

Synthesis and structure of some thienopyrimidine derivatives

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Abstract A series of substituted thieno[2,3-*d*]pyrimidines was synthesized starting from ethyl-2-amino-4-isopropylthiophene-3-carboxylate. Reaction of 2-hydrazino-5-isopropyl-thieno[2,3-*d*]pyrimidin-4(3H)-one and its 3-methyl analogue with different reagents afforded thieno[2,3-*d*]triazolo[4,3-*a*]pyrimidines and thieno[3,2-*e*]triazolo[4,3-*a*]pyrimidines, beside open chain derivatives.

Keywords Thieno[2,3-*d*]pyrimidines; Thieno[2,3-*d*]triazolo[4,3-*a*]pyrimidines; Thieno[3,2-*e*]triazolo[4,3-*a*]pyrimidines; Thieno[3,2-*e*]tetrazolo[1,5-*a*]pyrimidines; Thiosemicarbazides; Hydrazones.

Introduction

Thienopyrimidine derivatives have received considerable attention due to their wide range of biological activities such as antimicrobial [1, 2], antiviral [3], anticancer [4, 5], anti-inflammatory [6, 7], antihistaminic [8], antipyretics [9], antianaphylactic [10], anticonvulsant [11], and immunostimulant [12] properties. Besides, many thienopyrimidine compounds exhibited analgesic [13], neurotropic [14], molluscicidal and larvicidal [15] activities.

In fact, some of them have been reported to display good activity as Phosphodiesterase [16, 17],

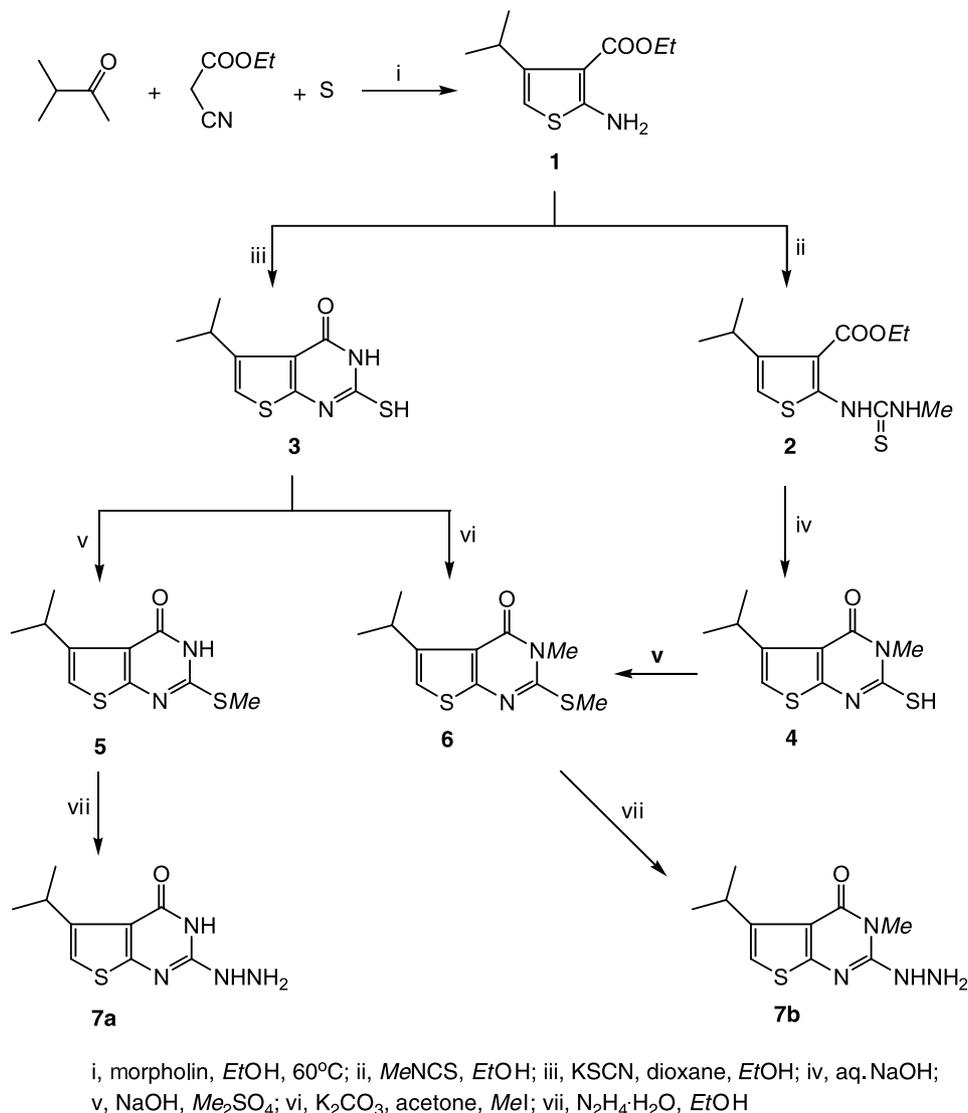
dihydrofolate reductase (DHFR) [18], VEGF kinase [19] inhibitors, in addition to prevention of cartilage destruction in articular disease [20, 21]. In continuation of our previous work on searching antiviral compounds [22, 23] and on the title compounds [24], we reported herein the synthesis and structure elucidation of a new series of thienopyrimidine derivatives.

