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Synthesis of 5-Methyl-4-oxo-2-(coumarin-3-yl)-*N*-aryl-3,4-dihydrothieno[2,3-d]-pyrimidine-6-carboxamides

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ABSTRACT: *Possible approaches to synthesis of 5-methyl-4-oxo-2-(coumarin-3-yl)-*N*-aryl-3,4-dihydrothieno[2,3-*d*]pyrimidine-6-carboxamides* **4** *have been discussed. It is shown that the preferable approach is cyclization of 2-iminocoumarin-3-carboxamides* **1**, *utilizing 5-amino-3-methyl-*N^2*-arylthiophene-2,4-dicarboxamides* **2** *as binucleophilic reagents. The proposed procedure allowed us to easily obtain* **4** *in two stages, using common reagents.* © 2007 Wiley Periodicals, Inc. Heteroatom Chem 18:341–346, 2007; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20303

INTRODUCTION

It is known that 5-methyl-4-oxo-3,4-dihydrothieno-[2,3-*d*]pyrimidine-6-carboxamides exhibit different types of biological activities. Among them, there are compounds that have been reported as serotoninergic receptor antagonists [1], and some of them can be useful for treatment of cerebral ischemia [2]. Substances with related structures are cyclin-dependent kinase 4 (Cdk4) inhibitors having antitumor activity owing to cell cycle regulation [3]. Some of 5-methyl-4-oxo-3,4-dihydrothieno[2,3-*d*]pyrimidine-6-carboxamides were patented as medicaments to cure obesity or diabetes [4]. However, compounds of this class, modified with a coumarin moiety, have not been reported yet.

Earlier, we reported the interaction of 2-iminocoumarin-3-carboxamides with 2-aminothiophene-3-carboxamides, which leads to the formation of 2-(coumarin-3-yl)thieno[2,3-*d*]pyrimidin-4-ones, and developed a method for the synthesis of this class of compounds via cyclization of 2-(3-carbamoyl-2-thienylimino)coumarine-3-carboxamides in DMF [5–7]. To scrutinize the scope and limitations of this method, we studied its capability with respect to the synthesis of 5-methyl-4-oxo-2-(coumarin-3-yl)-*N*-aryl-3,4-dihydrothieno[2,3-*d*]pyrimidine-6-carboxamides **4**.

RESULTS AND DISCUSSION

For the synthesis of **4**, a few routes can be considered. The most common approach is the Knoevenagel condensation of salicylic aldehydes with hetaryl acetates [8–16]. However, in spite of the wide synthetic potential of this reaction, its adaptation in this case is inconvenient due to the difficulties faced in the preparation of 2-(4-oxo-3,4-dihydrothieno[2,3-*d*]pyrimidine-2-yl)acetic acid derivatives [17–19].

As an alternative approach to the synthesis of **4**, previously discovered rearrangement of 2-iminocoumarin-3-carboxamides can be suggested [8,9,20]. It can be presumed that the cyclization

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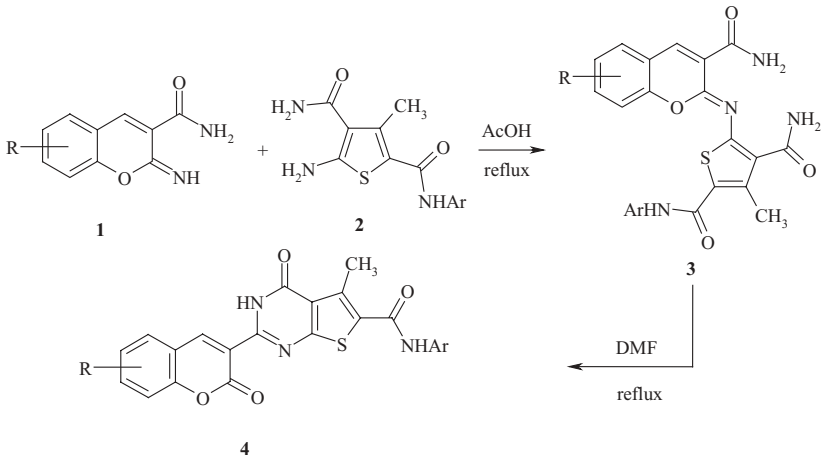

SCHEME 1

of 2-iminocoumarin-3-carboxamides **1** under the action of 5-amino-4-carbamoyl-3-methyl-2-thiophene-3-carboxylate will result in the formation of ethyl 5-methyl-4-oxo-2-(coumarin-3-yl)-3,4-dihydrothieno[2,3-*d*]pyridine-6-carboxylate. The proposed intermediate for this synthesis—5-amino-4-carbamoyl-3-methyl-2-thiophene-3-carboxylate—has not been obtained yet, neither using the Gewald synthetic procedure nor with the application of other methods [21]. In the synthesis of this compound, our experiments also gave unfavourable results.

