libraries is currently in progress.

Experimental Section

General Information. Thin-layer chromatography (TLC) was performed on aluminum sheets precoated with silica gel (Merck, Kieselgel 60 F-254). ^{1}H NMR spectra were recorded on Bruker AMX-400 and Varian spectrometers in DMSO-d_6 using TMS as an internal standard (chemical shifts in parts per million). LC/MS spectra were recorded with a PE SCIEX API 150EX liquid chromatograph equipped with a UV detector (λ_{max} 215 and 254 nm) and using a C_{18} column (100 × 4 mm). Elution started with water and ended with acetonitrile/water (95:5, v/v) and used a linear gradient at a flow rate of 0.15 mL/min and an analysis cycle time of 25 min. According to LC/MS data, all the synthesized compounds have purity > 95%. All solvents and reagents were obtained from commercial sources and were used without purification. All reagents were purchased from Acros Organics, Aldrich, or ChemDiv. The parallel solution-phase syntheses of compounds were accomplished on the 50−100 mg scale. Initial 2-substituted methyl 4*H*-thieno[3,2-*b*]-pyrrole-5-carboxylates **1a**−**d** were synthesized using a previously reported method with insignificant modifications.[42]

General Procedure for Synthesis of 4-Substituted Methyl 4*H*-Thieno[3,2-*b*]pyrrolo-5-carboxylates 3{*1*−*255*}. A mixture of carboxylate **1a**−**d** (0.20 mol), well-milled and freshly calcined K_2CO_3 (0.25 mol), 18-crown-6 (0.01 mol), and the alkylating agent **2**{*1*−*106*} (0.25 mol) in MeCN (1 L) was heated at reflux and stirred for 6 h. The solvent was evaporated in vacuo; water (1 L) was added to the residue; and after stirring for an additional 30 min, the precipitate was filtered off, washed with water, and dried. The resulting product was analyzed by LC/MS and, if necessary (purity < 95%), recrystallized from MeOH. The yields of **3**{*1*−*255*} were 65−85%.

4-(2-Chlorobenzyl)-2-ethyl-4*H*-thieno[3,2-*b*]pyrrole-5-carboxylic Acid Methyl Ester 3{*13*}. Yield 85%. ^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 1.30 (t, J = 7.1 Hz, 3H), 2.82 (q, J = 7.1 Hz, 2H), 3.73 (s, 3H), 5.73 (s, 2H), 6.40 (d, J = 7.4 Hz. 1H), 6.58 (s, 1H), 7.04 (t, J = 7.7 Hz, 1H), 7.09 (s, 1H), 7.17 (t, J = 7.6 Hz, 1H), 7.39 (d, J = 7.4 Hz. 1H). LC/MS m/z 334 (M + 1).

2-Chloro-4-[(4-*iso*-propylphenylcarbamoyl)methyl]-4*H*-thieno[3,2-*b*]pyrrole-5-carboxylic Acid Methyl Ester 3{*45*}. Yield 65%. ^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 1.40 (d, J = 6.8 Hz, 6H), 2.83−3.11 (m, 1H), 3.78 (s, 3H), 5.25 (s, 2H), 7.05−7.64 (m, 3H), 7.19 (s, 1H), 7.47 (d, J = 8.3 Hz, 2H), 9.80 (s, 1H). LC/MS m/z 391 (M + 1).

4-[(4-Ethoxycarbonylphenylcarbamoyl)methyl]-4*H*-thieno[3,2-*b*]pyrrole-5-carboxylic Acid Methyl Ester 3-{*54*}. Yield 71%. ^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 1.38 (t, J = 7.3 Hz, 3H), 3.80 (s, 3H), 4.30 (q, J = 7.3 Hz, 2H), 5.22 (s, 2H), 7.11 (d, J = 3.7 Hz, 1H), 7.14 (s, 1H), 7.37 (d, J = 3.7 Hz, 1H), 7.68 (d, J = 8.2 Hz, 2H), 7.88 (d, J = 8.2 Hz, 2H), 10.40 (s, 1H). LC/MS m/z 387 (M + 1).

4-[(3,5-Dimethylphenylcarbamoyl)methyl]-4*H*-thieno-[3,2-*b*]pyrrole-5-carboxylic Acid Methyl Ester 3{*59*}. Yield 77%. ^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 2.22 (s, 6H), 3.81 (s, 3H), 5.35 (s, 2H), 6.62 (s, 1H), 7.09 (d, J = 4.2 Hz, 1H), 7.18 (s, 2H), 7.36 (d, J = 4.2 Hz, 1H), 9.87 (s, 1H). LC/MS m/z 343 (M + 1).

General Procedure of Synthesis of 4-Substituted 4*H*-Thieno[3,2-*b*]pyrrolo-5-carboxylic Acids 4{*1*−*9*}. A solution of ester **3**{*1*−*9*} (0.30 mol) and NaOH (1.5 mol) in H_2O/MeOH (1:3) (400 mL) was stirred at 40 °C for 48 h. After cooling to 20 °C, the MeOH was evaporated in vacuo, and the residue was extracted with CH_2Cl_2. Activated charcoal (10 g) was added to the water phase, stirred at 40 °C (1 h) and cooled to room temperature, and the filtrate was acidified with 1% HCl until pH 5 was reached. The formed precipitate was filtered off, washed with cold water, and dried to give **4**{*1*−*9*} in 60−75% yield. Analytical samples of acids **37**{*1*−*9*} were obtained by recrystallization from 2-propanol.