Results and discussion

The starting material ethyl 2-amino-4-isopropylthiophene-3-carboxylate (**1**) is prepared according to the *Gewald* procedure [25]. Its reaction with thiourea or potassium thiocyanate in dioxane gave the corresponding thienopyrimidine **3**. Subsequent methylation with dimethylsulfate and aqueous NaOH afforded 2-methylthio derivative **5** which upon nucleophilic displacement of the *SMe* group with hydrazine furnished the respective hydrazino derivative **7a**. On the other hand, reaction of **3** with two equivalents of methyl iodide gave the corresponding 5-isopropyl-3-methyl-2-(methylthio)thieno[2,3-*d*]pyrimidin-4-one (**6**) which could be prepared by other route *via* the thiourea **2** followed by cyclization to thienopyrimidine **4**. Subjection of **6** to hydrazine hydrate resulted in the formation of the hydrazino derivative **7b** (Scheme 1). The structure proposal of the prepared compounds was derived from the analytical data (¹H NMR, ¹³C NMR, and IR) and satisfactory elemental analyses.

Dedicated to Prof. Dr. Erik B. Pedersen on the occasion of his 63th birthday

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Scheme 1

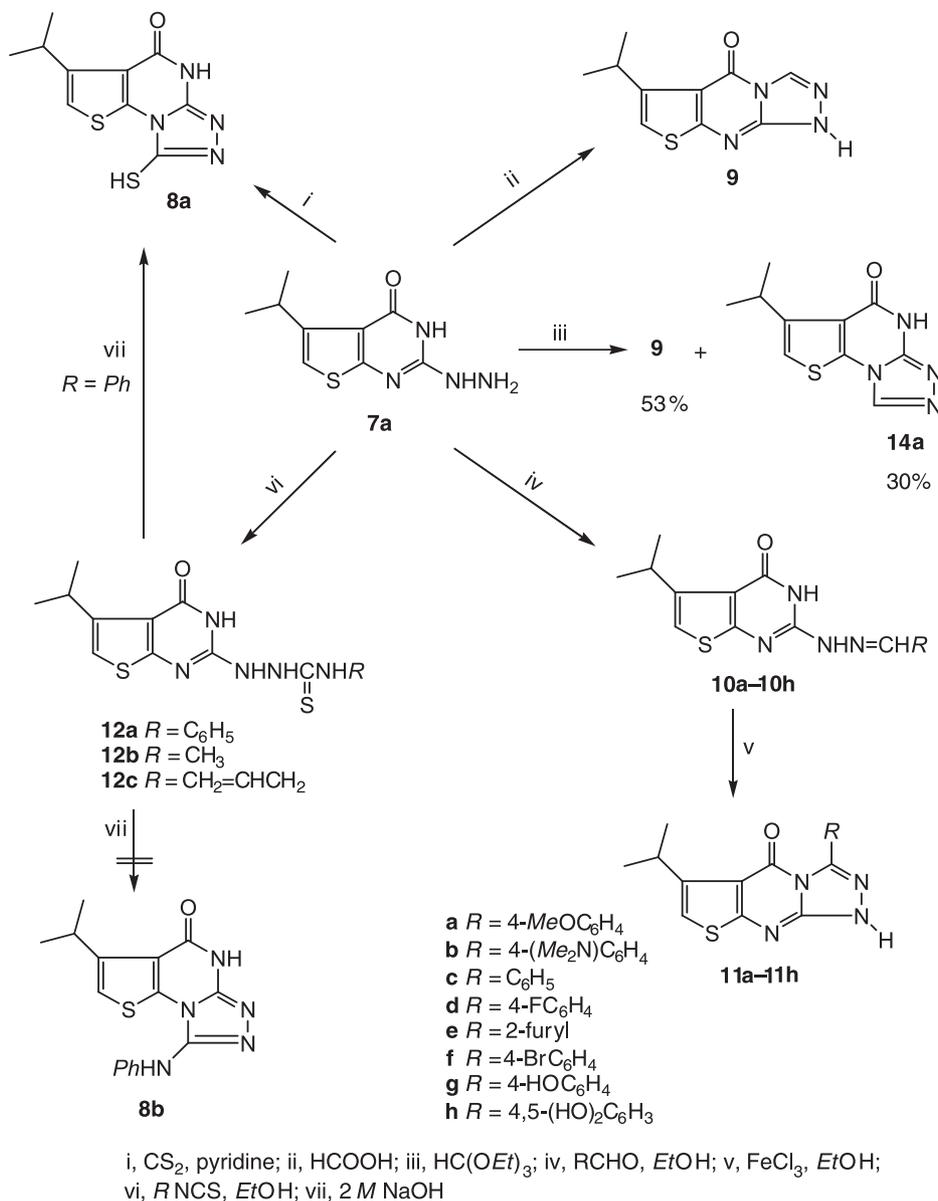
Synthesis of thieno[2,3-*d*]triazolo[4,3-*a*]pyrimidine derivatives