Therefore for the synthesis of **4**, we propose the use of 5-amino-3-methyl-N^2-arylthiophene-2,4-dicarboxamides **2** as *N*,*N*-binucleophilic reagents (Scheme 1). It is noteworthy that compounds **2** are also not much reported [22], notwithstanding the fact that they can be easily obtained using the standard Gewald procedure for 2-aminothiophene synthesis [23].

With regard to the above-mentioned conditions in order to obtain **4**, we studied the interaction of **2** with **1**. It was discovered that heating, as well as continuous refluxing of **1** and **2** in glacial acetic acid, does not result in the formation of **4**, although the similar rearrangement readily proceeds at refluxing in AcOH in this case when anthranilamide or 2-amino-1-benzenesulfonamide is used as a binucleophile [8,20,24]. In our experiment, only the products of iminogroup substitution, 2-(3-carbamoyl-2-thienylimno)coumarin-3-carboxamides **3**, were isolated. The desired cyclization proceeds only when products **3** are refluxed in DMF for 4–6 h. Evidently, the use of DMF as a solvent facilitates opening of the iminolactone ring [25], thereby promoting the reaction. At the same time, DMF medium simplifies the synthetic procedure comparatively with nitrobenzene or AcOH, barring hydrolysis or decarboxylation.

The progress of the reaction was monitored by the release of ammonia. The resulting **4** was isolated as bright yellow solid and was not further purified. Their data are listed in the Table 1.

Structures of the synthesized compounds **4**{**1–14**} were assigned by elemental analyses ^{1}H-NMR, IR, and UV spectral data. ^{1}H NMR spectra of all the derivatives **4** show the signals of protons of coumarin moiety at $\delta = 9.12$–6.89 ppm, the broad signal corresponding to position 3 of thieno[2,3-*d*]pyrimidin-4-one ring system at $\delta = 12.07$–12.23 ppm, and the signal of amide NH proton at $\delta = 10.45$–9.63. The signal of methyl group at position 5 of thieno[2,3-*d*]pyrimidin-4-one moiety is shifted downfield comparatively with the starting compounds **2** and can be observed at $\delta = 2.79$–2.69 ppm.

The IR spectra of all compounds **4**{**1–14**} exhibit strong absorption bands 1720–1668 cm^{-1} (C=O) and 3464–3152 cm^{-1} (N—H). Bands at 3092–2862 cm^{-1} (C—H) and 1616–1528 cm^{-1} (C=C, C=N) are also present in all the spectra.

The UV–VIS absorption spectra of compounds **4**{**1–14**} are very typical for 3-heterylcoumarins [26]. Almost all of them possess two or three intensive absorption maxima; the location of which much depends upon the electronic nature of the substituent in the coumarin ring. For the unsubstituted derivatives **4**{**1,10,13**}, there are two maxima at 33,600–33,580 cm^{-1} and at 25,500–25,260 cm^{-1}; in a similar manner, two maxima at 33,820–33,700 cm^{-1} and at 25,100–24,720 cm^{-1} are observed for 6-chlorocubstituted analogs **4**{**3,4,8,14**}. The spectra of compounds with electron-donating substituents (OMe) at positions 7 or 8 are characterized by the appearance of the third maxima with lower

