Synthesis of Thieno[2,3-d]pyrimidin-2-ylmethanamine Combinatorial Library with Four Diversity Points

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The parallel solution-phase synthesis of more than 230 substituted thieno[2,3-d]pyrimidin-2-ylmethanamines has been accomplished. This strategy is based on the cyclization of 2-aminothiophen-3-carboxylates with chloroacetonitrile to construct the thieno[2,3-d]pyrimidine core with two diversity points. Derivatization of the active chlorine and functionalization of C-4 position of the pyrimidine ring allow the introduction of other diversity points. The products containing ester groups at the 6-position of the thieno[2,3-d]pyrimidine were used in amide synthesis. Simple manual techniques for parallel reactions, coupled with simple purification procedures, gave highly pure final products. The scope and limitations of the approach are discussed.

Introduction

Solution-phase combinatorial techniques, in relation to the high demand for new drugs, are attracting the growing interest of chemists.[1] Among the broad range of templates, heterocyclic scaffolds represent the most promising molecules as leading structures for the discovery of novel synthetic drugs.[2] In particular, thienopyrimidine derivatives have been the focus of great interest because of their remarkable biological properties.[3] For example, some 2-alkoxy- and 2-alkyl-subsituted thienopyrimidinones show significant antifungal and antibacterial activities,[3a−d] whereas others exhibit good anticonvulsant and angiotensin II or H_1 receptor antagonistic activities.[3e−h] It is therefore surprising that thienopyrimidines containing four diversity points have not received more attention in combinatorial chemistry; only few library syntheses of these compounds have been carried out.[4]

The subject of our interest was the synthesis of the library of compounds based on the thienopyrimidines core coupled via the 2-position of the aromatic ring with an additional basic amine center through methylene link. To the best of our knowledge, compounds of such type are described only in a few patents.[5] The compounds, phosphodiesterase V inhibitors, are reported as agents for the treatment of erectile dysfunction (Figure 1).[5a,b]

Results and Discussion

Derivatives **3**, the products of the cyclocondensation of 2-aminothiophen-3-carboxylates **1** with chloroacetonitrile **2** (Scheme 1),[6] were chosen for the creation of a library. These key intermediates have two diversity points. It should be noted that a relatively poor diversity of substituents in the positions 2 and 3 is compensated by a wide choice of substituents in positions 4 and 6. In the case of the key compound **3**(*7*), the ester function was used for preparation of amides and that also increased the chemical diversity of the library.

For the creation of the 3-d diversity point via nucleophilic displacement of the chlorine atom, a set of secondary dialkylamines with low molecular weight was chosen (Scheme 2). In this case, when an excess of the corresponding amine **4** is used, the reaction proceeds readily and cleanly in DMF solution at 100 °C (water bath) affording compounds **5** in high yields. By treatment with an excess of $POCl_3$, pyrimidones **5** were transformed into chloropyrimidines **6** which were active toward nucleophiles. As the reaction runs cleanly in nearly quantitative yields, it allowed us to use compounds **6** for further conversions without purification. At this stage, primary amines were excluded because the corresponding compounds **5** (which were formed with good homogeneity in high yields), after treatment with $POCl_3$, gave complicated mixtures caused by the presence of the active chlorine atom and nucleophilic center in the molecule. Arylalkylamines were not used because their reaction with **3** proceeded in low yields, and the corresponding compounds **5**, in the most cases, required chromatographical purification.

Another approach was used to obtain the compounds containing the same amino substituent in the 4-position of the cycle and at the C(6)-Me group. Compounds **3** can be converted into compounds **7** by treatment with $POCl_3$.[7] They can be used further without additional purification, and treatment with amines in DMF at 50 °C in the presence of DIPEA as a base affords compounds **8** in high yields (Scheme 2).

Compounds **6**, obtained by us, are the starting materials for the synthesis of the final compounds of the library. The

