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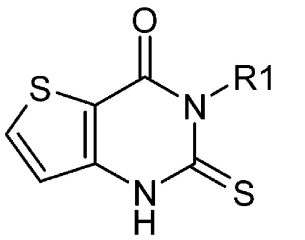

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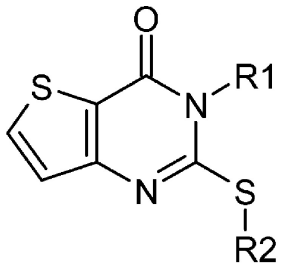

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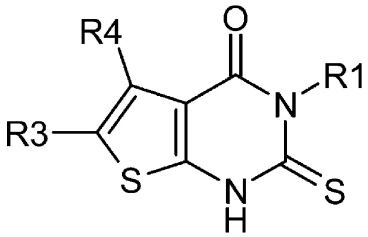

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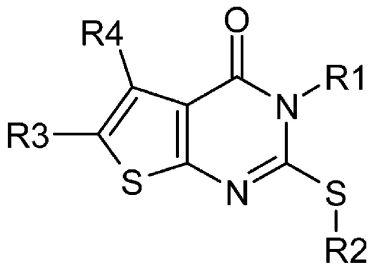

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Synthesis of Substituted Thienopyrimidine-4-ones

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The parallel solution-phase synthesis of more than 3000 substituted thienopyrimidin-4-ones has been accomplished. Key reactions include assembly of the 2-thioxopyrimidin-4-one ring by condensation of isomeric aminothiophenecarboxylates or their appropriate reactive derivatives (isothiocyanates or dithiocarbamates) with the corresponding isothiocyanates or amines. The libraries from libraries were then obtained in good yields and purities using solution-phase alkylation and acylation methodologies. Simple manual techniques for parallel reactions using special CombiSyn synthesizers were coupled with easy purification procedures (crystallization from the reaction mixtures) to give high-purity final products. The scope and limitations of the developed approach are discussed.

Introduction

Solution-phase combinatorial techniques in relation with 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 lead structures for the discovery of novel synthetic drugs.[2] In particular, substituted thienopyrimidin-4-ones, present in the core of many physiologically active agents, display interesting therapeutic properties. Such compounds have been shown to inhibit several enzymes as well as to modulate the activity of many receptors.[3,4] Thus, substituted thieno[3,2-*d*]pyrimidin-4(3*H*)-ones were described as anticoccidial,[3a] neuroprotective,[3b] anxiolytic,[3c] antihypertensive,[3d] and fungicidal[3e] agents. The isomeric thieno[2,3-*d*]pyrimidin-4(3*H*)-one scaffold is common to numerous bioactive compounds which include various antihyperlipaemic,[4a] bronchodilator,[4b] anxiolytic,[4c] antiischemic,[4d] and antiarthritic[4e] agents. The S[2]-alkylated thieno[2,3-*d*]pyrimidin-4(3*H*)-ones were reported as promising antidepressants.[5]

These recent examples highlight the level of ongoing interest toward new thienopyrimidin-4-one derivatives and have prompted us to explore this pharmacophoric scaffold in a combinatorial format as a promising source of bioactive molecules. This scaffold is perfectly suited for combinatorial library generation because it has a rigid core that possesses up to four sites for the incorporation of diversity. We are exploring a systematic approach to the parallel solution-phase synthesis and characterization of combinatorial libraries of 2-thioxo-2,3-dihydrothieno[3,2-*d*]pyrimidin-4(3*H*)-ones **A1**, 2-thioxo-2,3-dihydrothieno[2,3-*d*]pyrimidin-4(3*H*)-ones **B1**, and their *S*-alkyl derivatives **A2** and **B2** (Figure 1), using readily available starting materials. Reported herein are our continuing studies of the synthesis and characterization of fused pyrimidine libraries.[6]

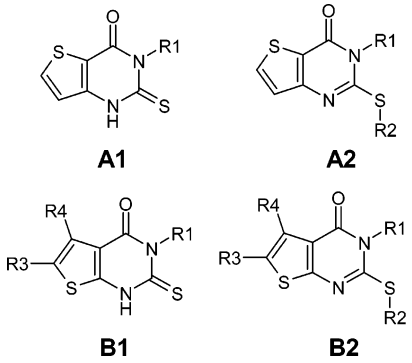

Figure 1. Combinatorial libraries of 2-thioxo-2,3-dihydrothieno-[3,2-*d*]pyrimidin-4(3*H*)-ones **A1**, 2-thioxo-2,3-dihydrothieno[2,3-*d*]pyrimidin-4(3*H*)-ones **B1** and their *S*-alkyl derivatives **A2** and **B2** synthesized in this work.

The methods of synthesis of substituted 2-thioxo-2,3-dihydrothienopyrimidin-4-ones have previously been described.[7] Usually, they include the condensation of substituted 2-aminothiophen-3-carboxylates or 3-aminothiophen-2-carboxylates with alkyl or aryl isothiocyanates yielding the corresponding thienylthioureas which cyclize to form 3-substituted thieno[2,3-*d*]- or thieno[3,2-*d*]pyrimidin-4-one-2-thiones. The preparation of the corresponding S-alkylated derivatives using reaction of 2-thioxo-2,3-dihydrothienopyrimidines with alkyl halides was also reported;[8] however, to the best of our knowledge, combinatorial approaches to these scaffolds have not been reported before.

Results and Discussion

Recently, we described two alternative synthetic procedures for the solution-phase parallel synthesis of substituted 4-oxo-2-thioxo-1,2,3,4-tetrahydroquinazolines.[6a] The first approach was based on the reaction of methyl anthranilates with isothiocyanates. The reaction led to 2-thioxoquinazoline-

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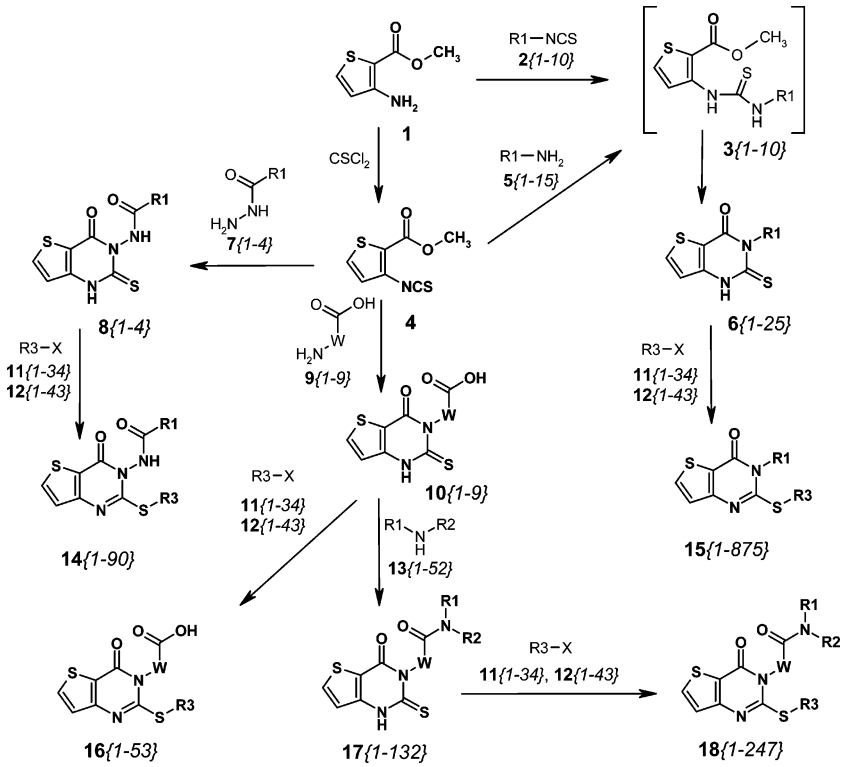
Scheme 1. Preparation of Substituted 2-Thioxo-2,3-dihydrothieno[3,2-*d*]pyrimidin-4(3*H*)-ones and 2,3-Dihydrothieno[3,2-*d*]pyrimidin-4(3*H*)-on-2-thiols



4-ones in good yields (45−90%) via the N,N′-disubstituted thiourea intermediates. The second approach involved reaction of initial 2-(methoxycarbonyl)phenylisothiocyanates with a variety of aliphatic and aromatic amines, amino acids, hydrazines, hydrazides, sulfohydrazides, or thiosemicarbazides, which smoothly afforded the target 2-thioxoquinazoline-4-ones in high yields. Both approaches had specific limitations related to the availability of the starting isothiocyanates or decreased reactivity of reactants with some particular substituents. In general, the second strategy proved to be more versatile and convenient for the solution-phase combinatorial synthesis of diverse 2-thioxoquinazoline-4-ones.

In this work, we explored the similar strategies to the substituted 2-thioxothienopyrimidin-4-ones (Scheme 1). The starting isothiocyanates **2**{*1*−*10*} were prepared from the corresponding amines by a thiophosgene method as previously reported.[9] The N,N′-disubstituted thiourea intermediates **3**{*1*−*10*} were generated through a reaction of isothiocyanates **2**{*1*−*10*} with carboxylate **1** in 2-propanol in the presence of triethylamine. The thienylthioureas **3**{*1*−*10*} were then cyclized in situ to give the corresponding 3-substituted thieno[3,2-*d*]pyrimidin-4(3*H*)-one-2-thiones **6**{*1*−*10*} in 60−70% yields from **1**. The satisfactory yields in this reaction were achieved only with the use of arylisothiocyanates shown in Table 1. In the case of aliphatic compounds, even a prolonged reaction under increased temperature led to the desired products in poor-to-moderate yields (10−30%). Similar results were obtained when we used arylisothiocyanates possessing an ortho substituent or a strong electron-withdrawing group, such as NO_2.