TABLE 1 ^{1}H NMR Spectral and UV–VIS Data **4**

	R/Ar	*Yields (%)*	*CH_3*	*3-NH*	*ν cm^{-1} ($log\varepsilon$)*
4{**1**}	H/Ph	83	2.69	12.19	33,600 (4.70), 25,260 (4.63)
4{**2**}	8-OCH_3/Ph	79	2.71	12.19	39,260 (4.45), 32,520 (4.53), 25,420 (4.47)
4{**3**}	6-Cl/Ph	75	2.67	12.19	33,700 (4.46), 25,100 (4.37)
4{**4**}	6-Cl/4-CH_3Ph	73	2.73	12.18	33,820 (4.38), 24,940 (4.29)
4{**5**}	8-OC_2H_5/4-CH_3Ph	87	2.69	12.19	39,000 (4.37), 32,540 (4.44), 25,240 (4.39)
4{**6**}	7-OCH_3/4-CH_3Ph	67	2.70	12.08	38,920 (4.35), 32,000 (4.39), 29,040 (4.24), 24,780 (4.58)
4{**7**}	8-OCH_3/4-OCH_3Ph	68	2.68	12.21	39,180 (4.53), 32,560 (4.64), 25,100 (4.53)
4{**8**}	6-Cl/4-OCH_3Ph	65	2.69	12.19	33,740 (4.38), 24,720 (4.27)
4{**9**}	7-OCH_3/4-OCH_3Ph	58	2.72	12.12	39,080 (4.45), 31,820 (4.52), 29,280 (4.35), 24,700 (4.69)
4{**10**}	H/3-FPh	65	2.72	12.23	33,580 (4.31), 25,240 (4.23)
4{**11**}	8-OCH_3/3-FPh	72	2.68	12.19	39,160 (4.20), 32,540 (4.29), 25,340 (4.24)
4{**12**}	7-OCH_3/3-FPh	82	2.69	12.07	32,040 (4.45), 29,000 (4.29), 24,900 (4.65)
4{**13**}	H/2,4-CH_3Ph	79	2.79	12.19	33,640 (4.33), 25,500 (4.27)
4{**14**}	6-Cl/2,4-CH_3Ph	75	2.79	12.17	33,740 (4.44), 24,900 (4.38)

intensity at 39,260–38,920 cm^{-1}. It should also be noticed that in the case of 7-methoxysubstituted compounds **4**{**6,9,12**}, the long-wave maxima is shifted to 24,900–24,700 cm^{-1} and its intensity noticeably increases.

CONCLUSION

The synthesis of **4** has been performed using the rearrangement of **1**, utilizing 5-amino-3-methyl-N^2-arylthiophene-2,4-dicarboxamides **2** as binucleophilic reagents. The proposed procedure appeared to be the most convenient as a two-step approach for the synthesis of **4** using available reagents.

EXPERIMENTAL

Melting points (°C) were measured with Buchi B-520 melting point apparatus and were not corrected. IR spectra were recorded on Specord M-80 spectrometer in KBr. ^{1}H-NMR spectra were recorded on Varian Mercury 200 (200 MHz) spectrometer in DMSO-d_6 using TMS as an internal standard (chemical shifts are reported in ppm). UV–VIS absorption spectra were registered at Specord M-40 spectrophotometer in 1,4-dioxane. Elemental analyses were within ±0.4% of the theoretical value.

2-Iminocoumarin-3-carboxamides **1** was prepared according to the reported methods [25,27,28].

General Procedure for Synthesis of **2**

To well-stirred equimolar suspension of acetoacetanilide, sulfur, and cyanoacetamide in ethanol quintuple, excess of morpholine was added at once. The mixture was stirred at 80°C for 1–2 h. The precipitate formed after cooling was filtered off and washed with propanol-2.

N^2-Phenyl-5-amino-3-methyl-2,4-thiophenecarboxamide **2**{**1**}. Yield, 67%, mp 234–235°C; IR (cm^{-1}): 3415, 3260, 3157, 3053, 3037, 3010, 2881, 1636, 1595, 1578, 1531, 1489; ^{1}H NMR: 2.55 (s, 3H, CH_3), 7.0 (m, 3H, NH_2 + 4′-H), 7.26 (m, 4H, 3′-H + 5′-H + $CONH_2$), 7.59 (d, 2H, $J = 6.6$ Hz, 2′−H + 6′-H), 9.48 (s, 1H, CONHAr). Calcd for $C_{13}H_{13}N_3O_2S$ (275.33): H, 4.76; C, 56.71; N, 15.26. Found: H, 4.65; C, 56.73; N, 15.24.