A series of thieno[2,3-*d*]triazolo[4,3-*a*]pyrimidine derivatives was synthesized by condensation of 2-hydrazino-5-isopropylthieno[2,3-*d*]pyrimidin-4-one (**7a**) with various one-carbon donors. For instance, it reacted with formic acid to give the triazolothienopyrimidine **9**, whereas with triethylorthoformate a mixture of **9** and its angular isomer **14a** in ratio of 2:1 was obtained. Condensation of **7a** with aromatic aldehydes resulted in the formation of hydrazones **10a–10h** in good yields. Oxidative cyclization of the latter compounds by ethanolic ferric chloride so-

lution gave 3-aryl thieno[2,3-*d*]triazolo[4,3-*a*]pyrimidine derivatives **11a–11h** (Scheme 2).

Synthesis of thieno[3,2-*e*]triazolo[4,3-*a*]pyrimidine derivatives

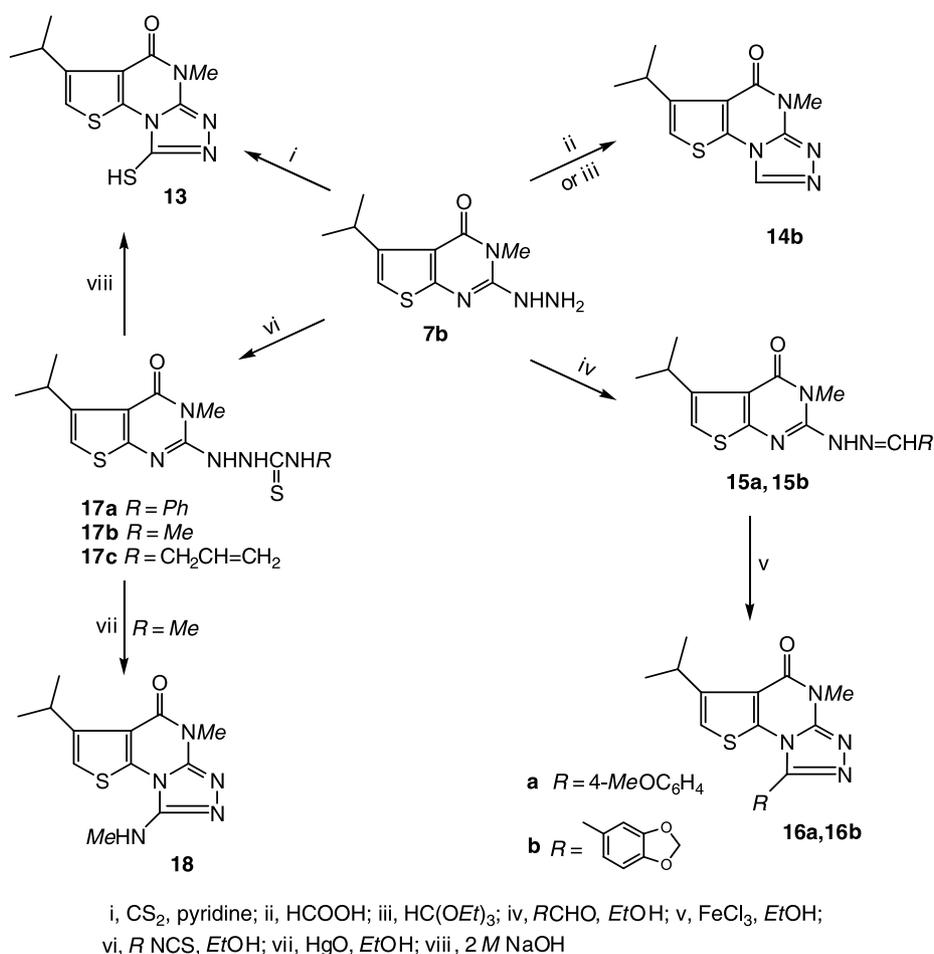
Treatment of the hydrazino compound **7b** with formic acid or triethylorthoformate gave exclusively the isomeric product thieno[3,2-*e*]triazolo[4,3-*a*]pyrimidine (**14b**), since N-3 is blocked by methyl group. Condensation of **7b** with aromatic aldehydes furnished the corresponding hydrazones **15a**, **15b**. Dehydrogenative cyclization by ethanolic FeCl₃