4-Methyl-4*H*-thieno[3,2-*b*]pyrrole-5-carboxylic Acid 4{*1*}. Yield 60%. ^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 4.06 (s, 3H), 6.89 (s, 1H), 6.94 (d, J = 4.1 Hz, 1H), 7.08 (d, J = 4.1 Hz, 1H), 11.7 (br. s, 1H). LC/MS m/z 182 (M + 1).

4-(4-Methylbenzyl)-4*H*-thieno[3,2-*b*]pyrrole-5-carboxylic Acid 4{*3*}. Yield 75%. ^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 2.28 (s, 3H), 5.72 (s, 2H), 6.88 (d, J = 4.0 Hz, 1H), 7.02−7.32 (m, 4H), 7.13 (s, 1H), 7.28 (d, J = 4.0 Hz, 1H), 11.7 (br. s, 1H). LC/MS m/z 272 (M + 1).

General Procedure for Synthesis of 4-Substituted 4*H*-Thieno[3,2-*b*]pyrrolo-5-carboxamides 6{*1*−*309*}. CDI (0.11 mol) was added by small portions to a solution of acid **4**{*1*−*9*} (0.10 mol) in DMF (100 mL). After the addition was completed, the resulting mixture was heated at 50−60 °C for 2.5 h, allowed to cool to room temperature, and transferred by portions of 3 mL to the tubes for parallel synthesis. Amine **5** (3.1 mmol) was added to each tube, heated at 70 °C for 4 h, and cooled to 20 °C. Then each of

the individual reaction mixtures was poured into a mixture of 5% aqueous $NaHCO_3$ solution (50 mL) and $CHCl_3$ (5 mL). After stirring, the organic layers were separated and dried with anhydrous Na_2SO_4. The solvent was evaporated in vacuo, and the residues were triturated with ether (5−7 mL). Solids were filtered off, analyzed by LC/MS, and (if purity <95%) recrystallized from cyclohexane. The yields of amides **6**{*1*−*309*} ranged from 45 to 70%.

4-Ethyl-4*H*-thieno[3,2-*b*]pyrrole-5-carboxylic Acid 4-Chlorobenzylamide 6{*3*}. Yield 55%. ^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 1.35 (t, J = 7.3 Hz, 3H), 4.41 (d, J = 5.9 Hz, 2H), 4.55 (q, J = 7.3 Hz, 2H), 6.98 (d, J = 3.9 Hz, 1H), 7.05 (s, 1H), 7.21 (d, J = 8.2 Hz, 1H), 7.27 (d, J = 3.9 Hz, 1H), 7.34 (d, J = 8.2 Hz, 2H), 9.52 (t, J = 5.9 Hz, 1H). LC/MS m/z 319 (M + 1).

4-(4-Methylbenzyl)-4*H*-thieno[3,2-*b*]pyrrole-5-carboxylic Acid Benzylamide 6{*4*}. Yield 60%. ^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 2.28 (s, 3H), 4.48 (d, J = 5.8 Hz, 2H), 5.61 (s, 2H), 6.94 (d, J = 3.7 Hz, 1H), 7.00 (d, J = 7.9 Hz, 2H), 7.05 (d, J = 7.9 Hz, 2H), 7.09 (s, 1H), 7.18 (d, J = 3.7 Hz, 1H), 7.26−7.76 (m, 5H), 8.54 (t, J = 1H). LC/MS m/z 361 (M + 1).

2-Chloro-4-methyl-4*H*-thieno[3,2-*b*]pyrrole-5-carboxylic Acid (2-Methoxyethyl)amide 6{*5*}. Yield 45%. ^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 3.31 (s, 3H), 3.40−3.84 (m, 4H), 3.97 (s, 3H), 6.94 (s, 1H), 7.19 (s, 1H), 8.08 (s, 1H, NH). LC/MS m/z 273 (M + 1).

General Procedure for Synthesis of 1-(4*H*-Thieno[3,2-*b*]pyrrole-5-carbonyl)piperidinecarboxylic Acids 7{*1*−*4*}. Ester **6**{*1*−*4*} (0.30 mol) was added to a solution of NaOH (1.5 mol) in H_2O/MeOH (1:3) (400 mL), and the resulting mixture was stirred at 20 °C for 72 h. The MeOH was evaporated in vacuo, and the residue was extracted by CH_2Cl_2. The water layer was stirred with activated charcoal (10 g) at 40 °C for 1 h and cooled to room temperature, and the filtrate was acidified by 1% HCl until pH 5. The formed precipitate was filtered off, washed on-filter with cold water and recrystallized from aqueous MeOH to afford pure acids **7**{*1*−*4*} in 45−65% yield.