N^2-(4-Methylphenyl)-5-amino-3-methyl-2,4-thiophenecarboxamide **2**{**2**}. Yield, 78%; mp 231–233°C; IR (cm^{-1}): 3481, 3408, 3269, 3034, 2917, 1633, 1616, 1593, 1557, 1538; ^{1}H NMR: 2.15 (s, 3H, $ArCH_3$), 6.94 (br s, 2H, NH_2), 7.07 (d, 2H, $J = 8.3$ Hz, 3′-H + 5′-H), 7.24 (br s, 2H, $CONH_2$), 7.46 (d, 2H, $J = 8.3$ Hz, 2′-H + 6′-H), 9.37 (s, 1H, CONHAr). Calcd for $C_{14}H_{15}N_3O_2S$ (289.36): H, 5.23; C, 58.11; N, 14.52. Found: H, 5.18; C, 58.04; N, 14.57.

*In some cases in ^{1}H NMR spectra, the signal of methyl group is masked with DMSO signal.

N^2-(4-Methoxyphenyl)-5-amino-3-methyl-2,4-thiophenecarboxamide **2**{**3**}. Yield, 84%; mp 223–225°C; IR (cm^{-1}): 3480, 3411, 3264, 2962, 2915, 2839, 1629, 1579, 1531, 1510; ^1H NMR: 3.69 (s, 3H, ArOC$\underline{H_3}$), 6.83 (d, 2H, $J = 8.4$ Hz, 3′-H + 5′-H), 6.97 (br s, 2H, NH_2), 7.23 (br s, 2H, CON$\underline{H_2}$), 7.38 (d, 2H, $J = 8.4$ Hz, 2′-H + 6′-H), 9.39 (s, 1H, CON$\underline{H}$Ar). Calcd for $C_{14}H_{15}N_3O_3S$ (305.36): H, 4.95; C, 55.07; N, 13.76. Found: H, 4.98; C, 55.18; N, 13.81.

N^2-(3-Fluorophenyl)-5-amino-3-methyl-2,4-thiophenecarboxamide **2**{**4**}. Yield 58%; mp 236–238°C; IR (cm^{-1}): 3462, 3416, 3267, 3158, 3072, 2773, 1639, 1605, 1579, 1534; ^1H NMR: 6.93 (t, 1H, $J = 8.3$ Hz, 5′-H), 6.99 (br s, 2H, NH_2), 7.3 (m, 4H, 2′-H + 4′-H + CON$\underline{H_2}$), 7.61 (d, 1H, $J = 12.6$ Hz, 6′-H), 9.62 (s, 1H, CON$\underline{H}$Ar).* Calcd for $C_{13}H_{12}FN_3O_2S$ (293.32): H, 4.12; C, 53.23; N, 14.33. Found: H, 4.27; C, 53.15; N, 14.37.

N^2-(2,4-Dimethylphenyl)-5-amino-3-methyl-2,4-thiophenecarboxamide **2**{**5**}. Yield 81%; mp 243–245°C; IR (cm^{-1}): 3473, 3270, 3000, 2918, 1630, 1560, 1535, 1455; ^1H NMR: 2.07 + 2.18 (s + s, 6H, 2,4-C$\underline{H_3}$Ar), 6.95 (m, 4H, 3′-H + 5′-H + N$\underline{H_2}$), 7.19 (m, 3H, 6′-H + CON$\underline{H_2}$), 8.89 (s, 1H, CON$\underline{H}$Ar).* Calcd for $C_{15}H_{17}N_3O_2S$ (303.39): H, 5.65; C, 59.39; N, 13.85. Found: H, 5.73; C, 59.21; N, 13.79.

General Procedure for Synthesis of **4**

To warm solution of **2** (2 mmol) in 20 mL of glacial acetic acid, **1** (2 mmol) was added. The mixture was refluxed for 1 h. The formed crystals of **3** were filtered off and thoroughly washed with 2-propanol and dried. The obtained product **3** (1.65 mmol) was refluxed in DMF for 4–6 h and then cooled. The precipitate was filtered off and washed with 2-propanol to give **4**.