Scheme 2

solution afforded the triazolothienopyrimidines **16a**, **16b**. Addition of **7b** to alkyl and aryl isothiocyanates resulted in the formation of thiosemicarbazides **17a-17c**. Reaction of **17b** with HgO in ethanol gave the expected N-methylamino-triazole **18**, whereas with aqueous $NaOH$ (2M) afforded the mercapto derivative **13**, which could also be obtained by the reaction of **7b** with CS_2 (Scheme 3). The 1H NMR spectra of the hydrazones **15a** and **15b** indicated its existence as a mixture of the *syn*- and *anti*- conformations as indicated by the presence of two doublets for $HC=N$ proton. Aryl and alkyl isothiocyanates reacted with **7a** to provide the corresponding thio-

semicarbazides **12a-12c** (Scheme 2). Treatment of **12a** with aqueous $NaOH$ (2M) did not give the expected 3-amino derivative **8b**. Instead, the 3-mercapto derivative **8a** was obtained, which could also be prepared by the action of CS_2 on **7a** in pyridine. The IR spectra of [3,2-*e*]thieno[1,2,4]triazolo[4,3-*a*]pyrimidines **13**, **14**, **16** and **18** (angular structure) showed absorption due to $C=O$ group in the range of $\bar{\nu} = 1651-1680\text{ cm}^{-1}$. Their 1H NMR spectra displayed resonance for the thiophene proton in the range of $\delta = 7.02-7.18$ ppm. However, the IR spectra of compounds **9** and **11a-11h** (linear structure) showed $C=O$ absorption between $\bar{\nu} = 1706$ and