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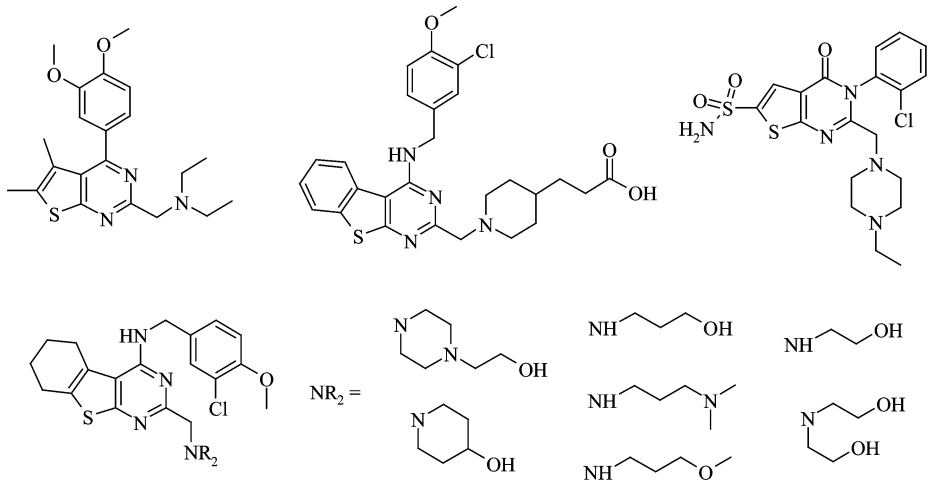
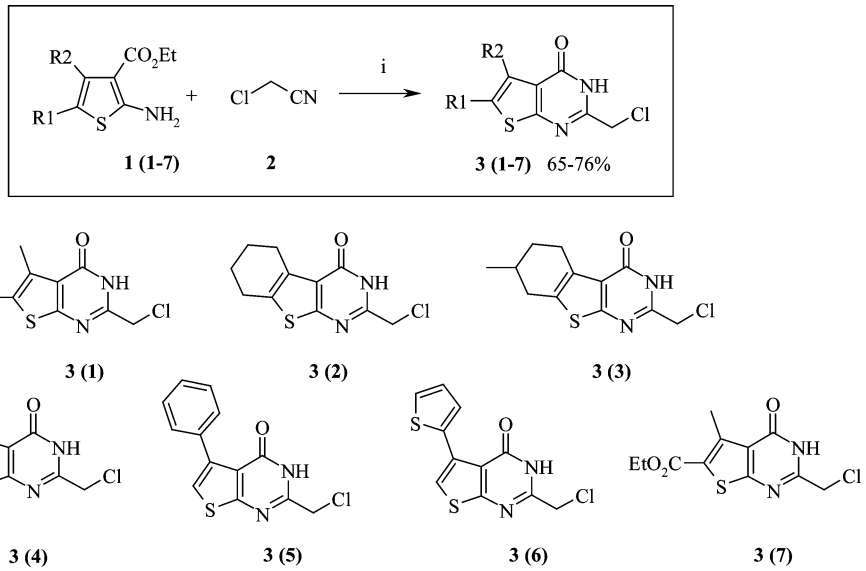


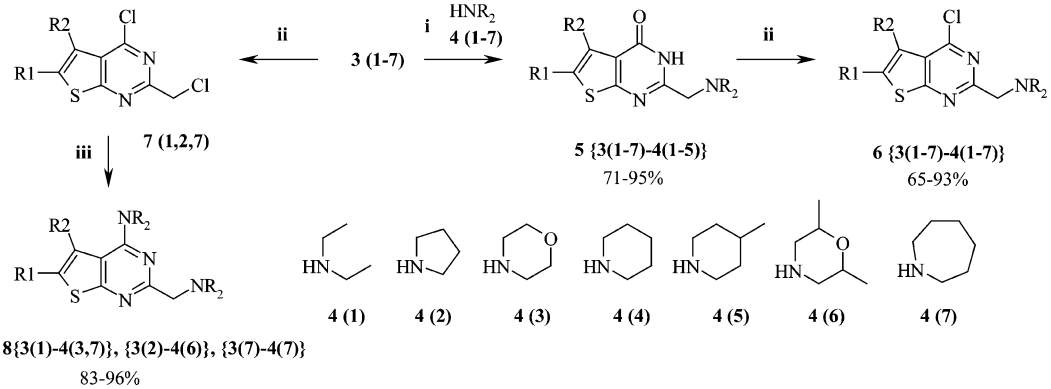
Figure 1. Examples of biologically active thieno[2,3-d]pyrimidin-2-ylmethanamines.

Scheme 1[a]



[a] Reagents and conditions: (i) dry HCl, dioxane, 2 h at room temp, then 2 h at reflux.

Scheme 2[a]



[a] Reagents and conditions: (i) 2.4 equiv **4**, DMF, 100 °C, 4 h; (ii) $POCl_3$, reflux, 4 h; (iii) 2.4 equiv **4**, 2.4 equiv DIPEA, DMF, 50 °C, 6 h.

replacement of the chlorine atom in the 4-position with different *N*-, *S*-, and *O*-nucleophiles is used in the last stage. Because of the wide set of reagents used on this step, the 4-th diversity points have the largest chemical variability. Chloropyrimidines **6** easily react with aliphatic amines **9**(*1*−*83*), hydrazines **9**(*84*,*85*), hydroxylamines **9**(*86*) (Figure 2), anilines **10** (Figure 3), phenols **11** (Figure 4), thioles **13**, and NH-acidic heterocycles **14** (Figure 5) in DMF at 100 °C (water bath) in the presence of DIPEA as a base, affording the corresponding final compounds **15**−**17**, **19**, and **20** in high yields with good homogeneity. In the synthesis of **17**, K_2CO_3 in the presence of 10 mol % TRIDENT (tris[2-(2-methoxyethoxy)ethyl]amine)[8] was used instead of DIPEA, and this system gave better results. The synthesis of **18**