We first chose library **6** as a synthetic target to test the second approach. The requisite 2-methoxycarbonylthiophene-3-isothiocyanate **4** was prepared from commercially available 2-methoxycarbonyl-3-aminothiophene **1** by treatment with thiophosgene, as reported.[9] Further condensation of this reactive intermediate **4** with various primary amines **5**{*1*−*15*} (Table 2) in a mixture of 2-propanol and 5% aqueous KOH under reflux smoothly afforded **6**{*11*−*25*} in good yields (65−75%), regardless of the nature of the amine. Encouraged by the success of this sequence, we then applied it to the synthesis of libraries **8**{*1*−*4*}, **10**{*1*−*9*}, and their related amide and *S*-alkyl derivatives. Thus, conversion of isothiocyanate **4** to *N*-carboxamides **8**{*1*−*4*} was achieved in good yields (75−85%) through condensation with the corresponding hydrazides **7**{*1*−*4*} (Table 3) in a mixture of 2-propanol and triethylamine under reflux. Alternatively, compounds **10**{*1*−*9*} were prepared in high yields from **4** and the corresponding amino acids **9**{*1*−*9*} (Table 4) in a mixture of 2-propanol and triethylamine at 90 °C. Library **10**{*1*−*9*} contains compounds with a bridge-connected carboxylate moiety, which can be used for further diversification of this combinatorial set. Reaction of acids **10**{*1*−*9*} (via their reactive imidazolide intermediates) with

Table 1. Arylisothiocyanates R−NCS **2**{*1*−*10*}

entry	compound	R
1	**2**{*1*}	2-methylphenyl
2	**2**{*2*}	2-methoxycarbonylphenyl
3	**2**{*3*}	3-fluorophenyl
4	**2**{*4*}	4-ethylphenyl
5	**2**{*5*}	4-ethoxyphenyl
6	**2**{*6*}	2,3-dimethylphenyl
7	**2**{*7*}	3,4-dimethylphenyl
8	**2**{*8*}	3,4-dichlorophenyl
9	**2**{*9*}	3-fluoro-4-methylphenyl
10	**2**{*10*}	4-ethoxycarbonylphenyl

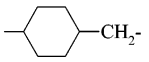
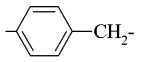
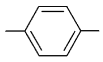
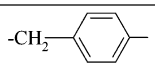
Table 2. Primary Amines R−NH_2 **5**{*1*−*15*}

entry	compound	R
1	**5**{*1*}	ethyl
2	**5**{*2*}	1-butyl
3	**5**{*3*}	2-butyl
4	**5**{*4*}	3-isopropyloxypropyl
5	**5**{*5*}	furfuryl
6	**5**{*6*}	benzyl
7	**5**{*7*}	4-methylbenzyl
8	**5**{*8*}	4-methoxybenzyl
9	**5**{*9*}	4-fluorobenzyl
10	**5**{*10*}	3,4-dimethoxybenzyl
11	**5**{*11*}	1,3-benzodioxol-5-ylmethyl
12	**5**{*12*}	2-(1-pyrrolidinyl)ethyl
13	**5**{*13*}	3-cyclohexylpropyl
14	**5**{*14*}	3-(1-piperidinyl)propyl
15	**5**{*15*}	3-[4-(4-methoxyphenyl)piperazin-1-yl]propyl

Table 3. Acyl Hydrazides R−$CONHNH_2$ **7**{*1*−*4*}

entry	compound	R
1	**7**{*1*}	phenyl
2	**7**{*2*}	3-methoxyphenyl
3	**7**{*3*}	3-bromophenyl
4	**7**{*4*}	2-bromophenyloxymethyl

Table 4. Amino Acids H_2N-W-COOH **9**{*1*−*9*}

entry	compound	W
1	**9**{*1*}	-CH_2-
2	**9**{*2*}	-$(CH_2)_2$-
3	**9**{*3*}	-$(CH_2)_3$-
4	**9**{*4*}	-$(CH_2)_4$-
5	**9**{*5*}	-$(CH_2)_5$-
6	**9**{*6*}	
7	**9**{*7*}	
8	**9**{*8*}	
9	**9**{*9*}	

various amines **13**{*1*−*52*} (Table 5) smoothly led to the expected amides **17**{*1*−*132*} in good yields (80−90%). It is worth noting that libraries **8**{*1*−*4*} and **10**{*1*−*9*} cannot be obtained by reaction of 2-methoxycarbonyl-3-aminothiophene **1** with the corresponding isothiocyanates because of synthetic inaccessibility of the latters.

All the obtained 3-substituted 2-thioxo-2,3-dihydrothieno-[3,2-*d*]pyrimidin-4(3*H*)-ones could be easily converted in high yields (70−90%) to the corresponding *S*-alkyl derivatives using conventional treatment with alkyl halides **11**{*1*−*28*}, α-chloroketones **11**{*29*−*34*} (Table 6), and α-halocarboxamides **12**{*1*−*43*} (Table 7) in DMF in the presence of triethylamine at 60 °C. The resulting combinatorial libraries **14**{*1*−*90*}, **15**{*1*−*875*}, **16**{*1*−*53*}, and

Table 5. Amines **13**{*1*−*52*}

Primary Amines R−NH_2		
entry	compound	R
1	**13**{*1*}	allyl
2	**13**{*2*}	1-butyl
3	**13**{*3*}	2-butyl
4	**13**{*4*}	1-pentyl
5	**13**{*5*}	1-(2-ethyl)hexyl
6	**13**{*6*}	2-methoxyethyl
7	**13**{*7*}	3-methoxypropyl
8	**13**{*8*}	2,2-dimethoxyethyl
9	**13**{*9*}	2-acetylaminoethyl
10	**13**{*10*}	cyclopropyl
11	**13**{*11*}	cyclopentyl
12	**13**{*12*}	cyclohexyl
13	**13**{*13*}	2-methylcyclohex-1-yl
14	**13**{*14*}	2,3-dimethylcyclohex-1-yl
15	**13**{*15*}	1-benzylpiperidin-1-yl
16	**13**{*16*}	tetrahydrofurfuryl
17	**13**{*17*}	benzyl
18	**13**{*18*}	1-phenylethyl
19	**13**{*19*}	4-methylbenzyl
20	**13**{*20*}	4-methoxybenzyl
21	**13**{*21*}	4-chlorobenzyl
22	**13**{*22*}	3-methoxybenzyl
23	**13**{*23*}	3-chlorobenzyl
24	**13**{*24*}	2-methoxybenzyl
25	**13**{*25*}	2-fluoroxybenzyl
26	**13**{*26*}	2-chloroxybenzyl
27	**13**{*27*}	1,3-benzodioxol-5-yl
28	**13**{*28*}	furfuryl
29	**13**{*29*}	pyridin-2-ylmethyl
30	**13**{*30*}	pyridin-3-ylmethyl
31	**13**{*31*}	2-(cyclohexen-1-yl)ethyl
32	**13**{*32*}	2-phenylethyl
33	**13**{*33*}	2-(4-methylphenyl)ethyl
34	**13**{*34*}	2-(4-chlorophenyl)ethyl
35	**13**{*35*}	2-(4-sulfamoylphenyl)ethyl
36	**13**{*36*}	2-(3,4-dimethoxyphenyl)ethyl
37	**13**{*37*}	3-(*N*-phenyl-*N*-ethylamino)propyl
38	**13**{*38*}	3-(2-oxopyrrolidin-1-yl)propyl
39	**13**{*39*}	phenyl
40	**13**{*40*}	4-fluorophenyl
41	**13**{*41*}	4-methoxyphenyl
42	**13**{*42*}	4-ethoxyphenyl
43	**13**{*43*}	3-methylphenyl
44	**13**{*44*}	3,4-dimethylphenyl
45	**13**{*45*}	indan-5-yl
46	**13**{*46*}	1,3-benzodioxol-5-yl
47	**13**{*47*}	1,4-benzodioxan-6-yl
Secondary Amines R1R2NH		
48	**13**{*48*}	pyrrolidin
49	**13**{*49*}	piperidin
50	**13**{*50*}	1,2,3,4-tetrahydroisoquinolin
51	**13**{*51*}	1-ethoxycarbonylpiperazin
52	**13**{*52*}	1-phenylpiperazin

18{*1*−*247*} include over 1200 novel 2,3-disubstituted thieno-[3,2-*d*]pyrimidin-4(3*H*)-on-2-thiols.

For illustration, 22 arbitrary compounds synthesized according to Scheme 1 are shown in Figure 2.