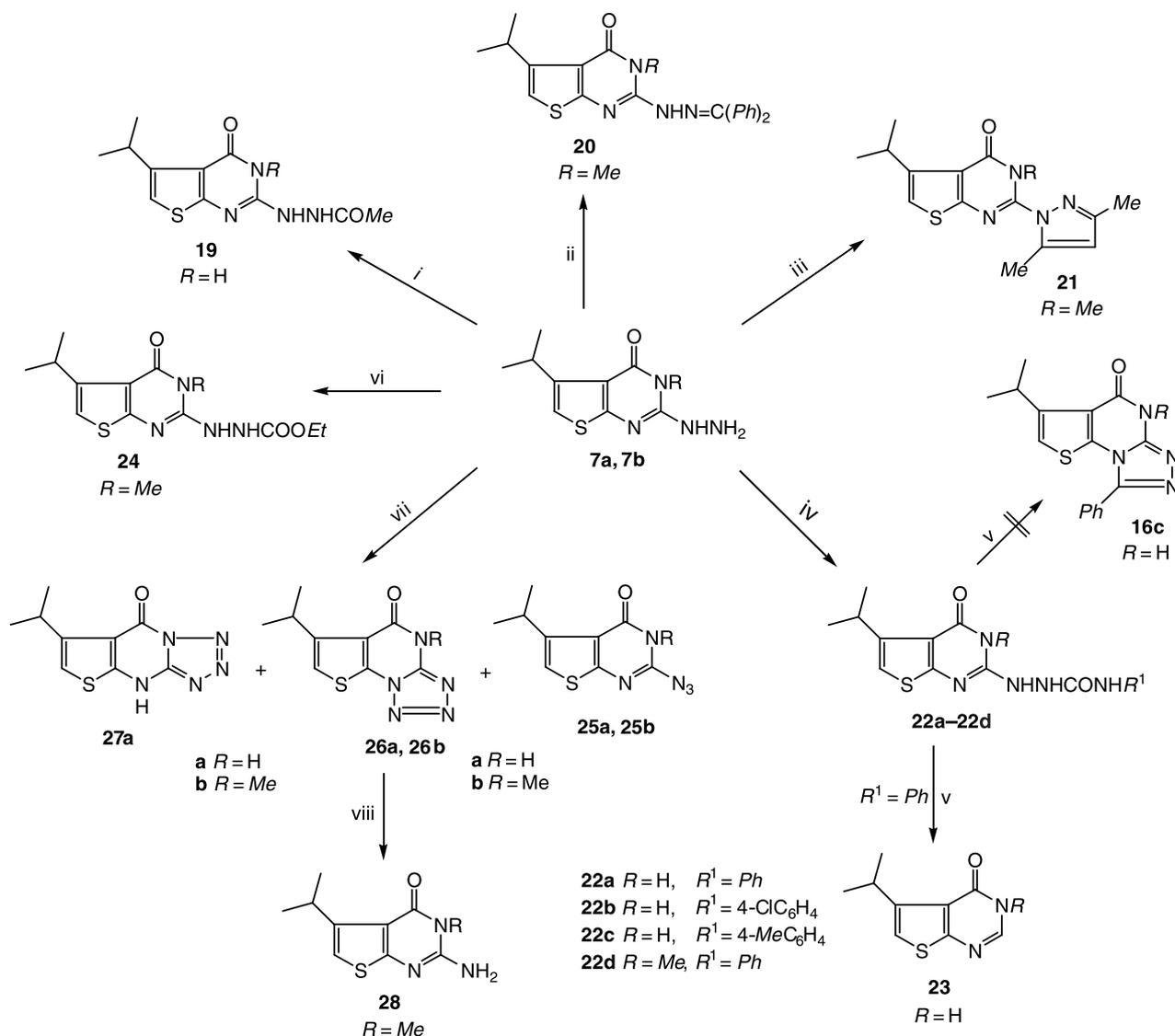


Scheme 3

1713 cm⁻¹ and resonance for thiophene proton in ¹H NMR in the range of $\delta = 6.55\text{--}6.80$ ppm. Compound **8a** which formed by the action of CS₂ in pyridine on **7a** exhibited in its IR spectrum C=O absorption at $\bar{\nu} = 1675$ cm⁻¹ and thiophene proton displayed singlet at $\delta = 7.13$ ppm in the ¹H NMR spectrum. Therefore we believe that compound **8a** possess probably the angular structure 6-isopropyl-3-mercaptothieno[3,2-*e*]triazolo[4,3-*a*]pyrimidin-5-one. Treatment of **7a** with triethylorthoformate afforded the two isomeric products **9** and **14a**, where their thiophene proton displayed resonances in ¹H NMR spectra at $\delta = 6.80$ and 7.16 ppm. The relatively high field region (more deshielded) of thiophene proton in the angular isomer can be attributed to proximity of the triazole ring. This observation could also be seen in ¹H NMR spectra of the tetrazolo compounds **25a**, **25b** where the thiophene proton resonated at $\delta = 7.37$ ppm.