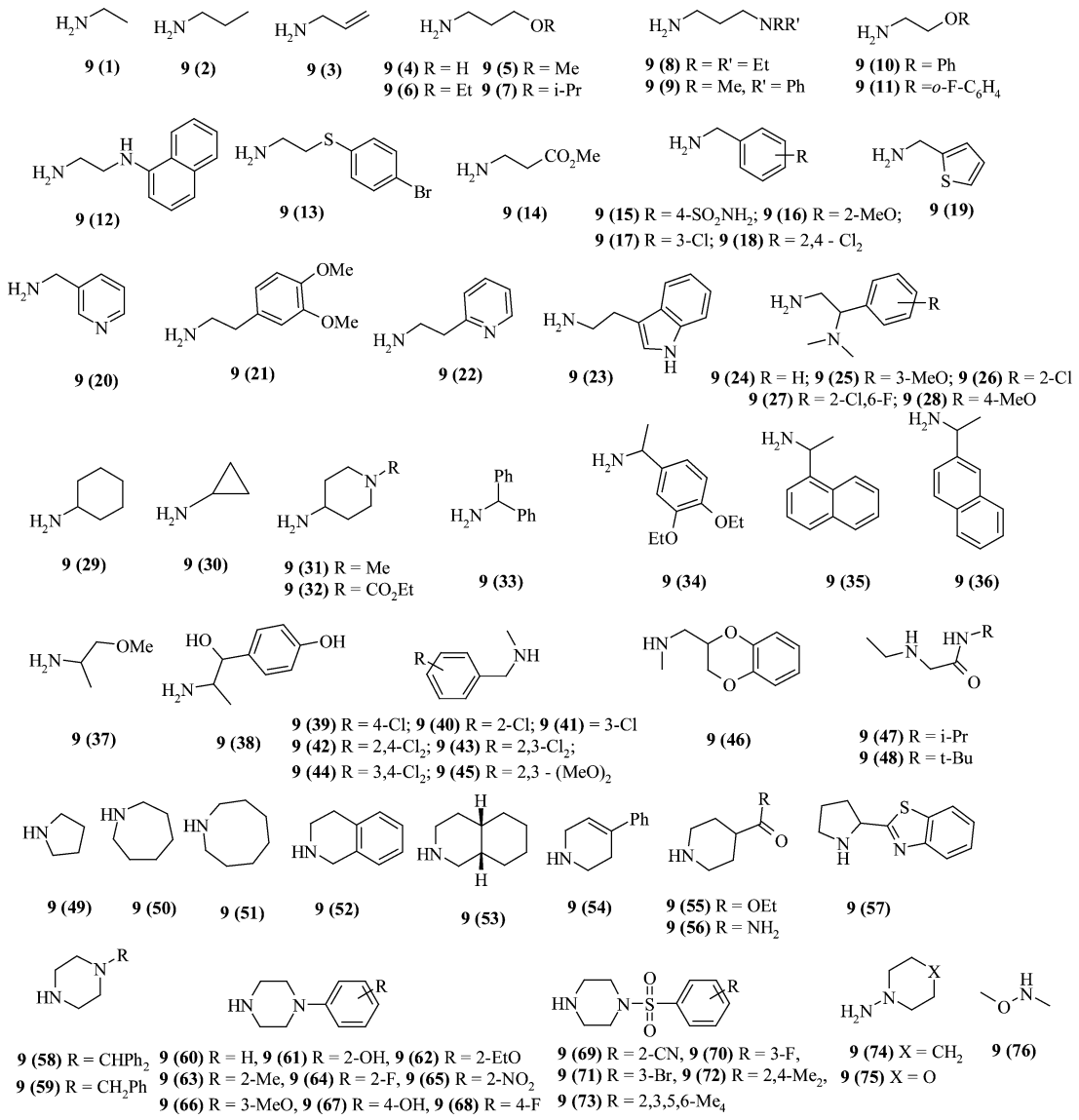


Figure 2. Alkylamines, hydrazines, and hydroxylamines **9**.