1-(4-Methyl-4*H*-thieno[3,2-*b*]pyrrole-5-carbonyl)piperidine-3-carboxylic Acid 7{*1*}. Yield 45%. ^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 3.79 (s, 3H), 6.49 (s, 1H), 6.98 (s, 1H), 7.16 (s, 1H), 1.55−2.54 (m, 1H), 1.74−1.96 (m, 2H), 2.05−2.54 (m, 1H), 2.42−2.75 (m, 1H), 3.30−3.82 (m, 2H), 4.08 (d, J = 6.6 Hz, 1H), 4.29 (d, J = 6.6 Hz, 1H). LC/MS m/z 293 (M + 1).

1-(4-Ethyl-4*H*-thieno[3,2-b]pyrrole-5-carbonyl)piperidine-4-carboxylic Acid 7{*2*}. Yield 55%. ^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 1.37 (t, J = 7.0 Hz, 3H), 4.24 (q, J = 7.0 Hz, 2H), 6.48 (s, 1H), 6.98 (d, J = 3.9 Hz, 1H), 7.15 (d, J = 3.9 Hz, 1H), 1.62−2.05 (m, 2H), 1.73−2.11 (m, 2H), 2.39−2.65 (m, 1H), 2.72 (t, J = 13.4 Hz, 2H), 4.32 (d, J = 13.2 Hz 2H).

1-(4-Ethyl-4*H*-thieno[3,2-*b*]pyrrole-5-carbonyl)piperidine-3-carboxylic Acid 7{*3*}. Yield 55%. ^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 1.37 (t, J = 7.1 Hz, 3H), 4.24 (q, J = 7.1 Hz, 2H), 6.48 (s, 1H), 6.98 (d, J = 4 Hz, 1H), 7.15 (d, J = 4 Hz, 1H), 1.56−1.74 (m, 1H), 1.72−1.93 (m, 2H), 2.11−2.55 (m, 1H), 2.40−2.66 (m, 1H), 3.15−3.74 (m, 1H), 3.27−3.48 (m, 1H), 4.16 (d, J = 6.6 Hz, 1H), 4.33 (d, J = 6.6 Hz, 1H). LC/MS m/z 307 (M + 1).

General Procedure of Synthesis of 1-(4*H*-Thieno[3,2-*b*]pyrrole-5-carbonyl)piperidine-4-carboxamides 8{*1*−*130*}. The synthetic procedure is similar to that described above for 4*H*-thieno[3,2-*b*]pyrrolo-5-carboxamides **39**{*1*−*309*}. Yields were 25−65%.

1-(4-Methyl-4*H*-thieno[3,2-*b*]pyrrole-5-carbonyl)piperidine-3-carboxylic Acid Benzylamide 8{*1*}. Yield 55%. ^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 3.79 (s, 3H), 4.33 (d, J = 5.7 Hz, 2H), 6.52 (s, 1H), 6.96 (d, J = 3.9 Hz, 1H), 7.10−7.30 (m, 6H), 8.22 (s, 1H), 1.53−1.76 (m, 1H), 1.74−1.92 (m, 2H), 1.96−2.11 (m, 1H), 2.42−2.69 (m, 1H), 3.0−3.2 (m, 2H), 4.25 (d, J = 2H). LC/MS m/z 382 (M + 1).

***N*-[2-(3,4-Dimethoxyphenyl)-ethyl]-*N*-[1-(4-ethyl-4*H*-thieno[3,2-*b*]pyrrole-5-carbonyl)piperidin-4-yl]formamide 8{*2*}.** Yield 48%. ^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 1.34 (t, J = 7.2 Hz, 3H), 3.03−3.64 (m, 2H), 3.29−3.65 (m, 2H), 3.74, 3.78 (s, s, 6H), 4.25 (q, J = 7.2 Hz, 2H), 6.46 (s, 1H), 6.64 (d, J = 8.1 Hz, 1H), 6.70 (s, 1H), 6.74 (d, J = 8.1 Hz, 1H), 7.00 (d, J = 3.7 Hz, 1H), 7.18 (d, J = 3.7 Hz, 1H), 7.58 (s, 1H), 1.62−1.86 (m, 2H), 1.73−1.91 (m, 2H), 2.39−2.55 (m, 1H), 2.65 (t, J = 13.5 Hz, 2H), 4.36 (d, J = 12.9 Hz 2H). LC/MS m/z 470 (M + 1).

***N*-Benzyl-*N*-[1-(4-ethyl-4*H*-thieno[3,2-*b*]pyrrole-5-carbonyl)piperidin-4-yl]formamide 8{*24*}.** Yield 60%. ^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 1.37 (t, J = 7.2 Hz, 3H), 4.26−4.46 (m, 4H), 6.48 (s, 1H), 6.98 (d, J = 3.9 Hz, 1H), 7.12−7.30 (m, 6H), 8.07 (s, 1H), 1.68−1.76 (m, 2H), 1.84−1.95 (m, 2H), 2.49−2.66 (m, 1H), 3.05 (t, J = 13.8 Hz, 2H), 4.41 (d, J = 12.7 Hz, 2H). LC/MS m/z 396 (M + 1).