N^6-Phenyl-5-methyl-4-oxo-2-(coumarin-3-yl)-3,4-dihydrothieno[2,3-d]pyrimidine-6-carboxamide **4**{**1**}. Yield, 83%; mp >300°C; IR (cm^{-1}): 3336, 3240, 3048, 1712, 1684, 1612, 1600, 1536; ^1H NMR: 2.69 (s, 3H, CH_3), 7.11 (t, 1H, $J = 8.0$ Hz, 4′-H), 7.33 (t, 2H, $J = 7.4$ Hz, 3′-H + 5′-H), 7.45 (m, 2H, 8H + 6H); 7.65 (d, 2H, $J = 7.6$ Hz, 2′-H + 6′-H); 7.77 (t, 1H, $J = 7.4$ Hz, 7H); 8.04 (d, 1H, $J = 7.2$ Hz, 5-H), 9.09 (s, 1H, 4-H), 10.25 (s, 1H, CON$\underline{H}$Ar), 12.9 (br s, 1H, NH). UV–Vis (dioxane), ν_{max} (log ε): 33,600 (4.70), 25,260 cm^{-1} (4.63). Calcd for $C_{23}H_{15}N_3O_4S$ (429.46): H, 3.52; C, 64.33; N, 9.78. Found: H, 3.64; C, 64.26; N, 9.81.

N^6-Phenyl-5-methyl-4-oxo-2-(8-methoxycoumarin-3-yl)-3,4-dihydrothieno[2,3-d]pyrimidine-6-carboxamide **4**{**2**}. Yield 79%; mp >300°C; IR (cm^{-1}): 3376, 3224, 3040, 2936, 1712, 1700, 1680, 1608, 1596, 1532. ^1H NMR: 2.71 (s, 3H, CH_3), 3.93 (s, 3H, OC$\underline{H_3}$), 7.11 (t, 1H, $J = 6.9$ Hz, 4′-H), 7.44 (m, 5H, 5H + 6-H + 7-H + 3′-H + 5′-H), 7.66 (d, 2H, $J = 7.8$ Hz, 2′-H + 6′-H), 9.08 (s, 1H, 4-H), 10.25 (s, 1H, CON$\underline{H}$Ar), 12.19 (br s, 1H, NH). UV–Vis (dioxane), ν_{max} (log ε): 39,260 (4.45), 32,520 (4.53), 25,420 cm^{-1} (4.47) Calcd for $C_{24}H_{17}N_3O_5S$ (459.48): H, 3.73; C, 62.74; N, 9.15. Found: H, 3.63; C, 62.71; N, 9.19.

N^6-Phenyl-5-methyl-4-oxo-2-(6-chlorocoumarin-3-yl)-3,4-dihydrothieno[2,3-d]pyrimidine-6-carboxamide **4**{**3**}. Yield 75%; mp >300°C; IR (cm^{-1}): 3420, 3352, 3216, 3052, 1716, 1684, 1668, 1600, 1528; ^1H NMR: 2.67 (s, 3H, CH_3), 7.11 (t, 1H, $J = 7.1$ Hz, 4′-H), 7.34 (t, 2H, $J = 7.3$ Hz, 3′H + 5′H), 7.63 (m, 3H, 8-H + 2′-H + 6′-H), 7.80 (dd, 1H, $J = 8.8$, 2.7 Hz, 7-H), 8.15 (d, 1H, $J = 2.7$ Hz, 5-H), 9.00 (s, 1H, 4-H), 10.24 (s, 1H, CON$\underline{H}$Ar), 12.19 (br s, 1H, NH). UV–Vis (dioxane), ν_{max} (log ε): 33,700 (4.46), 25,100 cm^{-1} (4.37) Calcd for $C_{23}H_{14}ClN_3O_4S$ (463.90): H, 3.04; C, 59.55; N, 9.06. Found: H, 2.95; C, 59.59; N, 9.12.

N^6-(4-Methylphenyl)-5-methyl-4-oxo-2-(6-chlorocoumarin-3-yl)-3,4-dihydrothieno[2,3-d]pyrimidine-6-carboxamide **4**{**4**}. Yield 73%; mp >300°C; IR (cm^{-1}): 3356, 3232, 3064, 2964, 1720, 1672, 1616, 1596, 1540; ^1H NMR: 2.21 (s, 3H, C$\underline{H_3}$), 2.73 (s, 3H, CH_3), 7.13 (d, 2H, $J = 8.6$ Hz, 3′-H + 5′-H), 7.55 (m, 3H, 8-H + 2′-H + 6′-H), 7.81 (dd, 1H, $J = 9.2$, 3.8 Hz, 7-H), 8.15 (d, 1H, $J = 3.8$ Hz, 5-H), 9.02 (s, 1H, 4-H), 10.17 (s, 1H, CON$\underline{H}$Ar), 12.18 (br s, 1H, NH). UV–Vis (dioxane), ν_{max} (log ε): 33,820 (4.38), 24,940 cm^{-1} (4.29) Calcd for $C_{24}H_{16}ClN_3O_4S$ (477.93): H, 3.37; C, 60.32; N, 8.79. Found: H, 3.43; C, 60.41; N, 8.84.