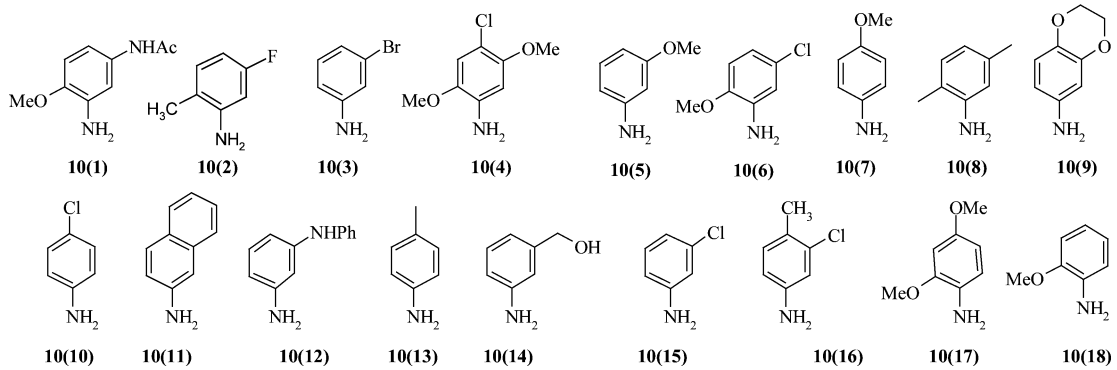


Figure 3. Anilines **10**.

required more drastic conditions: in this case, we used DMSO as a solvent and KOH as a base (Scheme 3). The limitations encountered during the development of the methodology are summarized in Table 1.

The yields of compounds **15**−**20** are in the range of 60−80%. In most cases, their purity, measured by LCMS, was higher than 95% without any additional purification. If the purity was lower than 95%, the compound was recrystallized from an appropriate solvent, usually from MeOH or MeCN.

In the course of the work, intermediate thieno[2,3-d]-pyrimidines **5** {**3**(*7*)−**4**(*3*−*4*)} having ester groups at the 6 position were used for the synthesis of an amide library. Intermediates **5** {**3**(*7*)−**4**(*3*−*4*)} were transformed into the corresponding acids via hydrolysis with NaOH in *i*-PrOH−H_2O in ∼75% yields (Scheme 4 and Figure 6). The amide coupling was performed by modified Mukayama's method using 2-chloro-1-methylpyridinium iodide as a condensing agent.[9] The referred procedure for amide coupling using

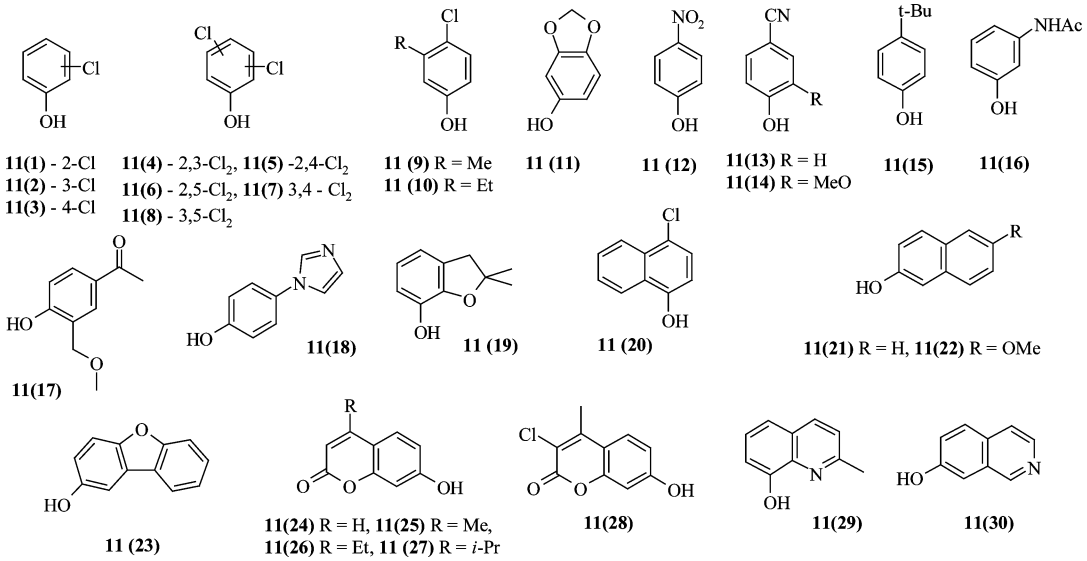


Figure 4. Phenols **11**.