General Procedure for Synthesis of 1-(4-Methyl-4*H*-thieno[3,2-*b*]pyrrole-5-carbonyl)ureas 11{*1*−*26*}. $(C_2H_5)_3N$ (1.2 mol) was added to a suspension of acid **4**{*1*, *2*} (1 mol) in acetone (1 L), and the mixture was stirred at 20 °C for 30 min, then cooled to 0−5 °C. $ClCO_2Et$ (1.2 mol) was added slowly dropwise, and the resulting mixture was stirred at 0 °C for 3 h, then a solution of NaN_3 (1.5 mol) in the minimal amount of water was added at 0−5 °C over 1 h. The reaction mixture was stirred at 20 °C for 5 h and poured into cold water (5 L). The precipitate was filtered off, washed with cold water, and dried in vacuo above P_2O_5 to afford pure azide **9a**,**b** (yield 80−85%), which was used at the next step without further purification. Azide **9a**,**b** (0.073 mol) was dissolved in toluene (300 mL, freshly dried above sodium) and slowly heated in a flask (1 L) supplied with a reflux condenser and bubble meter. The mixture was heated at reflux until N_2 evolution ceased and then was allowed to cool to room temperature. Toluene was evaporated in vacuo to afford isocyanate **10a**,**b** (yield ∼90%), which was used at the next step without further purification. Compound **10a**,**b** (0.065 mol) was dissolved in dry dioxane (∼160 mL) to concentration of ∼0.4 M. The solution was transferred in 5-mL portions to the tubes for parallel synthesis, the appropriate amine **5**{*55*−*65*} (2.1 mmol) was added to each tube, and the reaction mixtures were heated at reflux for 8 h. The mixtures were cooled to room temprature, and the formed precipitates were isolated and analyzed with LC/MS

and (if purity < 95%) recrystallized from EtOH. The yields of ureas **11**{*1*−*26*} were 60−90%.

1-(2,5-Dimethylphenyl)-3-(4-methyl-4*H*-thieno[3,2-*b*]-pyrrol-5-yl)urea 11{***1***}**.** Yield 90%. ^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 2.19, 2.29 (s, s, 6H), 3.66 (s, 3H), 6.19 (s, 1H), 6.71 (d, J = 7.9 Hz, 1H), 6.96−7.11 (m, 3H), 7.65−7.75 (m, 2H), 8.41 (s, 1H). LC/MS *m*/*z* 300 (M + 1).

1-(4-Methylpyridin-2-yl)-3-(4-methyl-4*H*-thieno[3,2-*b*]-pyrrol-5-yl)urea 11{***2***}.** Yield 60%. ^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 2.29 (s, 3H), 3.65 (s, 3H), 6.23 (s, 1H), 6.70 (d, J = 3.9 Hz, 1H), 6.91−7.22 (m, 2H), 7.09 (s, 1H), 8.02 (d, J = 6.1 Hz, 1H), 9.57 (s, 1H), 10.75 (s, 1H). LC/MS *m*/*z* 287 (M + 1).

1-(4-Ethoxyphenyl)-3-(4-methyl-4*H*-thieno[3,2-*b*]pyrrol-5-yl)urea 11{***5***}.** Yield 84%. ^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 1.37 (t, J = 7.4 Hz, 3H), 3.62 (s, 3H), 4.33 (q, J = 7.4 Hz, 2H), 6.15 (s, 1H), 6.73 (d, J = 8.1 Hz, 2H), 6.92−7.33 (m, 2H), 7.30 (d, J = 8.1 Hz, 2H), 7.98 (s, 1H), 8.28 (s, 1H). LC/MS *m*/*z* 316 (M + 1).

4-Methyl-4*H*-thieno[3,2-*b*]pyrrole-5-carboxylic Acid Hydrazide 12. A solution of ester **3**{*1*} (41.8 g, 0.20 mol) and hydrazine hydrate (100 g, 2.0 mol) in EtOH (400 mL) was heated at reflux for 6 h. The mixture was cooled to 20 °C, and the precipitate was filtered off, washed on the filter successively with water (500 mL) and cold EtOH (100 mL), then dried in vacuo to afford hydrazide **12** in 75% yield. ^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 2.49 (s, 3H), 6.76 (s, 1H), 6.90 (s, 1H), 9.32 (s, 1H), 11.34 (s, 1H). LC/MS *m*/*z* 196 (M + 1).

General Procedure for Synthesis of 4-Aryl-5-(4-methyl-4*H*-thieno[3,2-*b*]pyrrol-5-yl)-4*H*-[1,2,4]triazole-3-thiols 15a,b. Hydrazide **12** (19.5 g, 0.10 mol), isocyanate **13a**,**b** (0.10 mol) and 2−3 drops of $(C_2H_5)_3N$ were stirred in dioxane (100 mL) for 6 h. The mixture was poured into water (200 mL), and the precipitate was filtered off, washed with water, and dried in vacuo. The obtained product **14a**,**b** was dissolved in 4% aqueous solution of NaOH (250 mL, 0.25 mol), and the mixture was stirred at 40−50 °C for 3 h. The resulting mixture was filtered off, and the filtrate was acidified by 10% HCl until pH 3 was reached. The formed precipitate was filtered off, washed with water and dried to afford pure **15a**,**b** in 65−69% yield.