In the second part of our study, we explored synthetic pathways to combinatorial libraries of substituted 2-thioxo-2,3-dihydrothieno[2,3-*d*]pyrimidin-4(3*H*)-ones and their *S*-alkyl derivatives. The Gewald thiophene synthesis[10] allows for a convenient synthetic approach to 2-aminothiophene-3-carboxylates, which were used as starting materials to prepare the final thieno[2,3-*d*]pyrimidin-4-ones. The requisite aminothiophenes **20**{*1*−*11*} (Table 8) were synthesized from

Table 6. Alkyl Halides and α-Chloroketones R−CH_2Cl **11**{*1*−*34*}

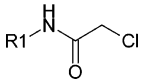
entry	compound	R
1	**11**{*1*}	cyano
2	**11**{*2*}	phenyl
3	**11**{*3*}	4-methylphenyl
4	**11**{*4*}	4-*tert*-butylphenyl
5	**11**{*5*}	4-fluorophenyl
6	**11**{*6*}	4-chlorophenyl
7	**11**{*7*}	4-trifluoromethoxyphenyl
8	**11**{*8*}	4-nitrophenyl
9	**11**{*9*}	3-methylphenyl
10	**11**{*10*}	3-fluorophenyl
11	**11**{*11*}	3-chlorophenyl
12	**11**{*12*}	3-bromophenyl
13	**11**{*13*}	3-nitrophenyl
14	**11**{*14*}	2-methylphenyl
15	**11**{*15*}	2-fluorophenyl
16	**11**{*16*}	2-chlorophenyl
17	**11**{*17*}	2-cyanophenyl
18	**11**{*18*}	2,5-dimethylphenyl
19	**11**{*19*}	2,6-difluorophenyl
20	**11**{*20*}	2-fluoro-6-chlorophenyl
21	**11**{*21*}	2,5-difluorophenyl
22	**11**{*22*}	2-methoxy-5-acetylphenyl
23	**11**{*23*}	6-fluoro-1,4-benzodioxan-5-yl
24	**11**{*24*}	4-ethoxycarbonyl-5-fluoro-1,4-benzodioxan-5-yl
25	**11**{*25*}	5-chlorobenzothien-3-yl
26	**11**{*26*}	4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl
27	**11**{*27*}	4-oxo-6-chloro-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl
28	**11**{*28*}	4-oxo-6-bromo-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl
29	**11**{*29*}	*tert*-butanoyl
30	**11**{*30*}	benzoyl
31	**11**{*31*}	4-fluorobenzoyl
32	**11**{*32*}	4-chlorobenzoyl
33	**11**{*33*}	4-bromobenzoyl
34	**11**{*34*}	3,4-dichlorobenzoyl

the appropriate ketone **19**{*1*−*11*}, sulfur, and ethyl cyanoacetate in the presence of an organic base by an one-pot thiolation/heterocyclization reaction (Scheme 2).[10a]

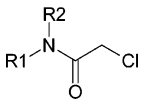
To our surprise, all our attempts to achieve cyclocondensation of **20**{*1*−*11*} with isothiocyanates or obtain the corresponding thiophene-2-isothiocyanates in a manner analogous to synthesis of compound **4** failed or had only limited success. In all these cases, low yields of the desired products and difficulties with their purification make these pathways impractical in this combinatorial synthesis strategy. Probably, in this case, the S atom of the thiophene ring interferes with the reactivity of the 2-amino group. On the other hand, the treatment with thiophosgene appears to be incompatible with most of substituents in the thiophene ring.

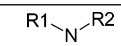
Therefore, we directed our effort to find a more suitable intermediate that could be used to generate any of the target compounds. Our preparation of this family of compounds took the following route (Scheme 2). 2-Aminothiophen-3-carboxylates **20**{*1*−*11*} (Table 8) were treated with CS_2 and dimethyl sulfate in the presence of aqueous NaOH, as previously reported.[11] The reaction proceeded smoothly and afforded thiophene dithiocarbamates **21**{*1*−*11*} in good yields (73−87%). This conversion route is compatible with many different 5- and 6-substituents of the thiophene ring, thus allowing for synthesis of a large number of reactive intermediates **21**{*1*−*11*} starting from a variety of easily accessible 2-aminothiophen-3-carboxylates **20**{*1*−*11*}. These intermediates appeared to be successful coupling partners for a variety of primary aliphatic amines, such as those shown

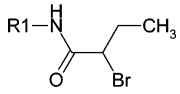
Table 7. α-Halocarboxamides **12**{*1*−*43*}



entry	compound	R1
1	**12**{*1*}	1-butyl
2	**12**{*2*}	2-butyl
3	**12**{*3*}	1-(3-methyl)butyl
4	**12**{*4*}	3-pentyl
5	**12**{*5*}	4-heptyl
6	**12**{*6*}	3-methoxypropyl
7	**12**{*7*}	cyclopentyl
8	**12**{*8*}	cyclohexyl
9	**12**{*9*}	2-(cyclohexen-1-yl)ethyl
10	**12**{*10*}	2-phenylethyl
11	**12**{*11*}	2-(3,4-dimethoxyphenyl)ethyl
12	**12**{*12*}	2-(4-sulfamoylphenyl)ethyl
13	**12**{*13*}	tetrahydrofurfuryl
14	**12**{*14*}	benzyl
15	**12**{*15*}	4-methylbenzyl
16	**12**{*16*}	2-methoxyphenyl
17	**12**{*17*}	furfuryl
18	**12**{*18*}	pyridin-3-ylmethyl
19	**12**{*19*}	4-ethylphenyl
20	**12**{*20*}	4-isopropylphenyl
21	**12**{*21*}	4-fluorophenyl
22	**12**{*22*}	4-methoxyphenyl
23	**12**{*23*}	4-ethoxyphenyl
24	**12**{*24*}	4-ethoxycarbonylphenyl
25	**12**{*25*}	4-dimethylaminophenyl
26	**12**{*26*}	2-truifluoromethylphenyl
27	**12**{*27*}	2-ethoxycarbonlyphenyl
28	**12**{*28*}	3-methoxyphenyl
29	**12**{*29*}	1,3-benzodioxol-5-yl
30	**12**{*30*}	isozazol-3-yl
31	**12**{*31*}	thiazol-2-yl



entry	compound	
32	**12**{*32*}	*N*,*N*-diethylamino
33	**12**{*33*}	pyrrolidin-1-yl
34	**12**{*34*}	4-methyl-pyrrolidin-1-yl
35	**12**{*35*}	4-phenyl-pyrrolidin-1-yl
36	**12**{*36*}	4-(2-methoxyphenyl)pyrrolidin-1-yl
37	**12**{*37*}	*N*-ethyl-*N*-(3-methylphenyl)amino



entry	compound	R1
38	**12**{*308*	4-chlorophenyl
39	**12**{*39*}	4-ethoxycarbonylphenyl
40	**12**{*40*}	4-chloro-2-methylphenyl
41	**12**{*41*}	1,3-benzodioxol-5-yl
42	**12**{*42*}	isoxazol-3-yl
43	**12**{*43*}	thiazol-2-yl

in Table 2. Their reaction in DMF under reflux yielded the desired 3-substituted 2-thioxothieno[2,3-*d*]pyrimidin-4(3*H*)-ones **22**{*1*−*90*} in 50−65% yields. However, the intermediates **21**{*1*−*11*} were unable to react with aromatic amines, amino acids, or acid hydrazides, probably because of reduced nucleophilicity of the latter. As in the case of 2-thioxo[3,2-*d*]pyrimidin-4(3*H*)-ones, thiones **22**{*1*−*90*} could be efficiently alkylated with the corresponding alkyl halides and

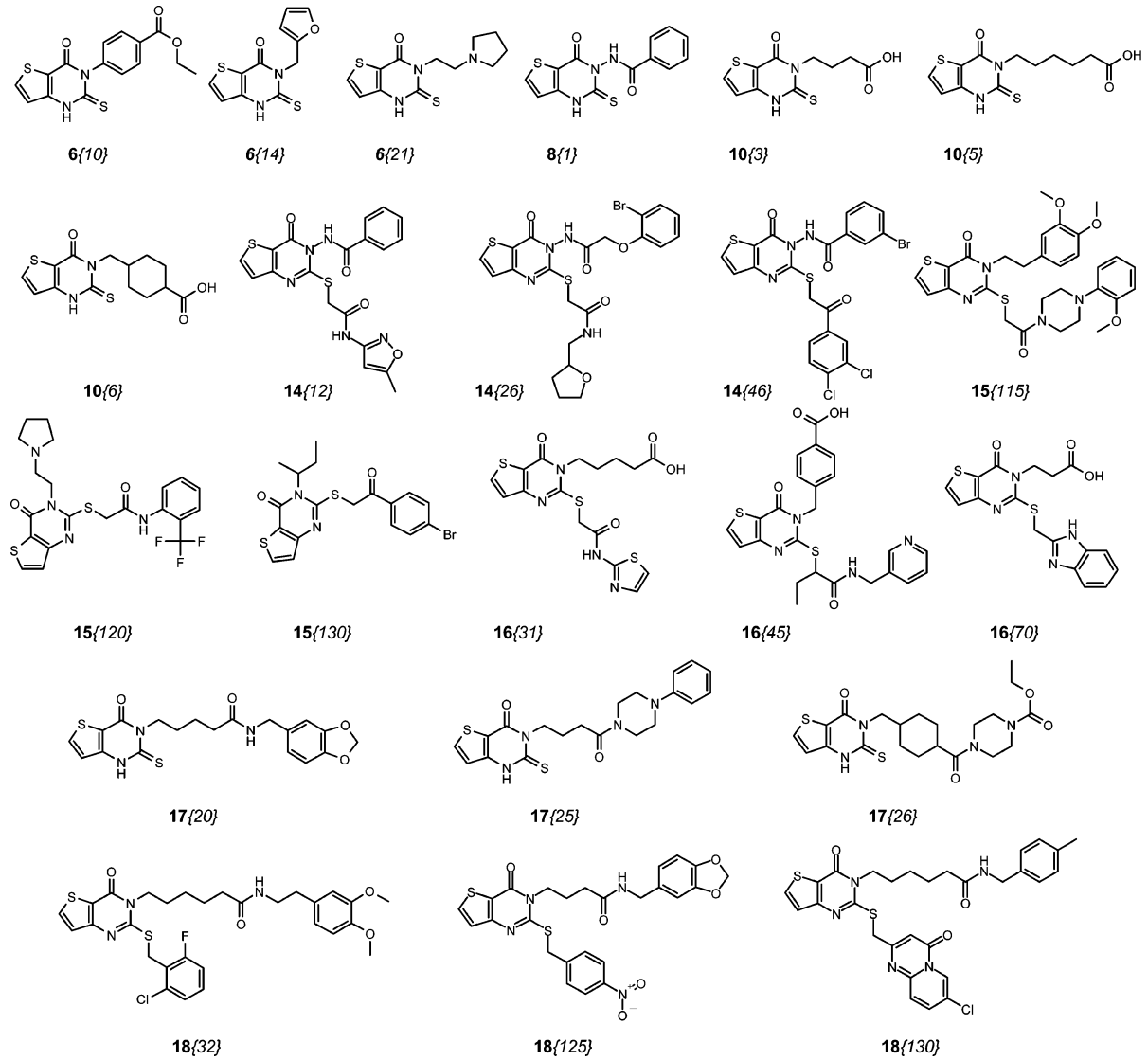


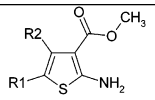
Figure 2. Examples of thieno[3,2-*d*]pyrimidin-4(3*H*)-ones of general formula **A1** and **A2** synthesized in this work.