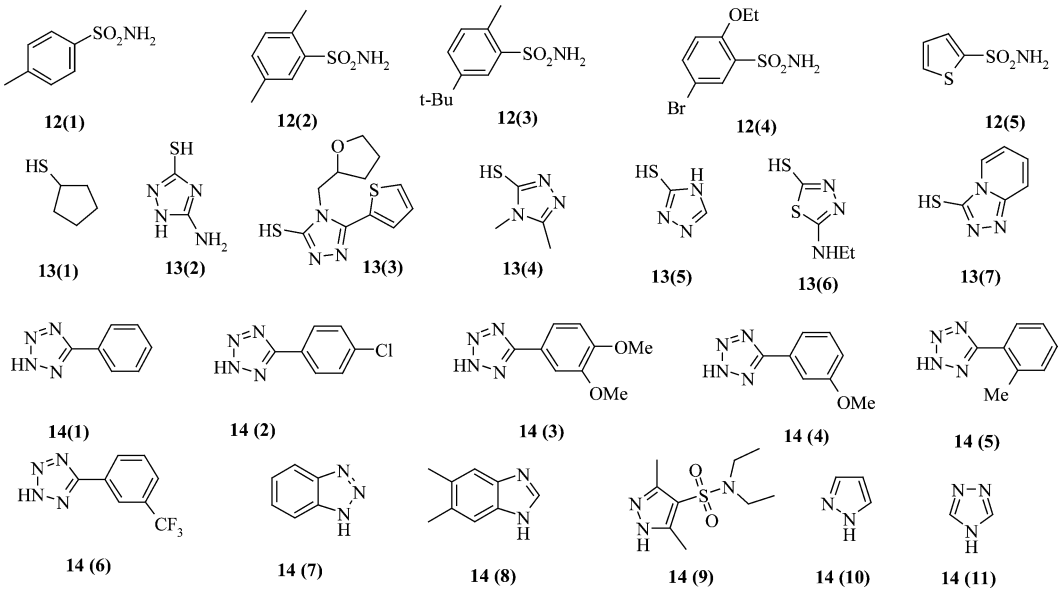


Figure 5. Sulfamides **12**, thioles **13**, and NH-heterocycles **14**.

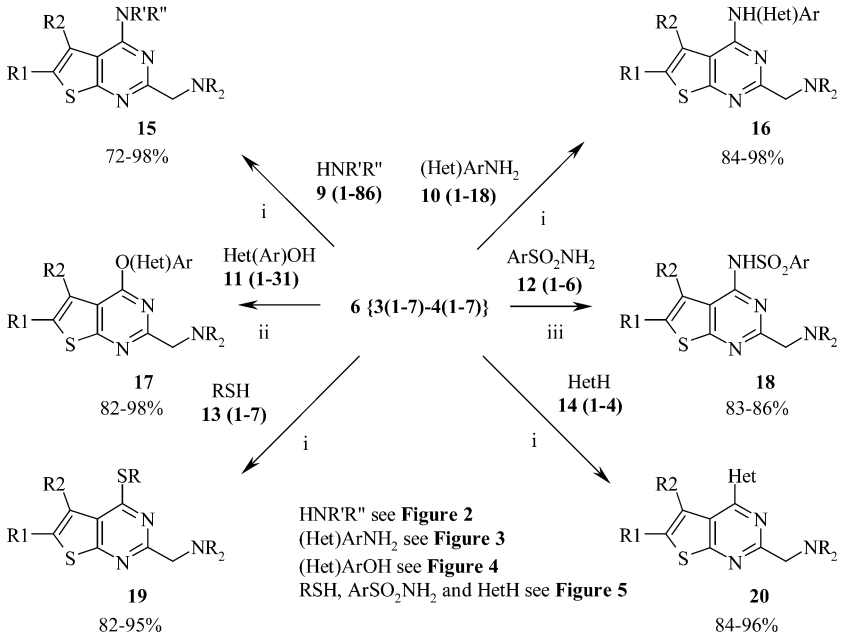
2-chloro-1-methylpyridinium iodide in our case was found to be inconvenient for parallel synthesis because of necessity of extraction procedures and the exact order of the addition of the reagents. We optimized the reaction conditions and separation procedure for parallel synthesis. In our case, we used MeCN at 100 °C in a pressure tube, and all components were added in one portion. After completion of the reaction, the mixture was treated with water, and the corresponding amides were precipitated, then filtered, and washed with small quantities of methanol. In most of cases the yields of final amides were more than 70%. The homogeneity of crude products was in the range of 80−90% before washing with solvent or crystallization.

Established criteria such as Lipinsky rule of 5[10] and Veber's rule[11] were used for the druglikeness analysis of the synthesized library. A number of calculated ADME parameters, for example, water solubility (log *S*), predicted apparent Caco-2 cell permeability (Caco2), predicted logarithm of the brain/blood partition coefficient (log BB), and predicted CNS activity were used. (The calculation of ADME parameters was performed using LigPrep/QikProp from Schrodinger's package). The results are as follows: 95% of the synthesized compounds comply with 3 of 4 criteria of Lipinsky Rule of 5; 99% of the compounds meet the requirements of Veber's rule: tPSA (topological polar surface area) does not exceed 150 Å;[2] the number of rotating bonds is not higher than 10; 86% of the compounds have moderate water solubility (log ≥ −6). The Caco2 value for 90% of the compounds exceeds 100 nm/s; 56% of the compounds show high CNS activity and moderate values of permeability for brain/blood barrier (log BB in the range of −3 to 1). Moreover, 35% of library representatives comply with leadlikeness.[12] Thus, the above data prove that the library contains a high percentage of druglike compounds and can be used as a useful source of potential drugs.