4-(2,5-Dimethylphenyl)-5-(4-methyl-4*H*-thieno[3,2-*b*]-pyrrol-5-yl)-4*H*-[1,2,4]triazole-3-thiol 15a. Yield 65%. ^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 2.08 (s, 3H), 2.47 (s, 3H), 4.05 (s, 3H), 5.59 (s, 1H), 6.98 (d, J = 3.9 Hz, 1H), 7.08 (d, J = 3.9 Hz, 1H), 7.14−7.19 (m, 2H), 7.22 (s, 1H), 13.95 (s, 1H). LC/MS *m*/*z* 341 (M + 1).

5-(4-Methyl-4*H*-thieno[3,2-*b*]pyrrol-5-yl)-4-(2,4,6-trimethylphenyl)-4*H*-[1,2,4]triazole-3-thioles 15b. Yield 69%. ^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 1.98 (s, 6H), 2.40 (s, 3H), 4.07 (s, 3H), 5.58 (s, 1H), 6.98 (d, J = 4.0 Hz, 1H), 7.05 (s, 2H), 7.19 (d, J = 4.0 Hz, 1H), 13.97 (s, 1H). LC/MS *m*/*z* 355 (M + 1).

General Procedure for Synthesis of Substituted 4-Methyl-5-(4-phenyl-5-sulfanyl-4*H*-[1,2,4]triazol-3-yl)-4*H*-thieno-[3,2-*b*]pyrroles 16{***1*−*44***}.** A 5 M solution of thiol **15a**,**b** in MeCN was prepared and kept under a nitrogen atmosphere at 20 °C. The resulting stock solution was pipetted into 10 vials of the CombiSyn reactor for parallel synthesis (6 mL per vial, ∼30 mmol of the corresponding thiol **15a**,**b**), followed by addition of well-milled, freshly calcined K_2CO_3 (43 mg, 31 mmol), 18-crown-6 (10 mg), and the appropriate alkylating agent from chemset **2**{*1*−*106*} (31 mmol). The reaction mixtures were stirred at 60 °C for 14 h and then allowed to cool to room temperature. Then they were transferred into standard glass vials, and water was added (50 mL per each vial). After stirring for 30 min, the precipitates were isolated by filtration, analyzed by LC/MS, and (if purity < 95%) recrystallized from EtOH. The yields of pyrroles **16**{*1*−*44*} were 30−60%.

5-[4-(3,5-Dimethylphenyl)-5-(4-fluorobenzylsulfanyl)-4*H*-[1,2,4]triazol-3-yl]-4-methyl-4*H*-thieno[3,2-*b*]pyrrole 16{***1***}.** Yield 55%. ^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 1.91 (s, 3H), 2.40 (s, 3H), 4.11 (s, 3H), 4.42 (s, 2H), 5.60 (s, 1H), 6.87−7.23 (m, 9H). LC/MS *m*/*z* 449 (M + 1).

N*-(2-Methoxyphenyl)-2-[5-(4-methyl-4*H*-thieno[3,2-*b*]-pyrrol-5-yl)-4-(2,4,6-trimethylphenyl)-4*H*-[1,2,4]triazol-3-yl-sulfanyl]acetamide 16**{2***}.** Yield 48%. ^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 1.96 (s, 6H), 2.42 (s, 3H), 3.86 (s, 3H), 4.18 (s, 2H), 4.33 (s, 3H), 5.62 (s, 1H), 6.80−6.96 (m, 4H), 7.09 (s, 2H), 7.19 (d, J = 3.7 Hz, 1H), 8.16 (d, J = 6.9 Hz, 1H), 9.68 (s, 1H). LC/MS *m*/*z* 518 (M + 1).

4*H*-Thieno[3,2-*b*]pyrrole-5-carbohydrazides 17a,b. The synthetic procedure is similar to that described above for 4-methyl-4*H*-thieno[3,2-*b*]pyrrole-5-carbohydrazide **12**. Yields 73, 77%.

General Procedure for Synthesis of 6*H*-Thieno[2′,3′:4,5]pyrrolo[1,2-*d*][1,2,4]triazin-7-ones 19a−f. A mixture of hydrazide **17a**,**b** (1 mol) and orthoester **18a**−**c** (1.1 mol) in DMF (1 L) was stirred at reflux for 12 h to accomplish the conversion of initial compounds into the corresponding derivatives **19a**−**f** (control by TLC, eluent $CHCl_3$−MeOH 19:1). The mixture was poured into water (2 L) under stirring, and the formed precipitate was filtered off, washed with water, and dried to afford **19a**−**f** in 50−60% yield.

6*H*-Thieno[2′,3′:4,5]pyrrolo[1,2-*d*][1,2,4]triazin-7-one 19a. Yield 50%. ^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 7.23 (s, 1H), 7.47 (d, J = 4.2 Hz, 1H), 7.56 (d, J = 4.2 Hz, 1H), 8.72 (s, 1H), 11.62 (s, 1H). LC/MS *m*/*z* 192 (M + 1).

4-Methyl-6*H*-thieno[2′,3′:4,5]pyrrolo[1,2-*d*][1,2,4]triazin-7-one 19b. Yield 56%. ^{1}H NMR (DMSO-d_6, 400 MHz) δ (ppm) 2.72 (s, 3H), 7.29 (s, 1H), 7.47 (d, J = 4.3 Hz, 1H), 7.55 (d, J = 4.3 Hz, 1H), 11.55 (s, 1H). LC/MS *m*/*z* 206 (M + 1).