N^6-(4-Methylphenyl)-5-methyl-4-oxo-2-(8-ethoxycoumarin-3-yl)-3,4-dihydrothieno[2,3-d]pyrimidine-6-carboxamide **4**{**5**}. Yield 84%; mp >300°C; IR (cm^{-1}): 3440, 3248, 3092, 2976, 1684, 1604, 1596, 1576; ^1H NMR: 1,39 (t, 3H, $J = 7.1$ Hz, $CH_2C\underline{H_3}$), 2.22 (s, 3H, C$\underline{H_3}$) 2.69 (s, 3H, CH_3), 4.19 (q, 2H, $J = 7.1$ Hz, OC$\underline{H_2}$$CH_3$), 7.14 (d, 2H, $J = 8.2$ Hz, 3′-H + 5′-H), 7.47 (m, 5H, 5-H + 6-H + 7-H + 2′-H + 6′-H), 9.03 (s, 1H, 4-H), 10.15 (s, 1H. CON$\underline{H}$Ar), 12.19 (br s, 1H, NH). UV–Vis (dioxane), ν_{max} (log ε): 39,000 (4.37), 32,540 (4.44), 25,240 cm^{-1} (4.39).

Calcd for $C_{26}H_{21}N_3O_5S$ (487.54): H, 4.34; C, 64.05; N, 8.62. Found: H, 4.37; C, 64.17; N, 8.68.

N^6-(4-Methylphenyl)-5-methyl-4-oxo-2-(7-methoxycoumarin-3-yl)-3,4-dihydrothieno[2,3-d]pyrimidine-6-carboxamide **4**{**6**}. Yield 67%; mp >300°C; IR (cm^{-1}): 3388, 3244, 2924, 1680, 1616, 1600, 1536; ^{1}H NMR: 2.23 (s, 3H, CH_3), 2.70 (s, 3H, CH_3), 3.90 (s, 3H, CouOCH_3), 7.12 (m, 4H, 6-H + 8-H + 3′-H + 5′-H), 7.54 (d, 2H, J = 8.5 Hz, 2′-H + 6′-H), 7.98 (d, 1H, J = 9.6 Hz, 5-H), 9.11 (s, 1H, 4-H), 10.12 (s, 1H, CONHAr), 12.08 (br s, 1H, NH). UV–Vis (dioxane), ν_{max} (log ε): 38,920 (4.35), 32,000 (4.39), 29,040 (4.24), 24,780 cm^{-1} (4.58). Calcd for $C_{25}H_{19}N_3O_5S$ (473.51): H, 4.04; C, 63.42; N, 8.87. Found: H, 4.07; C, 63.35; N, 8.95.

N^6-(4-Methoxyphenyl)-5-methyl-4-oxo-2-(8-methoxycoumarin-3-yl)-3,4-ydihydrothieno[2,3-d]pyrimidine-6-carboxamide **4**{**7**}. Yield 68%; mp >300°C; IR (cm^{-1}): 3364, 3196, 2948, 1696, 1656, 1608, 1576, 1536; ^{1}H NMR: 2.68 (s, 3H, CH_3), 3.93 (s, 3H, CouOCH_3), 3.74 (s, 3H, ArOCH_3), 6.92 (d, 2H, J = 8.4 Hz, 3′-H + 5′-H), 7.5 (m, 5H, 5-H + 6-H + 7-H + 2′-H + 6′-H), 9.07 (s, 1H, 4-H), 10.12 (s, 1H, CONHAr), 12,21 (br s, 1H, NH). UV–Vis (dioxane), ν_{max} (log ε): 39,180 (4.53), 32,560 (4.64), 25,100 cm^{-1} (4.53). Calcd for $C_{25}H_{19}N_3O_6S$ (489.51): H, 3.91; C, 61.34; N, 8.58. Found: H, 3.89; C, 61.35; N, 8.55.