Conclusion

Finally, an efficient approach to thieno[2,3-d]pyrimidin-2-ylmethanamine libraries was developed by means of combinatorial synthesis in solution. In the majority of cases,

Scheme 3[a]



[a] Reagents and conditions: (i) 1.2 equiv DIPEA, DMF, 100 °C, 2−4 h (HPLC MS monitoring); (ii) 2 equiv K_2CO_3, DMF, 100 °C, 2−4 h (HPLC MS monitoring); (iii) 1 equiv KOH, DMSO, 80 °C, 4 h.

the corresponding libraries were generated with low level of impurities using crystallization from the reaction mixtures. Product yields varied according to the reactant structure, but predominantly, the target products were obtained in high yields. The scope and limitations of the approach are discussed.

Experimental Section

General Information. All chemicals were obtained from commercially available sources and used without further purification (Aldrich, Fluka, Enamine Ltd). All solvents for the reactions (DMF, MeCN, DMSO, dioxane) were freshly distilled and dried by standard methods; monitoring of the water concentration in solvents (all solvents had <0.05%, usually 0.02% of water) was performed using Mettler Toledo DL31 KF titrator. All solvents for the crystallizations were used as acquired. Freshly prepared, according to literature method, 2-chloro-1-methylpyridinium iodide[9] was used. Polymer scavenger PL-SO_3H resin was purchased from Polymer Laboratories (A Varian, Inc. Company).

Melting points were measured with a Buchi melting point apparatus and are uncorrected. The ^1H NMR spectra were recorded on a Bruker Avance drx 500 using DMSO-d_6 as a solvent and TMS as an internal standard. LC/MS spectra were recorded using chromatography/mass spectrometric system consisting of high-performance liquid chromatograph Agilent 1100 Series equipped with diode-matrix and mass-selective detector Agilent LCMSD SL. The parameters of chromatography−mass analysis: column, Zorbax SB-C18, 1.8 μm, 4.6 × 15 mm; eluent A, MeCN−water with 0.1% of TFA (95:5) and B, water with 0.1% of TFA; flow rate, 3 mL s^{-1}; volume of the injected sample, 1 μl; UV detectors operate, 215, 254, and 265 nm; ionization method, chemical ionization under atmospheric pressure (APCI); ionization mode, simultaneous scanning of positive and negative ions in the mass range of 80−1000 *mz*. According to HPLC/MS data, all the synthesized compounds have purity over 95%.

General Procedure for Synthesis of 2-(Chloromethyl)-thieno[2,3-*d*]pyrimidin-4(3*H*)-ones 3(*1*−*7*). HCl was bubbled through a stirred mixture of 2-amino-3-carbethoxythiophene (0.2 mol) and chloroacetonitrile (0.25 mol) in dioxane (200 mL) for 2 h at room temperature followed by 2 h reflux. After it was cooled, the reaction mixture was diluted with water. The product was filtered and recrystallized from DMF.

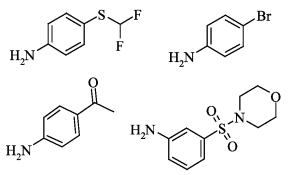
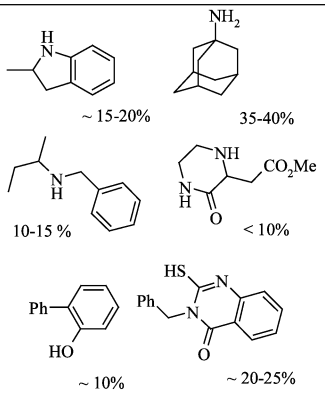
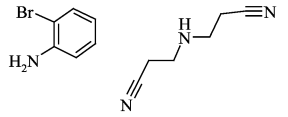
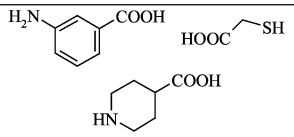
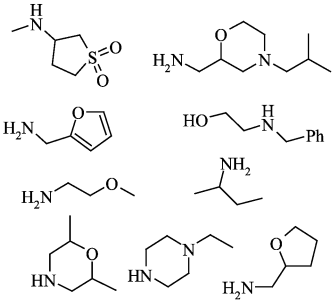
General Procedure for Synthesis of 2-(*N*,*N*-Dialkylamino)thieno[2,3-*d*]pyrimidin-4(3*H*)-ones 5(*1*−*7*). A mixture of compound **3** (0.1 mol) and the corresponding amine **4** (0.24 mol) in DMF (150 mL) was refluxed at 100 °C for 4 h. After it was cooled, the reaction mixture was poured into water. The precipitate formed was filtered and recrystallizated from DMF.