4-Ethyl-2-methyl-6*H*-thieno[2′,3′:4,5]pyrrolo[1,2-*d*][1,2,4]-triazin-7-one 19c. Yield 60%. ^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 1.38 (t, J = 7.2 Hz, 3H), 2.65 (s, 3H), 3.07 (q, J = 7.2 Hz, 2H), 7.10 (s, 1H), 7.18 (s, 1H), 11.45 (s, 1H). LC/MS *m*/*z* 234 (M + 1).

General Procedure for Synthesis of Ethyl (7-Oxo-7*H*-thieno[2′,3′:4,5]pyrrolo[1,2-*d*][1,2,4]triazin-6-yl)alkylcarboxylates 21{***1*−*24***}.** A mixture of **19a**−**f** (0.5 mol), well-milled and freshly calcined K_2CO_3 (0.6 mol), 18-crown-6 (25 mmol), KI (60 mol), and ethyl chloralkylcarboxylate **20a**−**d** (0.6 mol) in MeCN (300 mL) was heated at reflux for 12 h to accomplish the conversion of initial compounds (control by TLC, eluent $CHCl_3$−MeOH 19:1). After separat-

ing inorganic salts, the filtrate was evaporated in vacuo to dryness, and cold water (500 mL) was added to the residue under stirring. The formed precipitate was filtered off, washed with cold water, and recrystallized from EtOH to afford esters **22**{*1*−*24*} in 55−60% yield.

(4-Ethyl-2-methyl-7-oxo-7H-thieno[2′,3′:4,5]pyrrolo-[1,2-d][1,2,4]triazin-6-yl)acetic Acid 21{***1***}**.** Yield 60%. ^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 1.38 (t, J = 7.2 Hz, 3H), 7.22 (s, 1H), 2.62 (s, 3H), 3.08 (q, J = 7.2 Hz, 2H), 4.52 (s, 2H), 7.11 (s, 1H).

Ethyl 2-(5-Methyl-8-oxothieno[2′,3′:4,5]pyrrolo[1,2-*d*][1,2,4]triazin-7(8*H*)-yl)butanoate 21{***2***}**.** Yield 60%. ^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm): 0.88 (t, J = 6.9 Hz, 3H), 1.21 (t, J = 7.2 Hz, 3H), 2.12−2.33 (m, 2H), 2.77 (s, 3H), 4.11 (q, J = 7.2 Hz, 2H), 5.21−5.43 (m, 1H), 7.30 (s, 1H), 7.42 (d, J = 3.8 Hz, 1H), 7.57 (d, J = 3.8 Hz, 1H). LC/MS *m*/*z* 320 (M + 1).

Ethyl 2-(5-Methyl-8-oxothieno[2′,3′:4,5]pyrrolo[1,2-*d*][1,2,4]triazin-7(8*H*)-yl)propanoate 21{***3***}**.** Yield 57%. ^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm): 1.21 (t, J = 7.2 Hz, 3H), 1.57 (d, J = 6.8 Hz, 3H), 2.78 (s, 3H), 4.12 (q, J = 7.2 Hz, 2H), 5.35 (q, J = 6.8 Hz, 1H), 7.30 (s, 1H), 7.41 (d, J = 3.8 Hz, 1H), 7.58 (d, J = 3.8 Hz, 1H). LC/MS *m*/*z* 306 (M + 1).

General Procedure for Synthesis of (7-Oxo-7*H*-thieno-[2′,3′:4,5]pyrrolo[1,2-*d*][1,2,4]triazin-6-yl)alkylcarboxylic Acids 22{***1*−*24***}**.** Ester **21**{*1*−*24*} (0.2 mol) was added to 3% aqueous NaOH solution (0.3 mol) and heated at reflux until complete dissolution of the solid material (∼1 h). The mixture was cooled to 20 °C, filtered, and acidified to pH 3 by 10% HCl. The formed precipitate was filtered off, washed with water, and dried in vacuo over P_2O_5 to afford acids **22**{*1*−*24*} in 80−90% yield.

(8-Oxothieno[2′,3′:4,5]pyrrolo[1,2-*d*][1,2,4]triazin-7(8*H*)-yl)acetic Acid 22{***4***}**.** Yield 88%. ^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm): 4.23 (s, 2H), 7.31 (s, 1H), 7.62 (d, J = 3.8 Hz, 1H), 7.76 (d, J = 3.8 Hz, 1H), 8.89 (s,1H). LC/MS *m*/*z* 250 (M + 1).

(5-Ethyl-8-oxothieno[2′,3′:4,5]pyrrolo[1,2-*d*][1,2,4]triazin-7(8*H*)-yl)acetic Acid 22{***5***}**.** Yield 83%. ^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 4.23 (s, 2H), 7.31 (s, 1H), 7.62 (d, J = 3.8 Hz, 1H), 7.76 (d, J = 3.8 Hz, 1H), 8.89 (s,1H). LC/MS *m*/*z* 278 (M + 1).