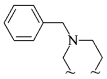
α-chloroketones **11**{*1*−*34*} (Table 6) and α-halocarboxamides **12**{*1*−*43*} (Table 7) in DMF and triethylamine at 60 °C to afford *S*-alkyl derivatives **23**{*1*−*470*} in high yields (70−90%). Examples of compounds from libraries **22**{*1*−*90*} and **23**{*1*−*470*} are shown in Figure 3.

If we compare the combinatorial libraries having general formula **A1**, **A2** and **B1**, **B2** corresponding to two different isomeric forms of the thienopyrimidine scaffold, we can observe some distinctive features of our synthetic strategy used in this work. Thus, up to three centers of molecular diversity can be identified for the obtained thieno[3,2-*d*]-pyrimidin-4-ones: the substituent at the N^3 nitrogen, the alkyl group at S-2, and the amide substituents on the bridge-connected carboxylate moiety. Molecular diversity of the thieno[2,3-*d*]pyrimidin-4-ones is even higher: four diversity points corresponding to the substituents at the atoms S-2, N^3, C^5, and C^6 are present. The described synthetic routes provide considerable diversity of substituents in positions 2 and 3 of the thieno[3,2-*d*]pyrimidine core **A1**, **A2**, whereas C^6 and C^7 of the thiophene ring remain unsubstituted. An opposite situation is observed in the case of the thieno[2,3-*d*]pyrimidine scaffolds **B1**, **B2**: a relatively poor diversity of substituents in positions 2 and 3 is compensated by a wide choice of substituents in positions 5 and 6. This imbalance is due to the aforementioned different availability and nonequivalent reactivity of the starting isomeric 2-aminothiophen-3-carboxylates and 3-aminothiophen-2-carboxylates. This fact should be taken into consideration while planning the combinatorial synthesis of these libraries for biological screening: an asymmetric substituent pattern can lead to a distinctly different enzyme/receptor binding mode of these closely related bioisosteric forms of thienopyrimidine scaffold.

All thienopyrimidin-4-ones within these two series were characterized by ^{1}H NMR and LC/MS analysis. The ^{1}H NMR spectra were clean, and mass spectral data obtained on an LC/MS instrument were also satisfactory. The thiophene protons H6 and H7 in thieno[3,2-*d*]pyrimidine structures **A1** are sometimes concealed by other signals, but usually clearly observed as douplets in the range of δ 8.10−8.20 ppm (H6) and 6.98−7.02 ppm (H7) for N^3-aryl and N^3-alkyl substituted compounds. The same protons have resonances at δ 8.20−8.27 and 7.05−7.09 ppm in the case of N^3-carboxamides. *S*-Alkylation leading to structures **A2** usually causes a

Table 8. 2-Aminothiophen-2-carboxylates **20**{*1*−*11*}



entry	compound	R1	R2
1	**20**{*1*}	methyl	methoxycarbonyl
2	**20**{*2*}	methyl	ethoxycarbonyl
3	**20**{*3*}	methyl	*N,N*-diethylcarbamoyl
4	**20**{*4*}	methyl	1-pyrrolidinecarbonyl
5	**20**{*5*}	methyl	1-piperidinecarbonyl
6	**20**{*6*}	methyl	*N*-(2-trifluoromethylphenyl)carbamoyl
7	**20**{*7*}		
8	**20**{*8*}		
9	**20**{*9*}		
10	**20**{*10*}		
11	**20**{*11*}		

downfield shift of 0.15−0.20 ppm for the H7 signals. The protons of NH fragments in all the obtained 2-thioxothienopyrimidin-4-ones show the singlets at δ 13.2−13.8 ppm. As expected, these signals disappear in the spectra of S-alkylated compounds.

The preparation of such a significant number of compounds required utilization of special laboratory equipment; thus, the described parallel solution-phase reactions were performed using laboratory synthesizers CombiSyn-012−3000[12] (Figure 4), which provide some advanced opportunities for high-throughput solution-phase combinatorial synthesis. All the workup, isolation, purification, and analytical procedures were carried out using a proprietary technology platform, which includes all the equipment required for parallel synthesis of large combinatorial libraries.[13]

Conclusion

An efficient synthetic route was developed for the combinatorial synthesis of thienopyrimidin-4-one libraries in solution. In all of the reactions investigated, the corresponding libraries were generated with low levels of impurities using a simple crystallization from the reaction mixtures. Product yields varied according to the condensation method used and reactant structures, but in most cases, the desired products were obtained in high yields, even using bulky side chain substituents with various functional groups. Biological evaluation of these thienopyrimidin-4-ones is currently in progress with respect to a number of GPCR and protein kinase biotargets and may lead to the design and synthesis of analogues possessing interesting physiological activity. Finally, the results provide further confirmation of the scope and generality of the applied approach to fused pyrimidines: >6000 analogues of these molecules have been made in our laboratories in the past 2 years by parallel synthesis methods.[6]

Experimental Section

General Information. Melting points (°C) were measured with a Koeffler melting point apparatus and are uncorrected. 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 spectrometer in DMSO-d_6 using TMS as an internal standard (chemical shifts in ppm). LC/MS spectra were recorded with 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 used without purification. Methyl 3-aminothiophene-2-carboxylate **1** was purchased from Aldrich. Reagents shown in Tables 1−7 were purchased from Acros Organics, Aldrich, or ChemDiv. 2-Methyloxycarbonylthiophene-3-isothiocyanate **4** was prepared by reaction of thiophosgene with methyl 3-aminothiophene-2-carboxylate.[9] Methyl 2-aminothiophene-3-carboxylates **20**{*1*−*11*} were prepared using the Gewald thiophene synthesis.[10]

The parallel solution-phase syntheses of compounds **14**{*1*−*90*}, **15**{*1*−*875*}, **16**{*1*−*53*}, **17**{*1*−*132*}, **18**{*1*−*247*}, and **23**{*1*−*470*} were accomplished using a laboratory synthesizer CombiSyn-012-3000 on the 50−100-mg scale. The parallel solution-phase syntheses of libraries **6**{*1*−*25*}, **8**{*1*−*4*}, **10**{*1*−*9*}, **20**{*1*−*11*} and **21**{*1*−*11*} were performed using standard laboratory equipment.

General Procedure for the Synthesis of 3-Substituted 2-Thioxo-2,3-dihydrothieno[3,2-*d*]pyrimidin-4(3*H*)-ones 6{*1*−*25*}. 1. Method A. Isothiocyanate **2**{*1*−*10*} (50 mmol) and triethylamine (0.5 mL) were successively added to a solution of 3-aminothiophene-2-carboxylate **1** (50 mmol) in $CHCl_3$ (30 mL). The mixture was heated at reflux for 2−2.5 h, depending on reactivity of the isothiocyanate. The formed precipitate was filtered off from the hot reaction mixture, washed with $CHCl_3$, and dried to afford pure **6**{*1*−*10*} in 60−70% yield. The analytical samples were obtained by crystallization from ethanol/DMF.

2. Method B. Amine **5**{*1*−*15*} (55 mmol) was slowly added to a stirred solution of **4** (50 mmol) in 2-propanol (40 mL). After the addition was completed, the mixture was allowed to cool to room temperature, and 50% KOH (6 mL) was added. The reaction mixture was heated at reflux for 0.5 h. The mixture was cooled to room temperature, poured into water (100 mL), and acidified with acetic acid until neutral pH was reached. The formed precipitate was filtered off and crystallized from ethanol/DMF (1:1) to give pure **6**{*11*−*25*} in 65−75% yields.