Miscellaneous reactions of **7a** and **7b** with different reagents

Compound **7b** reacted with benzophenone to give the hydrazone **20**, while with pentane-2,4-dione, the pyrazolyl derivative **21** was obtained. Addition of arylisocyanate to **7a**, **7b** afforded the corresponding semicarbazides **22a–22d**. Treatment of **22a** with aqueous NaOH (2 M) did not give the corresponding triazolo derivative **16c**. Instead, 2-unsubstitued thienopyrimidine **23** was formed. Reaction of **7a** with acetic acid furnished the hydrazone **19** whereas with ethyl chloroformate, ethyl-2-(5-isopropyl-3-methyl-4-oxo-3,4-dihydrothieno[2,3-*d*]pyrimidin-2-yl) hydrazinecarboxylate **24** was produced. Compound **7a** and **7b** reacted with nitrous acid at 0°C to give the corresponding tetrazolo derivatives **26a** and **26b** and **27a** beside the azido isomer **25a** and **25b** as indicated by ¹H NMR and IR spectra. Treatment of **25b** with Zinc dust in CH₃COOH afforded the corresponding



Scheme 4

2-aminothienopyrimidine **28** (Scheme 4). The constitution of the prepared compounds was secured by their NMR, IR, and MS spectra.

Experimental

Melting points were measured with a *Kofler* Block apparatus. IR spectra were recorded with Perkin – Elmer Model 1720 FTIR spectrometer. 1H NMR and ^{13}C NMR spectra were determined with a varian EM 390 and Bruker AC – 250 spectrometers. The chemical shifts in ppm are expressed in the δ scale using tetramethylsilane as internal standard. Coupling constants are given in Hz. Mass spectra were recorded on an

AEIMS 30 spectrometer. TLC was performed on Merck silica gel 60-F 254 precoated plastic plates. Microanalyses were performed in the unit of microanalysis at the universities of Cairo (Egypt) and Odense (Denmark); the results were in satisfactory agreement with the calculated values.

Ethyl-2-amino-4-isopropylthiophene-3-carboxylate (**1**, $C_{10}H_{15}NO_2S$)

To a stirred mixture of 8.16 g isopropylmethylketone (100 mmol), 11.30 g ethyl cyanoacetate (100 mmol), 9.00 g morpholin (100 mmol) and absolute ethanol 3.00 cm^3 , 3.20 g sulfur (100 mmol) was added gradually with continuous stirring in a water bath ($60^\circ C$) for 6 h. The reaction mixture was cooled and poured into crushed ice (100 cm^3). The sep-

arated solid was filtered off, washed and crystallized from ethanol to give yellow sheets. Yield 12.80 g (60%); mp 52–54°C; ^1H NMR (DMSO-d_6): δ = 1.13 (d, 6H, 2CH₃), 1.27 (t, J = 7.1 Hz, 3H, CH₃), 3.34 (m, 1H, H), 4.20 (q, J = 7.0 Hz, 2H, CH₂), 5.93 (s, 1H, CH), 7.29 (s, 2H, NH₂) ppm; ^{13}C NMR (DMSO-d_6): δ = 14.14 (CH₃), 23.09 (2CH₃), 28.38 (CH), 58.73 (OCH₂), 99.55, 102.81, 146.75, 164.83 (thiophene), 165.52 (C=O) ppm.

Ethyl-4-isopropyl-2-(3-methylthiourenyl)-3-carboxylate
(**2**, C₁₂H₁₈N₂O₂S₂)

A mixture of 2.13 g **1** (10 mmol) and 0.73 g methyl isothiocyanate (10 mmol) in 10 cm³ absolute ethanol, was boiled under reflux for 3 h. The reaction mixture was cooled and poured onto cold water. The separated solid was filtered off, washed with H₂O, dried and crystallized from ethanol to give brown crystals. Yield 2.03 g (71%); mp 118–120°C; IR (KBr): $\bar{\nu}$ = 1574 (C=C), 1639 (C=O), 3243 (NH) cm⁻¹; ^1H NMR (DMSO-d_6): δ = 1.12 (m, 9H, CH₃), 1.33 (d, 3H, NCH₃), 2.91 (q, 2H, CH₂), 4.30 (m, 1H, CH), 6.52 (s, 1H, CH), 9.40, 11.51 (2bs, 2H, 2NH) ppm.