General Procedure for Synthesis of (7-Oxo-7*H*-thieno-[2′,3′:4,5]pyrrolo[1,2-*d*][1,2,4]triazin-6-yl)alkylcarboxamides 23{***1*−*664***}**.** The procedure is similar to that described above for 4*H*-thieno[3,2-*b*]pyrrolo-5-carboxamides **6**{*1*−*309*}. Amides **23**{*1*−*664*} were obtained in 40−65% yields.

N*-(4-Chlorobenzyl)-2-(2-methyl-7-oxo-7*H*-thieno[2′,3′:4,5]pyrrolo[1,2-*d*][1,2,4]triazin-6-yl)acetamide 23**{1***}**.** Yield 65%. ^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 2.63 (s, 3H), 4.29 (d, J = 5.9 Hz, 2H), 4.59 (s, 2H), 7.20 (s, 1H), 7.22−7.35 (m, 5H), 8.41 (t, J = 5.9 Hz, 1H), 8.79 (s, 1H). LC/MS *m*/*z* 372 (M + 1).

N*-(4-Methoxybenzyl)-2-(7-oxo-7*H*-thieno[2′,3′:4,5]pyrrolo[1,2-*d*][1,2,4]triazin-6-yl)acetamide 23**{37***}**.** Yield 60%. ^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 3.75 (s, 3H), 4.26 (d, J = 5.6 Hz, 2H), 4.63 (s, 2H), 6.80 (d, J = 8.1 Hz, 2H), 7.19 (d, J = 8.1 Hz, 2H), 7.30 (s, 1H), 7.46 (d, J = 4.1 Hz ,1H), 7.61 (d, J = 4.1 Hz, 1H), 8.87 (s, 1H), 8.31 (t, J = 5.6 Hz, 1H). LC/MS *m*/*z* 354 (M + 1).

General Procedure for Synthesis of 6*H*-Thieno[2′,3′:4,5]pyrrolo[1,2-*d*][1,2,4]triazin-7-thiones 24a−f. A mixture of **19a**−**f** (0.5 mol) and Lawesson's reagent (0.25 mol) in benzene (250 mL) was heated at reflux for 4 h to accomplish the conversion of initial **19a**−**f** (control by TLC, eluent $CHCl_3$−MeOH 19:1). The mixture was cooled down to 20 °C, and the precipitate was filtered off, washed with hexane, and dried to afford thiones **24a**−**f** in 85−90% yield.

4-Ethyl-6*H*-thieno[2′,3′:4,5]pyrrolo[1,2-*d*][1,2,4]triazin-7-thione 24b. Yield 90%. ^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 1.45 (t, J = 7.2 Hz, 3H), 3.37 (q, J = 7.2 Hz, 2H), 7.47 (d, J = 3.7 Hz, 1H), 7.58 (s, 1H), 7.61 (d, J = 3.7 Hz, 1H), 13.45 (s, 1H). LC/MS *m*/*z* 236 (M + 1).

General Procedure for Synthesis of 7-Sulfanylthieno-[2′,3′:4,5]pyrrolo[1,2-*d*][1,2,4]triazines 25{***1*−*255***}**.** A 1 M solution of thione **24a**−**f** in MeCN was prepared and kept at 20 °C. The resulting stock solution was pipetted into 10 vials of the CombiSyn reactor for parallel synthesis (3 mL per vial, ∼3 mmol of the corresponding thione **24a**−**f**), followed by addition of well-milled, freshly calcined K_2CO_3 (3 mmol); 18-crown-6 (10 mg); and the appropriate alkylating agent from chemset **2**{*1*−*106*} (3.1 mmol). The reaction mixtures were stirred at 60 °C for 14 h and then allowed to cool to room temperature. Then they were transferred into standard glass vials, and water was added (50 mL per each vial). After stirring for 30 min, the precipitates were isolated by filtration, analyzed by LC/MS, and (if purity < 95%) recrystallized from EtOH to afford **25**{*1*−*255*} in 40−70% yield.

7-[2-(3,4-Dimethoxyphenyl)-5-methyloxazol-4-yl-methylsulfanyl]-4-ethyl-2-methylthieno[2′,3′:4,5]pyrrolo[1,2-*d*]-[1,2,4]triazine 25{***30***}**.** Yield 66%. ^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 1.45 (t, J = 6.9 Hz, 3H), 2.46 (s, 3H), 2.61 (s, 3H), 3.25 (q, J = 6.9 Hz, 2H), 3.75 (s, 3H), 3.80 (s, 3H), 4.47 (s, 2H), 6.88 (d, J = 7.7 Hz, 1H), 7.01 (s, 1H), 7.30 (s, 1H), 7.37 (s, 1H), 7.43 (d, J = 7.7 Hz, 1H). LC/MS *m*/*z* 480 (M + 1).

7-(4-Chlorobenzylsulfanyl)-4-ethylthieno[2′,3′:4,5]pyrrolo[1,2-*d*][1,2,4]triazine 25{***33***}**.** Yield 70%. ^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 1.48 (t, J = 7.2 Hz, 3H), 3.30 (q, J = 7.2 Hz, 2H), 4.57 (s, 2H), 6.96 (s, 1H), 7.25 (d, J = 7.9 Hz, 2H), 7.46 (d, J = 7.9 Hz, 2H), 7.53−7.75 (m, 2H). LC/MS *m*/*z* 362 (M + 1).