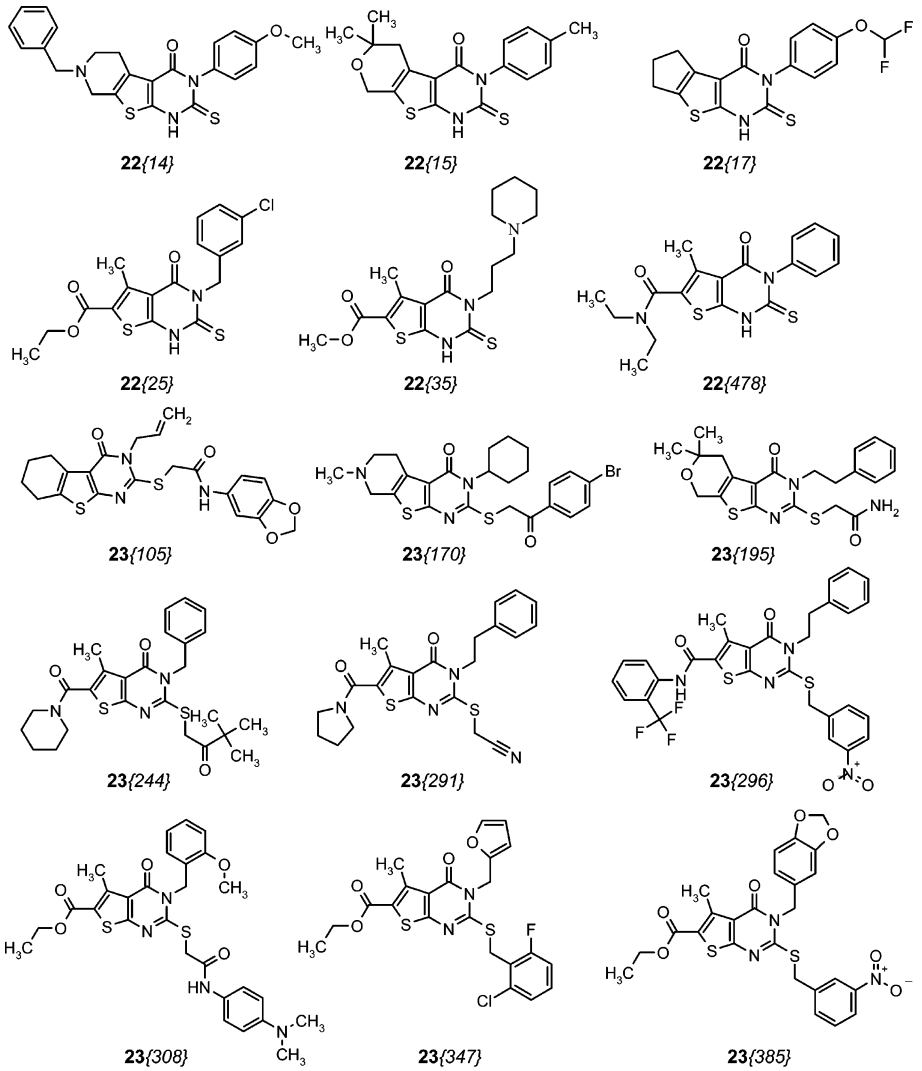
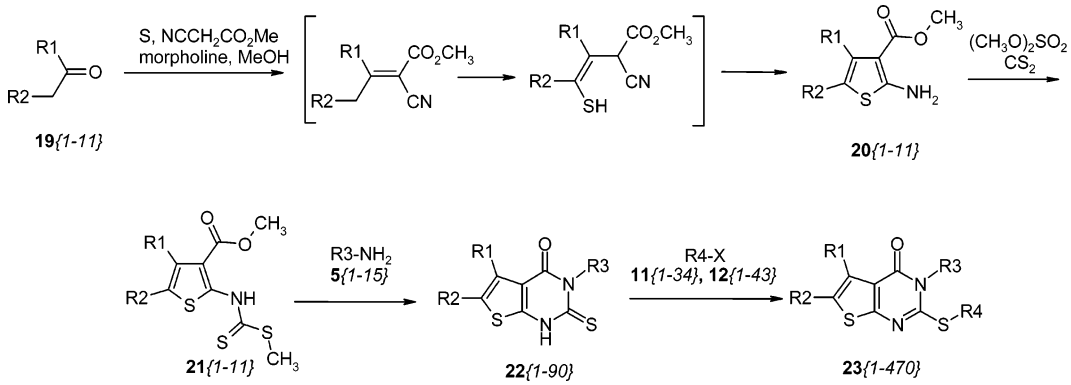


Figure 3. Examples of thieno[2,3-*d*]pyrimidin-4(3*H*)-ones of general formula **B1** and **B2** synthesized in this work.

Scheme 2



3-(4-Ethoxycarbonylphenyl)-2-thioxo-2,3-dihydrothieno-[3,2-*d*]pyrimidin-4(3*H*)-one 6{*10*}. Yield 63%; mp 182 °C; ^{1}H NMR δ: 13.36 (s, 1H), 8.16 (d, J = 7.5 Hz, 1H), 7.59 (d, J = 7.8 Hz, 2H), 7.32 (d, J = 7.8 Hz, 1H), 7.00 (d, J = 7.5 Hz, 2H), 4.36−4.32 (dd, J = 6.7 Hz, 2H), (t, J = 6.7 Hz, 3H).

3-Furfuryl-2-thioxo-2,3-dihydrothieno[3,2-*d*]pyrimidin-4(3*H*)-one 6{*14*}. Yield 75%; mp 174 °C; ^{1}H NMR δ: 13.22 (s, 1H), 7.89 (d, J = 7.5 Hz, 1H), 7.32 (s, 1H), 7.00 (d, J = 7.5 Hz, 1H), 6.33 (s, 1H), 6.28 (s, 1H), 5.61 (s, 2H).

3-(2-Pyrrolidin-1-ylethyl)-2-thioxo-2,3-dihydrothieno-[3,2-*d*]pyrimidin-4(3*H*)-one 6{*21*}. Yield 72%; mp 143 °C; ^{1}H NMR δ: 13.20 (s, 1H), 8.12 (d, J = 7.5 Hz, 1H), 7.00 (d, J = 7.5 Hz, 1H), 4.49 (t, J = 6.4 Hz, 2H), 3,57 (t, J = 6.4 Hz, 2H), 1.92 (t, 4H), 1.02 (q, 4H). LC/MS: *m*/*z* 282 ($M^{+\bullet}$).

General Procedure for the Synthesis of *N*-(4-Oxo-2-thioxo-1,4-dihydrothieno[3,2-*d*]pyrimidin-3(2*H*)-yl)carboxamides 8{*1*−*4*}. Triethylamine (0.5 mL) was added to a stirred solution of **4** (50 mmol) and hydrazide **7**{*1*−*4*} (50

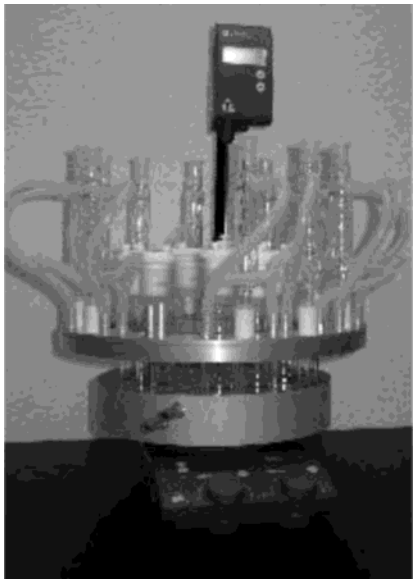


Figure 4. Laboratory synthesizer CombiSyn-012−3000 with 12 reaction units.

mmol) in 2-propanol (30 mL). The mixture was heated at reflux for 2 h and then allowed to cool to room temperature. Water (100 mL) was added, and the formed precipitate was filtered off and crystallized from methanol/DMF (1:1) to give pure **8**{*1*−*4*} in 75−85% yields.

3-Phenylcarboxamido-2-thioxo-2,3-dihydrothieno[3,2-*d*]pyrimidin-4(3*H*)-one 8{***1***}**.** Yield 76%; mp 186 °C; ^{1}H NMR δ: 13.55 (s, 1H), 11.41 (s, 1H), 8.27 (d, J = 7.8 Hz, 2H), 7.95 (d, J = 7.5 Hz, 1H), 7.65−7.53 (m, 3H), 7.08 (d, J = 7.5 Hz, 1H).

3-(3-Methoxyphenyl)carboxamido-2-thioxo-2,3-dihydrothieno[3,2-*d*]pyrimidin-4(3*H*)-one 8{***2***}**.** Yield 74%; mp 218 °C; ^{1}H NMR δ: 11.32 (s, 1H), 8.20 (d, J = 7.8 Hz, 1H), 7.56−7.42 (m, 3H), 7.20 (d, J = 7.8 Hz, 1H), 7.06 (d, J = 7.5 Hz, 1H), 3.82 (s, 3H).

3-(3-Bromophenyl)carboxamido-2-thioxo-2,3-dihydrothieno[3,2-*d*]pyrimidin-4(3*H*)-one 8{***3***}**.** Yield 80%; mp 235 °C; ^{1}H NMR δ: 11.51 (s, 1H), 8.22 (d, 1 J = 7.5 Hz, H), 8.13 (s, 1H), 7.92 (d, J = 7.8 Hz, 1H), 7.85 (d, J = 7.8 Hz, 1H), 7.52 (t, J = 7.8 Hz, 1H), 7.09 (d, J = 7.5 Hz, 1H).

General Procedure for the Synthesis of 2-Thioxo-2,3-dihydrothieno[3,2-*d*]pyrimidin-4(3*H*)-ones 10{***1***−***9***}**.** A mixture of amino acid **9**{*1*−*9*} (50 mmol) and triethylamine (60 mmol) in a minimal volume of water (2−3 mL) was added to a stirred solution of **4** (50 mmol) in 2-propanol (30 mL). The mixture was heated at 90 °C for 1.5−2 h. The hot reaction mixture was diluted with water (40 mL) and then acidified with acetic acid until neutral pH was reached. After the mixture was cooled to room temperature, the formed precipitate was filtered off and crystallized from ethanol/DMF (1:1) to give pure **10**{*1*−*9*} in 85−90% yields.