N^6-(4-Methoxyphenyl)-5-methyl-4-oxo-2-(6-chlorocoumarin-3-yl)-3,4-dihydrothieno[2,3-d]pyrimidine-6-carboxamide **4**{**8**}. Yield 65%; mp >300°C; IR (cm^{-1}): 3336, 3228, 2936, 1720, 1672, 1616, 1596, 1532; ^{1}H NMR: 2.69 (s, 3H, CH_3), 3.73 (s, 3H, ArOCH_3), 6.89 (d, 2H, J = 9.8 Hz, 3′-H + 5′-H), 7.56 (m, 3H, 8-H + 2′-H + 6′-H), 7.79 (dd, 1H, J = 9.1, 2.7 Hz, 7-H), 8.15 (d, 1H, J = 2.7 Hz, 5-H), 9.00 (s, 1H, 4-H), 10.09 (s, 1H, CONHAr), 12.19 (br s, 1H, NH). UV–Vis (dioxane), ν_{max} (log ε): 33,740 (4.38), 24,720 cm^{-1} (4.27). Calcd for $C_{24}H_{16}ClN_3O_5S$ (493.93): H, 3.27; C, 58.36; N, 8.51. Found: H, 3.24; C, 58.28; N, 8.64.

N^6-(4-Methoxyphenyl)-5-methyl-4-oxo-2-(7-methoxycoumarin-3-yl)-3,4-dihydrothieno[2,3-d]pyrimidine-6-carboxamide **4**{**9**}. Yield 58%; mp >300°C; IR (cm^{-1}): 3328, 3244, 2932, 1704, 1672, 1620, 1604, 1536; ^{1}H NMR: 2.72 (s, 3H, CH_3), 3.74 (s, 3H, ArOCH_3), 3.92 (s, 3H, CouOCH_3), 6.89 (d, 2H, J = 9.3 Hz, 3′-H + 5′-H), 7.09 (dd, 1H, J = 9.1, 2.6 Hz, 6-H); 7.16 (d, 1H, J = 2.6 Hz, 8-H); 7.56 (d, 2H, J = 9.3 Hz, 2′-H + 6′-H); 7.99 (d, 1H, J = 9.1 Hz, 5-H), 9.12 (s, 1H, 4-H), 10.09 (s, 1H, CONHAr), 12.12 (br s, 1H, NH). UV–Vis (dioxane), ν_{max} (log ε): 39,080 (4.45), 31,820 (4.52), 29,280 (4.35), 24,700 cm^{-1} (4.69). Calcd for $C_{25}H_{19}N_3O_6S$ (489.51): H, 3.91; C, 61.34; N, 8.58. Found: H, 3.97; C, 61.29; N, 8.61.

N^6-(3-Fluorophenyl)-5-methyl-4-oxo-2-(coumarin-3-yl)-3,4-dihydrothieno[2,3-d]pyrimidine-6-carboxamide **4**{**10**}. Yield 65%; mp >300°C; IR (cm^{-1}): 3340, 3232, 3046, 2928, 1712, 1684, 1604, 1568, 1536; ^{1}H NMR: 2.72 (s, 3H, CH_3), 6.95 (t, 1H, J = 6.7 Hz, 5′-H), 7.5 (m, 5H, 7-H + 8-H + 6′-H + 2′-H + 4′-H), 7.79 (t, 1H, J = 8.6 Hz, 7-H), 8.04 (d, 1H, J = 8.7 Hz, 5-H), 9.09 (s, 1H, 4-H), 10.45 (s, 1H, CONHAr), 12.23 (br s, 1H, NH). UV–Vis (dioxane), ν_{max} (log ε): 33,580 (4.31), 25,240 cm^{-1} (4.23). Calcd for $C_{23}H_{14}FN_3O_4S$ (447.45): H, 3.15; C, 61.74; N, 9.39. Found: H, 3.09; C, 61.80, N, 9.44.

N^6-(3-Fluorophenyl)-5-methyl-4-oxo-2-(8-methoxycoumarin-3-yl)-3,4-dihydrothieno[2,3-d]pyrimidine-6-carboxamide **4**{**11**}. Yield 72%; mp >300°C; IR (cm^{-1}): 3356, 3224, 2924, 2886, 1684, 1604, 1576, 1536; ^{1}H NMR: 2.68 (s, 3H, CH_3), 3.92 (s, 3H, CouOCH_3), 6.95 (t, 1H, J = 7.9 Hz, 5′-H), 7.5 (m, 6H, 5-H + 6-H + 7-H + 6′-H + 2′-H + 4′-H), 9.04 (s, 1H, 4-H), 10.39 (s, 1H, CONHAr), 12,19 (br s, 1H, NH). UV–Vis (dioxane), ν_{max} (log ε): 39,160 (4.20), 32,540 (4.29), 25,340 cm^{-1} (4.24). Calcd for $C_{24}H_{16}FN_3O_5S$ (477.47): H, 3.38; C, 60.37; N, 8.80. Found: H, 3.43; C, 60.39, N, 8.75.