4-Ethyl-2-methylthieno[2′,3′:4,5]pyrrolo[1,2-*d*][1,2,4]-triazin-7-yl-sulfanyl)-*N*-(4-ethyl-phenyl)butyramide 25-{***36***}**.** Yield 48%. ^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 1.17 (t, J = 6.9 Hz, 3H), 1.48 (t, J = 7.2 Hz, 3H), 2.55 (q, J = 6.9 Hz, 2H), 2.65 (s, 3H), 3.26 (q, J = 7.2 Hz, 2H), 4.17 (s, 2H), 7.05−7.33 (m, 3H), 7.25 (s, 1H), 7.45 (d, J = 8.0 Hz, 2H), 10.13 (s, 1H). LC/MS *m*/*z* 469 (M + 1).

4-[(4-Carboxyphenylcarbamoyl)methyl]-4*H*-thieno[3,2-*b*]pyrrole-5-carboxylic Acid 26. Ester **3**{*10*} (0.2 mol) was added to 3% aqueous NaOH solution (0.3 mol, 400 mL), and the mixture was heated at reflux for 18 h, then cooled, filtered, and acidified to pH 3 by 1% HCl. The formed precipitate was filtered off, washed with water, and dried to

afford **26** in 75% yield. ^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 5.21 (s, 2H), 7.28 (d, $J = 4.1$ Hz, 1H), 7.48 (s, 1H), 7.52 (d, $J = 4.1$ Hz, 1H), 7.82 (d, $J = 7.8$ Hz, 2H), 7.92 (d, $J = 7.8$ Hz, 2H), 10.28 (s, 1H), 12.75 (br. s, 2H). LC/MS *m*/*z* 345 (M + 1).

4-(5,7-Dioxo-4,5-dihydro-7*H*-thieno[2′,3′:4,5]pyrrolo-[1,2-*a*]pyrazin-6-yl)benzoic Acid 27. Acid **26** (10 g, 30 mmol) was heated at reflux in Dowtherm (150 mL) for 48 h under N_2 atmosphere to accomplish the conversion into **27** (control by TLC, eluent $CHCl_3$−CH_3OH 1:1). The precipitate was filtered off and washed from Dowtherm by 5-fold refluxing in EtOH, followed by washing with hexane to afford pure acid **27** (4.74 g, 50%). ^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 5.34 (s, 2H), 7.27 (d, $J = 4.1$ Hz, 1H), 7.36 (s, 1H), 7.42 (d, $J = 7.9$ Hz, 2H), 7.70 (d, $J = 4.1$ Hz, 1H), 8.04 (d, $J = 7.9$ Hz, 2H), 10.28 (s, 1H), 12.90 (br. s, 1H). LC/MS *m*/*z* 327 (M + 1).

General Procedure for Synthesis of *N*-Benzyl-4-(5,7-dioxo-4,5-dihydro-7*H*-thieno[2′,3′:4,5]pyrrolo[1,2-*a*]pyrazin-6-yl)benzamides 28{*1*−*7*}. The procedure is similar to that described above for 4*H*-thieno[3,2-*b*]pyrrolo-5-carboxamides **6**{*1*−*309*}. The yields of products **28**{*1*−*7*} were 50−80%.

***N*-Benzyl-4-(5,7-dioxo-4,5-dihydro-7*H*-thieno[2′,3′:4,5]-pyrrolo[1,2-*a*]pyrazin-6-yl)benzamide 28{*1*}.** Yield 55%. ^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 4.52 (d, $J = 5.8$ Hz, 2H), 5.30 (s, 2H), 7.15−35 (m, 9H), 7.52 (d, $J = 4.0$ Hz, 1H), 8.00 (d, $J = 7.8$ Hz, 2H), 8.95 (t, $J = 5.8$ Hz, 1H). LC/MS *m*/*z* 416 (M + 1).

***N*-(4-Methoxybenzyl)-4-(5,7-dioxo-4,5-dihydro-7*H*-thieno-[2′,3′:4,5]pyrrolo[1,2-*a*]pyrazin-6-yl)benzamide 28{*6*}.** Yield 75%. ^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 3.76 (s, 3H), 4.42 (d, $J = 5.7$ Hz, 2H), 5.30 (s, 2H), 6.83 (d, $J = 8.1$ Hz, 2H), 7.24−7.54 (m, 3H), 7.28 (s, 1H), 7.35 (d, $J = 8.1$ Hz, 2H), 7.59 (d, $J = 4.0$ Hz, 1H), 7.98 (d, $J = 7.9$ Hz, 2H), 8.92 (t, $J = 5.7$ Hz, 1H). LC/MS *m*/*z* 446 (M^{1+}).

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Supporting Information Available. ^{1}H NMR spectra of synthesized compounds from libraries **3**, **6**, **8**, **11**, **16**, **23**, **25**, **28**, and structures of alkylating agents **2**{*1*−*106*} and amines **5**{*1*−*192*} evaluated in this work. This material is available free of charge via the Internet at http://pubs.acs.org.

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