General Procedure for Synthesis of *N*-[(4-Chlorothieno-[2,3-*d*]pyrimidin-2-yl)methyl]-*N*,*N*-dialkylamines 6. A mixture of compound **5** (0.05 mol) and $POCl_3$ (30 mL) was refluxed for 4 h. The excess of $POCl_3$ was evaporated in vacuum, and the residue was added to a mixture of ice (100 g) and K_2CO_3 (10 g). The precipitate was filtered and recrystallyzed from *i*-PrOH or from a toluene−hexane mixture.

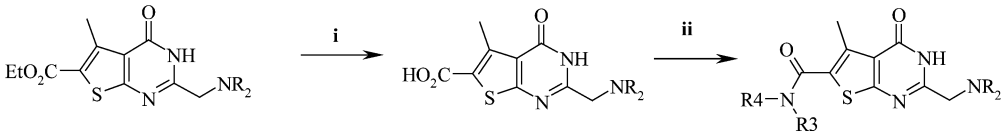
General Procedure for Synthesis of 4-Chloro-2-(chloromethyl)thieno[2,3-*d*]pyrimidines 7. Compounds **7** were prepared from compounds **3** using the above procedure for compounds **6**.

General Procedure for Synthesis of 2-[(*N*,*N*-Dialkylamino)methyl]-*N*,*N*- dialkylaminothieno[2,3-*d*]pyrimidin-4-amines 8. A mixture of compound **7** (0.50 mmol), aliphatic amine **4** (1.20 mmol), and DIPEA (0.2 mL, 1.20 mmol) in DMF (2 mL) was heated at 50−60 °C for 6 h in an 8 mL pressure tube. The reaction mixture was diluted with water

Table 1. Limitations of the Procedure for Obtaining Compounds **15**−**20** from 4-chlorothieno[2,3-d]pyrimidines **6** and *N*-, *S*-, *O*-nucleophiles **9**−**14**

Entry	Nucleophile	Results	Comments
1		The yields (conversions) of target products using general procedure are 40-60%, the purification procedure needs chromatographical separation.	Under more drastic conditions such as higher temperature (> 110 ^{0}C starting compounds **6** decomposed under the reaction conditions) or longer reaction time yields of the target products remain almost the same, but side processes lead to various by-products. The reason is lower nucleophilicity of anilines.
2		The yields of target products using general procedure are 10-40%, the purification procedure of crude products (impurities – starting compounds) requires chromatographical separation.	Under more drastic conditions such as higher temperature (> 110 ^{0}C starting compounds **6** decomposed under the reaction conditions) or longer reaction time yields of the target products remain almost the same, but side processes lead to various by-products. The reason is steric hindrance of reaction centers.
3		The yields of target products using general procedure are 10-15%.	The concurrent action of lower nucleophilicity and steric hindrance.
4		The major products are the corresponding acid esters.	The reaction proceeds non-chemoselectively and the compound bearing a free acid function can not be used
5		The yields of crude targeted products using general procedure are > 90%, homogeneity > 85%. The purification to homogeneity > 95% requires original approach to each compound (the chromatography or polymer scavengers, such as SO_3H Resin can be used).	Final products have good solubility in water. Their solubility in organic solvents is comparable with the one of starting compounds and impurities.

Scheme 4[a]



5 {3(7)-4(2-4)}

R3 and R4 see **Figure 6**

21 {3(7)-4(2-4)}

70-76%

23 {3(7)-4(2-4)-25(1-10)}

82-91%

[a] Reagents and conditions: (i) 2 equiv NaOH, *i*-PrOH−H_2O, reflux, 2 h; **(ii)** HNR_3R_4, 1.2 equiv 2-chloro-1-methylpyridinium iodide, 2.44 equiv DIPEA, MeCN, 100 °C, pressure tube, 4 h.

(5 mL). The precipitate formed was filtered, washed with water (4 mL) and an *i*-PrOH−water mixture (1:1, 4 mL), and dried.

General Procedure for Synthesis of 2-[(*N*,*N*-Dialkylamino)methyl]-thieno[2,3-*d*]pyrimidin-4-amines 15. A mixture of compound **6** (0.60 mmol), the corresponding amine **9** (0.66 mmol) (Figure 2), and DIPEA (0.2 mL, 0.68 mmol) in DMF (2 mL) was heated at 100 °C for 4 h in an 8 mL pressure tube. The reaction mixture was diluted with water (5 mL). The precipitate formed was filtered, washed with water (4 mL) and an *i*-PrOH−water mixture (1:1, 4 mL), and dried.