3-(3-Carboxypropyl)-2-thioxo-2,3-dihydrothieno[3,2-*d*]-pyrimidin-4(3*H*)-one 10{***3***}**.** Yield 87%; mp 238 °C; ^{1}H NMR δ: 12.08 (s, 1H), 8.15 (d, J = 7.5 Hz, 1H), 7.00 (d, J = 7.5 Hz, 1H), 4.41 (t, J = 6.5 Hz, 2H), 2.29 (t, J = 6.5 Hz, 2H), 1.93 (q, J = 6.5 Hz, 2H).

3-(5-Carboxypentyl)-2-thioxo-2,3-dihydrothieno[3,2-*d*]-pyrimidin-4(3*H*)-one 10{***5***}**.** Yield 84%; mp 201 °C; ^{1}H NMR δ: 13.14 (s, 1H), 11.62 (s, 1H), 7.83 (d, J = 7.5 Hz, 1H), 7.00 (d, J = 7.5 Hz, 1H), 4.38 (t, J = 6.5 Hz, 2H), 2.20 (t, J = 6.5 Hz, 2H), 1.69−1.58 (m, 4H), 1.39 (q, J = 6.5 Hz, 2H). LC/MS: m/z 299 ($M^{+\bullet}$).

3-(4-Carboxycyclohexylmethyl)-2-thioxo-2,3-dihydrothieno[3,2-*d*]pyrimidin-4(3*H*)-one 10{***6***}**.** Yield 87%; mp 287 °C; ^{1}H NMR δ: 13.38 (s, 1H), 12.02 (s, 1H), 8.14 (d, J = 7.5 Hz, 1H), 7.00 (d, J = 7.5 Hz, 1H), 4.21 (d, J = 6.4 Hz, 2H), 2.14−1.89 (m, 4H), 1.62−1.60 (d, J = 6.4 Hz, 2H), 1.25−1.04 (m, 4H). LC/MS: m/z 325 ($M^{+\bullet}$).

General Procedure for the Synthesis of 2-Thioxo-2,3-dihydrothieno[3,2-*d*]pyrimidin-4(3*H*)-ones 17{***1***−***132***}**.** A mixture of acid **10**{*1*−*9*} (1 mmol) and 1,1′-carbonyldiimidazole (1.1 mmol) in anhydrous 1,4-dioxane (20 mL) was heated at 70 °C for 3 h. Amine **13**{*1*−*52*} was added, and the mixture was heated for an additional 2 h (at 70 °C for alkylamines, at reflux for arylamines). The hot reaction mixture was poured into water (100 mL) and acidified with acetic acid until neutral pH was reached. The formed precipitate was filtered off and crystallized from 2-propanol/DMF (3:1) to give pure **17**{*1*−*132*} in 80−90% yields.

3-[5-(1,3-Benzodioxol-5-ylmethylcarbamoyl)pentyl]-2-thioxo-2,3-dihydrothieno[3,2-*d*]pyrimidin-4(3*H*)-one 17{***20***}**.** Yield 85%; mp 173 °C; ^{1}H NMR δ: 13.38 (s, 1H), 8.22 (t, J = 6.7 Hz, 1H), 8.13 (d, J = 7.5 Hz, 1H), 7.00 (d, J = 7.5 Hz, 1H), 6.81 (d, J = 7.6 Hz, 1H), 6.78 (s, 1H), 6.64 (d, J = 7.6 Hz, 1H), 5.97 (s, 2H), 4.18 (t, J = 6.5 Hz, 2H), 4.06 (d, J = 6.7 Hz, 2H), 2.08 (t, J = 6.5 Hz, 2H), 1.68−1.52 (m, 4H). LC/MS: m/z 418 ($M^{+\bullet}$).

3-[4-Oxo-4-(4-phenylpiperazin-1-yl)butyl]-2-thioxo-2,3-dihydrothieno[3,2-*d*]pyrimidin-4(*3H*)-one 17{***25***}**.** Yield 80%; mp 157 °C; ^{1}H NMR δ: 13.07 (s, 1H), 8.05 (d, J = 7.5 Hz, 1H), 7.17 (d, J = 7.8 Hz, 2H), 7.00 (d, J = 7.5 Hz, 1H), 6.81 (d, J = 7.8 Hz, 2H), 6.78 (t, J = 7.8 Hz, 1H), 4.22 (t, J = 6.7 Hz, 2H), 3.27 (t, J = 6.8 Hz, 4H), 3.07 (t, J = 6.8 Hz, 4H), 2.20 (t, J = 6.7 Hz, 2H), 1.99 (q, J = 6.7 Hz, 2H). LC/MS: m/z 415 ($M^{+\bullet}$).

3-[4-(4-Ethoxycarbonylpiperazin-1-yl)cyclohexylmethyl]-2-thioxo-2,3-dihydrothieno[3,2-*d*]pyrimidin-4(3*H*)-one 17{***26***}**.** Yield 78%; mp 183 °C; ^{1}H NMR δ: 8.11 (d, J = 7.5 Hz, 1H), 7.00 (d, J = 7.5 Hz, 1H), 4.27 (d, J = 6.7 Hz, 2H), 4.04 (dd, J = 6.7 Hz, 2H), 3.45−3.28 (m, 9H), 2.07−1.97 (m, 1H), 1.64−1.58 (m, 4H), 1.33−1.10 (m, 7H). LC/MS: m/z 465 ($M^{+\bullet}$).

General Procedure for the Synthesis of Ethyl-2-{[(methylsulfanyl)carbonothioyl]amino}thiophene-3-carboxylates 21{***1***−***11***}**.** To a stirred solution of **20**{*1*−*11*} (44 mmol) in DMSO (20 mL), CS_2 (9.6 mL) and NaOH (1.8 g) dissolved in water (3 mL) were successively added. The reaction flask was stoppered, and the mixture was stirred at 15−20 °C in a water bath for 15 min. The stopper was removed, and the reaction mixture was stirred at room temperature for 12 h. Methyl iodide (3.5 mL) was slowly added under vigorous stirring, and the resulting mixture was stirred at room temperature for 1 h. Water (100 mL) was added, and the formed precipitate was filtered off and

crystallized from ethanol/DMF (1:1) to give pure **21**{*1*−*11*} in 73−87% yields.

General Procedure for the Synthesis of 2-Thioxo-2,3-dihydrothieno[2,3-*d*]pyrimidin-4(3*H*)-ones 22{*1*−*90*}. A solution of **21**{*1*−*11*} (40 mmol) and primary amine **5**{*1*−*15*} (50 mmol) in DMF (20 mL) was heated at reflux for 2.5 h. After being cooled to room temperature, the mixture was stirred at room temperature for 24 h. Water (100 mL) was added, and the formed precipitate was filtered off and crystallized from 2-propanol/DMF (1:1) to give pure **22**{*1*−*90*} in 50−65% yields.

7-Benzyl-3-(4-methoxyphenyl)-2-thioxo-3,4,5,6,7,8-hexahydropyrido[4′,3′:4,5]thieno[2,3-*d*]pyrimidin-4(3*H*)-one 22{*14*}. Yield 62%; mp 201 °C; ^{1}H NMR δ: 13.40 (s, 1H), 7.40−7.26 (m, 5H), 7.10 (d, J = 7.6 Hz, 2H), 6.97 (d, J = 7.6 Hz, 2H), 3.63 (s, 2H), 3.18 (t, J = 6.7 Hz, 2H), 2.78 (t, J = 6.7 Hz, 2H), 2.53 (s, 2H).

6,6-Dimethyl-3-(4-methylbenzyl)-2-thioxo-2,3,4,5,6,8-hexahydro-3H-pyrano[4′,3′:4,5]thieno[2,3-*d*]pyrimidin-4(3*H*)-one 22{*15*}. Yield 56%; mp 232 °C; ^{1}H NMR δ: 13.60 (s, 1H), 7.27 (d, J = 7.6 Hz, 2H), 7.04 (d, J = 7.6 Hz, 2H), 4.28 (s, 2H), 3.19 (s, 3H), 2.72 (s, 2H), 1.23 (s, 6H). LC/MS: m/z 359 ($M^{+\bullet}$).

3-(4-Difluoromethoxyphenyl)-2-thioxo-2,3,6,7-tetrahydro-5H-cyclopenta[*d*]thieno[2,3-*d*]pyrimidin-4(3*H*)-one 22{*17*}. Yield 59%; mp 236 °C; ^{1}H NMR δ: 13.62 (s, 1H), 7.21 (d, J = 7.6 Hz, 2H), 7.10 (d, J = 7.6 Hz, 2H), 7.04 (t, J = 5.8 Hz, 1H), 2.85 (t, J = 6.7 Hz, 4H), 2.37 (q, J = 6.7 Hz, 2H). LC/MS: m/z 367 ($M^{+\bullet}$).

3-(3-Chlorobenzyl)-5-methyl-6-ethoxycarbonyl-2-thioxo-2,3-dihydrothieno[2,3-*d*]pyrimidin-4(3*H*)-one 22{*25*}. Yield 60%; mp 207 °C; ^{1}H NMR δ: 13.8 (s, 1H), 7.44 (s, 1H), 7.35 (d, J = 7.8 Hz, 1H), 7.27−7.19 (m, 2H), 5.58 (s, 2H), 4.30 (dd, J = 6.8 Hz, 2H), 2.74 (s, 3H), 1.41 (t, J = 6.8 Hz, 3H).

3-(3-Pyrrolidin-1-ylpropyl)-5-methyl-6-methoxycarbonyl-2-thioxo-2,3-dihydrothieno[2,3-*d*]pyrimidin-4(3*H*)-one 22{*35*}. Yield 60%; mp 207 °C; ^{1}H NMR δ: 4.48 (t, J = 6.8 Hz, 2H), 3.74 (s, 3H), 3.00 (t, J = 6.8 Hz, 2H), 2.72 (s, 3H), 2.45, (m, 4H), 2.11 (q, J = 6.8 Hz, 2H), 1.73−1.47 (m, 6H).