5-Isopropyl-2-mercaptothieno[2,3-d]pyrimidin-4(3H)-one
(**3**, C₉H₁₀N₂OS₂)

A mixture of 4.26 g **1** (20 mmol) and excess of potassium thiocyanate (3.88 g, 40 mmol) in 25 cm³ dioxan and 5 cm³ absolute ethanol was stirred with gradually addition of 5 cm³ hydrochloric acid 37%. The reaction mixture was boiled under reflux for 6 h. Then, it was cooled and poured into cold water. The separated solid was boiled in sodium hydroxide (1 M, 50 cm³) for 10 min, then cooled and neutralized by addition of 1 M hydrochloric acid. The precipitate was filtered off, washed, and crystallized from ethanol as colorless crystals. Yield 2.26 g (50%); mp 52–54°C; IR (KBr): $\bar{\nu}$ = 1536 (C=C), 1671 (C=O) cm⁻¹; ^1H NMR (DMSO-d_6): δ = 1.18 (d, 6H, 2CH₃), 3.46 (m, 1H, CH), 6.88 (s, 1H, CH), 12.34, 13.44 (2s, 2H, 2NH) ppm; ^{13}C NMR (DMSO-d_6): δ = 22.62 (2CH₃), 27.85 (CH), 11.37, 115.90, 145.59, 152.83 (thiophene), 156.89 (C=O), 172.95 (C=S) ppm.

5-Isopropyl-2-mercapto-3-methylthieno[2,3-d]pyrimidin-4-one
(**4**, C₁₀H₁₂N₂OS₂)

A solution of 2.86 g **2** (10 mmol) in 15 cm³ 2 M sodium hydroxide was boiled under reflux for 1 h. After cooling the reaction mixture was neutralized by 2 M hydrochloric acid. The precipitate was filtered off, dried, and crystallized from ethanol as white crystals. Yield 1.39 g (67%); mp 178–180°C; IR (KBr): $\bar{\nu}$ = 1266 (C=S), 1543 (C=C), 1568 (C=N), 1693 (C=O) cm⁻¹; ^1H NMR (DMSO-d_6): δ = 1.20 (d, 6H, 2CH₃), 3.33 (s, 3H, NCH₃), 3.53 (m, 1H, CH), 6.90 (s, 1H, CH), 13.64 (s, 1H, SH) ppm.

5-Isopropyl-2-(methylthio)thieno[2,3-d]pyrimidin-4(3H)-one
(**5**, C₁₀H₁₂N₂OS₂)

A solution of 3.39 g **3** (15 mmol) in 150 cm³ 0.1 M sodium hydroxide and 15 cm³ dimethylsulfate was stirred for 5 min. The precipitated solid was dissolved by addition of 4 M sodi-

um hydroxide and the solution was heated at 70°C for 10 min. After cooling, the solution was filtered and neutralized by 2 M hydrochloric acid. The precipitate was filtered off, dried, and recrystallized from ethanol as brown crystals. Yield 2.88 g (80%); mp 178–180°C; ^1H NMR (DMSO-d_6): δ = 1.23 (d, 6H, 2CH₃), 2.49 (s, 3H, SCH₃), 3.55 (m, 1H, CH), 7.00 (s, 1H, CH), 12.51 (bs, 1H, NH) ppm.

5-Isopropyl-3-methyl-2-(methylthio)thieno[2,3-d]pyrimidin-4-one
(**6**, C₁₁H₁₄N₂OS₂)

Method A: A mixture of 2.26 g **3** (10 mmol) and 2.76 g potassium carbonate (20 mmol) in 50 cm³ dry acetone was stirred for 2 h. Methyl iodide (2.84 g, 20 mmol) was added gradually with stirring over night. The reaction mixture was filtered and the solvent was evaporated under vacuum. The solid residue was washed and crystallized from ethanol as brown crystals. Yield 1.39 g (67%); mp 178–180°C; IR (KBr): $\bar{\nu}$ = 1561 (C=C, C=N), 1667 (C=O) cm⁻¹; ^1H NMR (DMSO-d_6): δ = 1.22 (d, 6H, 2CH₃), 2.57 (s, 3H, SCH₃), 3.45 (s, 3H, NCH₃), 3.61 (m, 1H, CH), 6.99 (s, 1H, CH) ppm.

Method B: A mixture of 2.08 g **4** (10 mmol) and 1.38 g potassium carbonate (10 mmol) in 50 cm³ dry acetone was stirred for 1 h. Methyl iodide (1.42 g, 10 mmol) was added gradually. Working up as described before afforded brown crystals. Yield 1.45 (70%).