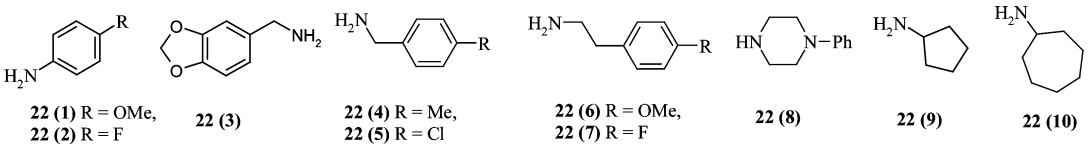


Figure 6. Amines **22**.

General Procedure for Synthesis of 2-[(*N*,*N*-Dialkylamino)methyl]-*N*-arylthieno[2,3-*d*]pyrimidin-4-amines 16. Compounds **16** were prepared from compounds **6** and anilines **10** (Figure 3) using the above procedure for compounds **15**.

General Procedure for Synthesis of *N*,*N*-Dialkyl-*N*-[(4-aryloxythieno[2,3-*d*]pyrimidin-2-yl)methyl]amines 17. A mixture of **6** (0.60 mmol), the corresponding phenol (0.62 mmol), K_2CO_3 (160 mg, 1.2 mmol), and TRIDENT (11 mg, 0.06 mmol) in DMF (2 mL) was heated at 100 °C for 6 h in an 8 mL pressure tube. The reaction mixture was diluted with water (5 mL). The precipitate formed was filtered, washed with water (4 mL) and a *i*-PrOH−water mixture (1:1, 4 mL), and dried.

General Procedure for Synthesis of *N*-{2-[(Dialkylamino)methyl]thieno[2,3-*d*]pyrimidin-4-yl}arenesulfonamides 18. A mixture of compound **4** (0.6 mmol), sulfamide (0.62 mmol), and powdered KOH (0.66 mmol) in DMSO (2 mL) was stirred at 50−60 °C for 4 h. The reaction mixture was diluted with water (5 mL) and acidified with AcOH; the precipitate was filtered, washed subsequently with water (4 mL) and a *i*-PrOH−water mixture (1:1, 4 mL), and dried.

General Procedure for Synthesis of 2-[(Dialkylamino)-methyl]thieno[2,3-*d*]pyrimidine-4-thiols 19. Compounds **19** were prepared from compounds **6** and thiols **13** (Figure 5) using the above procedure for compounds **15**.

General Procedure for Synthesis of *N*-{[4-(Azol-*N*-yl)-thieno[2,3-*d*]pyrimidin-2-yl]methyl}-*N*,*N*-dialkylamines 20. A mixture of **6** (0.60 mmol), the corresponding NH-heterocycle **14** (0.62 mmol), K_2CO_3 (160 mg, 1.2 mmol), and TRIDENT (11 mg, 0.06 mmol) in DMF (2 mL) was heated at 100 °C for 6 h in an 8 mL pressure tube. After it was cooled, the reaction mixture was diluted with water. The precipitated solid was collected and recrystallized from a mixture of *i*-PrOH−DMF.

General Procedure for Synthesis of 2-[(Dialkylamino)-methyl]-5-methyl-4-oxo-3,4-dihydrothieno[2,3-*d*]pyrimidine-6-carboxylic Acids 22. A solution of NaOH (0.1 mol) in water (20 mL) was added to a suspension of substance **3** {**3**(*6*),**4**(*3*)} (0.05 mol) in *i*-PrOH (200 mL); the mixture obtained was stirred at reflux for 2 h. The solvents were evaporated in vacuum; the residue was dissolved in water (150 mL). The solution was filtered, and the filtrate was neutralized with HCl (30% aq. solution); the precipitate was filtered and recrystallized from water.

General Procedure for Synthesis of Amides of 2-[(Dialkylamino)methyl]-5-methyl-4-oxo-3,4-dihydrothieno-[2,3-*d*]pyrimidine-6-carboxylic Acids 23. A mixture of acid **6** or **7** (0.60 mmol), amine **10**{*1*−*20*} (0.62 mmol), DIPEA (1.2 mmol), 1-methyl-2-chloropyridinium iodide (0.84 mmol), and MeCN (2 mL) was stirred at 100 °C for 1 h. The reaction mixture was diluted with 5% Na_2CO_3 solution (5 mL). The precipitate formed was filtered, washed with water and MeOH, and dried.

Supporting Information Available. Characterization data (including ^{1}H and ^{13}C NMR spectra, HPLC APCI MS data, yields, and melting points) for all compounds obtained and library characterization histograms. This material is available free of charge via the Internet at http://pubs.acs.org.

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