3-Phenyl-5-methyl-6-diethylcarbamoyl-2-thioxo-2,3-dihydrothieno[2,3-*d*]pyrimidin-4(3*H*)-one 22{*478*}. Yield 69%; mp 183 °C; ^{1}H NMR δ: 13.70 (s, 1H), 7.54−7.42 (m, 3H), 7.17 (d, J = 7.8 Hz, 2H), 3.44 (dd, J = 6.7 Hz, 4H), 2.50 (s, 3H), 1.19 (t, J = 6.7 Hz, 6H).

General Procedure for S-Alkylation of 2-Thioxothienopyrimidin-4-ones. To a mixture of the 2-thione derivative (0.5 mmol) and triethylamine (1.5 mmol) in DMF (5 mL), the appropriate halide (0.6 mmol) was added. The reaction mixture was stirred at 60 °C for 1 h and then cooled to room temperature. Water (30 mL) was added, and the formed precipitate was filtered off and then crystallized from a mixture of ethanol/DMF (1:1).

2-[2-Oxo-2-(4-bromophenyl)-ethylsulfanyl]-3-(2-butyl)-thieno[3,2-*d*]pyrimidin-4(3*H*)-one 15{*130*}. Yield 83%; mp 94 °C; ^{1}H NMR δ: 7.88 (d, J = 7.5 Hz, 1H), 7.63 (d, J = 7.8 Hz, 2H), 7.41 (d, J = 7.8 Hz, 2H), 7.01 (d, J = 7.5 Hz, 1H), 4.48 (s, 2H), 4.08 (m, 1H), 1.64 (dd, J = 6,8 Hz, 2H), 1.03 (d, J = 6.7 Hz, 3H), 0.98 (t, J = 6.7 Hz, 3H).

2-(2-Trifluoromethylphenylaminocarbonylmethylsulfanyl)-3-(2-pyrrolidin-1-ylethyl)-thieno[3,2-*d*]pyrimidin-4(3*H*)-one 15{*120*}. Yield 87%; mp 238 °C; ^{1}H NMR δ: 9.80 (s, 1H), 7.97 (t, J = 7.5 Hz, 1H), 7.22 (t, J = 7.7 Hz, 1H), 7.01 (d, J = 7.5 Hz, 1H), 6.95 (d, J = 7.7 Hz, 1H), 6.79 (t, J = 7.7 Hz, 1H), 6.72 (d, J = 7.7 Hz, 1H), 4.49 (t, J = 6.4 Hz, 2H), 4.39 (s, 2H), 3,57 (t, J = 6.4 Hz, 2H), 1.92 (t, 4H), 1.02 (q, 4H).

2-[2-Oxo-2-{4-(2-methoxyphenyl)piperazin-1-yl}-ethylsulfanyl]-3-[2-(3,4-dimethoxyphenyl)ethyl]-thieno[3,2-*d*]-pyrimidin-4(3*H*)-one 15{*115*}. Yield 72%; mp 236 °C; ^{1}H NMR δ: 7.95 (d, J = 7.5 Hz, 1H), 7.22 (t, J = 7.7 Hz, 1H), 7.01 (d, J = 7.5 Hz, 1H), 6.95 (d, J = 7.7 Hz, 1H), 6.82 (d, J = 7.7 Hz, 1H), 6.79 (t, J = 7.7 Hz, 1H), 6.78 (s, 1H), 6.72 (d, J = 7.7 Hz, 1H), 6.64 (d, J = 7.7 Hz, 1H), 3.96 (t, J = 6,8 Hz, 2H), 3.79 (s, 3H), 3.71 (s, 3H), 3.67 (s, 3H), 3.27 (t, J = 6.8 Hz, 4H), 3.19 (t, J = 6,8 Hz, 2H), 3.07 (t, J = 6.8 Hz, 4H). LC/MS: m/z 581 ($M^{+\bullet}$)

2-(Thiazol-2-ylaminocarbonylmethylsulfanyl)-3-(4-carboxybutyl)-thieno[3,2-*d*]pyrimidin-4(3*H*)-one 16{*31*}. Yield 87%; mp 210 °C; ^{1}H NMR δ: 12.22 (s, 1H), 8.01 (d, J = 7.5 Hz, 1H), 7.49 (d, J = 7.7 Hz, 1H), 7.19 (d, J = 7.7 Hz, 1H), 7.04 (d, J = 7.5 Hz, 1H), 4.31 (s, 2H), 4.08 (t, J = 6,8 Hz, 2H), 2.29 (t, J = 6,8 Hz, 2H), 1.78−1.60 (m, 4H). LC/MS: m/z 424 ($M^{+\bullet}$).

2-[1-(Pyridin-3-ylmethylaminocarbonyl)propylsulfanyl]-3-(4-carboxybenzyl)-thieno[3,2-*d*]pyrimidin-4(3*H*)-one 16{*45*}. Yield 82%; mp 260 °C; ^{1}H NMR δ: 12.63 (s, 1H), 8.80 (t, J = 7.6 Hz, 1H), 8.41 (t, J = 7.6 Hz, 1H), 8.20 (d, J = 7.5 Hz, 1H), 7.90 (d, J = 7.8 Hz, 2H), 7.56 (d, J = 7.6 Hz, 1H), 7.35−7.18 (m, 5H), 5.42 (dd, J = 6.8 Hz, 2H), 4.50 (t, J = 6.8 Hz, 1H), 4.28 (d, J = 6.6 Hz, 2H), 1.92−1.80 (m, 2H), 0.93 (t, J = 6.8 Hz, 3H). LC/MS: m/z 424 ($M^{+\bullet}$).

2-(Benzimidazol-2-ylmethylsulfanyl)-3-(2-carboxyethyl)-thieno[3,2-*d*]pyrimidin-4(3*H*)-one 16{*70*}. Yield 86%; mp 233 °C; ^{1}H NMR δ: 12.33 (s, 1H) 8.14 (d, J = 7.5 Hz, 1H), 7.92 (s, 1H), 7.52−7.47 (m, 2H), 7.33 (d, J = 7.5 Hz, 1H), 7.17−7.11 (m, 2H), 4.76 (s, 2H), 4.31 (t, J = 6.8 Hz, 2H), 2.67 (t, J = 6.8 Hz, 2H). LC/MS: m/z 387 ($M^{+\bullet}$).

2-(5-Methylisoxazol-3-ylaminocarbonylmethylsulfanyl)-3-phenylcarboxamido-thieno[3,2-*d*]pyrimidin-4(3*H*)-one 14{*12*}. Yield 80%; mp 218 °C; ^{1}H NMR δ: 11.82 (s, 1H), 11.21 (s, 1H), 8.21 (d, J = 7.5 Hz, 1H), 7.97 (d, J = 7.8 Hz, 2H), 7.70−7.68 (m, 3H), 7.23 (d, J = 7.5 Hz, 1H), 6.53 (s, 1H), 4.12 (dd, J = 6.8 Hz, 2H), 2.34 (s, 3H). LC/MS: m/z 442 ($M^{+\bullet}$).

2-Tetrahydrofurfurylaminocarbonylmethylsulfanyl-3-(2-bromophenyloxymethylcarboxamido)-thieno[3,2-*d*]pyrimidin-4(3*H*)-one 14{*26*}. Yield 73%; mp 159 °C; ^{1}H NMR δ: 11.39 (s, 1H), 8.23 (d, J = 7.8 Hz, 1H), 8.09 (t, J = 7.5 Hz, 1H), 8.58 (d, J = 7.8 Hz, 1H), 7.40−7.28 (m, 2H), 7.17 (d, J = 7.5 Hz, 1H), 6.97 (t, J = 7.8 Hz, 1H), 4.97 (dd, J = 6.6 Hz, 2H), 3.95−3.56 (m, 5H), 3.15 (s, 2H), 1.87−1.71 (m, 3H), 1.56−1.47 (m, 1H). LC/MS: m/z 553 ($M^{+\bullet}$).

2-[2-Oxo-2-(3,4-dichlorophenyl)-ethylsulfanyl]-3-(2-bromophenyloxymethylcarboxamido)-thieno[3,2-*d*]pyrimidin-4(3*H*)-one 14{***46***}**.** Yield 79%; mp 107 °C; ^{1}H NMR δ: 11.91 (s, 1H), 8.26 (d, J = 7.8 Hz, 1H), 8.16 (d, J = 7.5 Hz, 1H), 8,14 (s, 1H), 8.05−7.81 (m, 4H), 7.57 (t, J = 7.8 Hz, 1H), 7.00 (d, J = 7.5 Hz, 1H), 5.72 (dd, J = 6,8 Hz, 2H). LC/MS: m/z 569 ($M^{+\bullet}$).

2-(2-Fluoro-6-chlorophenylmethylsulfanyl)-3-[5-{2-(3,4-dimethoxyphenyl)ethylcarbamoyl}pentyl]-thieno[3,2-*d*]-pyrimidin-4(3*H*)-one 18{***32***}**.** Yield 85%; mp 140 °C; ^{1}H NMR δ: 8.19 (d, J = 7.8 Hz, 2H), 8.79 (t, J = 6.8 Hz, 1H), 7.47−7.23 (m, 3H), 6.82 (d, J = 7.7 Hz, 1H), 6.78 (s, 1H), 6.64 (d, J = 7.7 Hz, 1H), 4.65 (s, 2H), 3.96 (t, J = 6.8 Hz, 2H), 3.71 (s, 3H), 3.67 (s, 3H), 3.19 (dd, J = 6.8 Hz, 2H), 2.61 (t, J = 6,7 Hz, 2H), 2.00 (t, J = 6.7 Hz, 2H), 1.64−1.42 (m, 4H), 1.25 (q, J = 6.7 Hz, 2H). LC/MS: m/z 604 ($M^{+\bullet}$).