N^6-(3-Fluorophenyl)-5-methyl-4-oxo-2-(7-methoxycoumarin-3-yl)-3,4-dihydrothieno[2,3-d]pyrimidine-6-carboxamide **4**{**12**}. Yield 82%; mp >300°C; IR (cm^{-1}): 3245, 3236, 2862, 1684, 1616, 1604, 1540; ^{1}H NMR: 2.69 (s, 3H, CH_3), 3.89 (s, 3H, CouOCH_3), 6.93 (t, 1H, J = 8.4 Hz, 5′-H), 7.04 (d, 1H, J = 9.1 Hz, 6-H), 7.12 (s, 1H, 8-H), 7.4 (m, 2H, 2′-H + 4′-H), 7.61 (d, 1H, J = 10.9 Hz, 6-H), 7.97 (d, 1H, J = 9.1 Hz, 5-H), 9.08 (s, 1H, 4-H), 10.39 (s, 1H, CONHAr), 12.07 (br s, 1H, NH). UV–Vis (dioxane), ν_{max} (log ε): 32,040 (4.45), 29,000 (4.29), 24,900 cm^{-1} (4.65) Calcd for $C_{24}H_{16}FN_3O_5S$ (477.47): H, 3.38; C, 60.37; N, 8.80. Found: H, 3.46; C, 60.43, N, 8.84.

N^6-(2,4-Dimethylphenyl)-5-methyl-4-oxo-2-(coumarin-3-yl)-3,4-dihydrothieno[2,3-d]pyrimidine-6-carboxamide **4**{**13**}. Yield 79%; mp >300°C; IR (cm^{-1}): 3456, 3188, 3152, 2969, 2920, 1684, 1652, 1608, 1536; ^{1}H NMR: 2.12 + 2.22 (s + s, 6H, ArCH_3), 2.79 (s, 3H, CH_3), 6.98 (d, 1H, J = 8.2 Hz, 5′-H), 7.05 (s, 1H, 3′-H), 7.23 (d, 1H, J = 8.2 Hz, 6′-H), 7.5 (m, 2H, 8-H + 6-H), 7.77 (t, 1H, J = 7.8 Hz, 7-H), 8.03 (d, 1H, J = 7.9 Hz, 5-H), 9.09 (s, 1H, 4-H), 9.65 (s, 1H, CONHAr), 12,19 (br s, 1H, NH). UV–Vis (dioxane), ν_{max} (log ε): 33,640 (4.33), 25,500 cm^{-1} (4.27). Calcd

for $C_{25}H_{19}N_3O_4S$ (457.51): H, 4.19; C, 65.63; N, 9.18. Found: H, 4.12; C, 65.72, N, 9.21.

N^6-(2,4-Dimethylphenyl)-5-methyl-4-oxo-2-(6-chlorocoumarin-3-yl)-3,4-dihydrothieno[2,3-d]pyrimidine-6-carboxamide **4**{**14**}. Yield 75%; mp >300°C; IR (cm^{-1}): 3408, 3225, 2919, 1671, 1541; ^1H NMR: 2.16 + 2.22 (s + s, 6H, $ArCH_3$), 2.79 (s, 3H, CH_3), 6.98 (d, 1H, J = 9.4 Hz, 5′-H), 7.04 (s, 1H 3′-H); 7.19 (d, 1H, J = 9.4 Hz, 6′-H), 7.58 (d, 1H, J = 9.6 Hz, 8-H), 7.7 (dd, 2H, J = 9.6, 2.0 Hz, 7-H), 8.12 (d, 1H, J = 2.0 Hz, 5-H), 8.99 (s, 1H, 4-H), 9.63 (s, 1H, CONHAr), 12.17 (br s, 1H, NH). UV–Vis (dioxane), ν_{max} (log ε): 33,740 (4.44), 24,900 cm^{-1} (4.38) Anal. Calcd for $C_{25}H_{18}ClN_3O_4S$ (491.96): H, 3.69; C, 61.04; N, 8.54. Found: H, 3.67, C, 61.12, N, 8.48.

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