2-(4-Nitrophenylmethylsulfanyl)-3-[3-(1,3-benzodioxol-5-ylmethylcarbamoyl)propyl]-thieno[3,2-*d*]pyrimidin-4(3*H*)-one 18{***125***}**.** Yield 81%; mp 224 °C; ^{1}H NMR δ: 8.30 (t, J = 6.6 Hz, 1H), 8.21 (d, J = 7.5 Hz, 1H), 8.14 (d, J = 7.8 Hz, 2H), 7.77 (d, J = 7.8 Hz, 2H), 7.36 (d, J = 7.5 Hz, 1H), 6.81 (d, J = 7.6 Hz, 1H), 6.78 (s, 1H), 6.17 (d, J = 7.6 Hz, 1H), 5.94 (s, 2H), 4.62, (s, 2H), 4.13 (d, J = 6.6 Hz, 2H), 4.07 (t, J = 6.8 Hz, 2H), 2.20 (t, J = 6.8 Hz, 2H), 1.89 (q, J = 6.8 Hz, 2H).

2-(4-Oxo-6-chloro-4H-pyrido[1,2-*a*]pyrimidin-2-ylmethylsulfanyl)-3-[5-(4-methylbenzylcarbamoyl)pentyl]-thieno[3,2-*d*]pyrimidin-4(3*H*)-one 18{***130***}**.** Yield 80%; mp 175 °C; ^{1}H NMR δ: 7.95 (d, J = 7.5 Hz, 2H), 7.62 (d, J = 7.6 Hz, 1H), 7.39 (d, J = 7.6 Hz, 1H), 7.24−7.20 (m, 3H), 7.09 (d, J = 7.8 Hz, 2H), 7.02 (d, J = 7.8 Hz, 2H), 4.58 (s, 2H), 4.19 (d, J = 6.6 Hz, 2H), 4.01 (t, J = 6.8 Hz, 2H), 2.29 (s, 3H), 2.10 (t, J = 6.8 Hz, 2H), 2.74−2.59 (m, 4H), 1.37 (q, J = 6.8 Hz, 2H).

2-(1,3-Benzodioxol-5-ylaminocarbonylmethylsulfanyl)-3-allyl-5,6,7,8-tetrahydrobenzo[*b*]thieno[2,3-*d*]pyrimidin-4(3*H*)-one 23{***105***}**.** Yield 76%; mp 212 °C; ^{1}H NMR δ: 10.00 (s, 1H), 7.27 (s, 1H), 6.94 (d, J = 7.8 Hz, 1H), 6.69 (d, J = 7.8 Hz, 1H), 5.97 (s, 2H), 5.95−5.91 (m, 1H), 5.27 (d, J = 6.9 Hz, 2H), 4.75 (d, J = 6.9 Hz, 2H), 4.08 (s, 2H), 2.96 (t, J = 6.8 Hz, 2H), 2.75 (t, J = 6.8 Hz, 2H), 2.92−2.84 (m, 4H).

2-[2-Oxo-2-(4-bromophenyl)-ethylsulfanyl]-3-cyclohexyl-7-methyl-3,4,5,6,7,8-hexahydropyrido[4′,3′:4,5]thieno[2,3-*d*]pyrimidin-4(3*H*)-one 23{***170***}**.** Yield 86%; mp 204 °C; ^{1}H NMR δ: 7.97 (d, J = 7.8 Hz, 2H), 7.68 (d, J = 7.8 Hz, 2H), 4.60 (s, 2H), 4.21−4.10 (m, 1H), 3.49 (s, 2H), 2.91−2.60 (m, 4H), 2.39 (s, 3H), 1.96−1.72 (m, 6H), 1.48−1.27 (m, 4H). LC/MS: m/z 532 ($M^{+\bullet}$).

6,6-Dimethyl-2-aminocarbonylmethylsulfanyl-3-(2-phenylethyl)-4,5,6,8-tetrahydro-3*H*-pyrano[4′,3′:4,5]thieno-[2,3-*d*]pyrimidin-4(3*H*)-one 23{***195***}**.** Yield 81%; mp 201 °C; ^{1}H NMR δ: 7.60 (s, 1H), 7.37−7.25 (m, 5H), 7.22 (s, 1H), 4.73 (s, 2H), 4.23 (t, J = 6.7 Hz, 2H), 3.96 (s, 2H), 2.98 (t, J = 6.7 Hz, 2H), 2.84 (s, 2H), 1.26 (s, 6H).

2-(2-Oxo-2-*tert*-butylethylsulfanyl)-3-benzyl-5-methyl-6-(piperidine-1-ylcarbonyl)-thieno[2,3-*d*]pyrimidin-4(3*H*)-one 23{***244***}**.** Yield 84%; mp 162 °C; ^{1}H NMR δ: 7.41−7.30 (m, 5H), 5.39 (s, 2H), 4.37 (s, 2H), 3.52−3.47 (m, 4H), 2.51 (s, 3H), 1.69−1.54 (m, 6H), 1.24 (s, 9H).

2-(Cyanomethylsulfanyl)-3-(2-phenylethyl)-5-methyl-6-(pyrrolidine-1-ylcarbonyl)-thieno[2,3-*d*]pyrimidin-4(3*H*)-one 23{***291***}**.** Yield 76%; mp 157 °C; ^{1}H NMR δ: 7.32−7.21 (m, 5H), 4.30 (s, 2H), 4.21 (t, J = 6.7 Hz, 2H), 4.52−4.47 (m, 4H), 2.99 (t, J = 6.7 Hz, 2H), 2.53 (s, 2H), 1.98 (s, 3H).

2-(3-Nitrobenzylsulfanyl)-3-(2-phenylethyl)-5-methyl-6-(3-trifluoromethylphenylcarbamoyl)-thieno[2,3-*d*]pyrimidin-4(3*H*)-one 23{***296***}**.** Yield 85%; mp 145 °C; ^{1}H NMR δ: 9.20 (s, 1H), 8.42 (s, 1H), 8.12 (d, J = 7.5 Hz, 1H), 7.90 (d, J = 7.8 Hz, 1H), 7.82 (d, J = 7.8 Hz, 1H), 7.73 (d, J = 7.5 Hz, 1H), 7.72 (t, J = 7.8 Hz, 1H), 7.59 (t, J = 7.8 Hz, 1H), 7.44 (t, J = 7.8 Hz, 1H), 7.25−7.19 (m, 5H), 4.64 (s, 2H), 4.21 (t, J = 6.7 Hz, 2H), 2.98 (t, J = 6.7 Hz, 2H), 2.72 (s, 3H). LC/MS: m/z 625 ($M^{+\bullet}$).

2-(4-Dimethylaminophenylaminocarbonylmethylsulfanyl)-3-(2-methoxybenzyl)-5-methyl-6-ethoxycarbonyl-thieno-[2,3-*d*]pyrimidin-4(3*H*)-one 23{***308***}**.** Yield 78%; mp 196 °C; ^{1}H NMR δ: 9.80 (s, 1H), 7.31 d, J = 7.8 Hz, 2H), 7.22 (t, J = 7.7 Hz, 1H), 6.95 (d, J = 7.7 Hz, 1H), 6.79 (t, J = 7.7 Hz, 1H), 6.72 (d, J = 7.7 Hz, 1H), 6.59 (d, J = 7.8 Hz, 2H), 5.29 (s, 2H), 4.30 (dd, J = 6.7 Hz, 2H), 4.04 (s, 2H), 3.92 (s, 3H), 2.88 (s, 6H), 2.80 (s, 3H), 1.35 (t, J = 6.7 Hz, 3H). LC/MS: m/z 567 ($M^{+\bullet}$).

2-(2-Fluoro-6-chlorobenzylsulfanyl)-3-furfuryl-5-methyl-6-ethoxycarbonyl-thieno[2,3-*d*]pyrimidin-4(3*H*)-one 23{***347***}**.** Yield 73%; mp 130 °C; ^{1}H NMR δ: 7.39 (d, J = 7.8 Hz, 1H), 7.33 (t, J = 7.8 Hz, 1H), 7.25 (d, J = 7.8 Hz, 1H), 7.12 (s, 1H), 6.34 (s, 1H), 6.29 (s, 1H), 5.20 (s, 2H), 4.63 (s, 2H), 4.30 (dd, J = 6.8 Hz, 2H), 2.28 (s, 3H), 1.37 (t, J = 6.8 Hz, 3H).

2-(3-Nitrobenzylsulfanyl)-3-(1,3-benzodioxol-5-ylmethyl)-5-methyl-6-ethoxycarbonylthieno[2,3-*d*]pyrimidin-4(3*H*)-one 23{***385***}**.** Yield 87%; mp 155 °C; ^{1}H NMR δ: 8.65 (s, 1H), 8.10 (d, J = 7.8 Hz, 1H), 7.60 (t, J = 7.8 Hz, 1H), 6.78 (m, 3H), 6.73 (d, J = 7.7 Hz, 1H), 5.96 (s, 2H), 5.17 (s, 2H), 4.61 (s, 2H), 4.34 (dd, J = 6.7 Hz, 2H), 2.81 (s, 3H), 1.35 (t, J = 6.7 Hz, 3H). LC/MS: m/z 540 ($M^{+\bullet}$).

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Supporting Information Available. ^{1}H NMR spectra of synthesized compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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