2-Hydrazino-5-isopropylthieno[2,3-d]pyrimidin-4(3H)-one
(**7a**, C₉H₁₂N₄OS)

A mixture of 0.24 g **5** (1 mmol) and 5 cm³ NH₂NH₂ · H₂O in 15 cm³ absolute ethanol was boiled under reflux for 3 h. The colorless product that separated on cooling was filtered off and recrystallized from ethanol to provide colorless crystals. Yield 0.15 g (70%); mp 244–246°C; IR (KBr): $\bar{\nu}$ = 1614 (C=C, C=N), 1778 (C=O), 3264 (NH) cm⁻¹; ^1H NMR (DMSO-d_6): δ = 1.21 (d, 6H, 2CH₃), 3.47 (m, 1H, CH), 4.80 (bs, 2H, NH₂), 6.58 (s, 1H, CH) 8.29, (bs, 1H, NH) ppm; ^{13}C NMR (DMSO-d_6): δ = 22.72 (2CH₃), 28.23 (CH), 107.70, 113.16, 145.07, 154.62 (thiophene), 157.80, (C=N), 168.72 (C=O) ppm.

2-Hydrazino-5-isopropyl-3-methylthieno[2,3-d]pyrimidin-4-one
(**7b**, C₁₀H₁₄N₄OS)

From 0.22 g **6** (1 mmol) and hydrazine hydrate as described for **7a** to give colorless crystals. Yield 0.17 g (72%); mp 250–252°C; IR (KBr): $\bar{\nu}$ = 1530 (C=C, C=N), 1675 (C=O) 3210 (NH) cm⁻¹; ^1H NMR (DMSO-d_6): δ = 1.20 (d, 6H, 2CH₃), 3.29 (s, 1H, CH₃), 3.50 (m, 1H, CH), 4.42 (bs, 2H, NH₂) 6.62 (s, 1H, CH), 8.23 (bs, 1H, NH) ppm.

6-Isopropyl-3-mercaptothieno[3,2-e][1,2,4]triazolo[4,3-a]-pyrimidin-5(1H)-one
(**8**, C₁₀H₁₀N₄OS₂)

Method A: A mixture of 2.24 g **7a** (10 mmol) and 0.91 g CS₂ (12 mmol) in 15 cm³ pyridine was heated under reflux for 6 h and then allowed to cool. The solid product was washed and recrystallized from ethanol to give white powder. Yield 1.86 g (70%); mp 282–284°C; IR (KBr): $\bar{\nu}$ = 1647 (C=C, C=N), 1676 (C=O), 3118 (NH) cm⁻¹; ^1H NMR (DMSO-d_6): δ = 1.25 (s, 6H, 2CH₃), 3.72 (m, 1H, CH), 7.15 (s, 1H, CH), 12.54, 13.83 (2bs, 2H, 2NH) ppm; ^{13}C NMR δ = 23.01 (2CH₃), 27.16 (CH),

114.51, 117.30, 142.04, 145.35 (thiophene), 149.49 (C=N), 157.18 (C=O), 158.50 (C=S) ppm.

Method B: A solution of 0.36 g **12a** (1 mmol) and 25 cm³ 2 M sodium hydroxide was boiled for 20 min and then neutralized by addition of 2 M hydrochloric acid. The precipitate formed was collected, washed and crystallized from ethanol as white crystals. Yield 0.19 g (71%).

6-Isopropylthieno[2,3-d][1,2,4]triazolo[4,3-a]pyrimidin-5(1H)-one (9, C₁₀H₁₀N₄O₅)

Method A: A solution of 2.24 g **7a** (10 mmol) in 10 cm³ formic acid was heated under reflux for 8 h. The reaction mixture was allowed to cool and then poured onto 100 cm³ ice cold water. The separated product was filtered off, washed with water, dried, and crystallized from ethanol as colorless crystals. Yield 1.63 g (70%); mp 203–205°C; IR (KBr): $\bar{\nu}$ = 1620 (C=C, C=N), 1704 (C=O), 3097 (NH) cm⁻¹; ¹H NMR (DMSO-d₆): δ = 1.25 (d, 6H, 2CH₃), 3.58 (m, 1H, CH), 6.80 (s, 1H, CH), 9.08 (s, 1H, N=CH), 13.84 (bs, 1H, NH) ppm; ¹³C NMR (DMSO-d₆): δ = 22.69 (2CH₃), 28.47 (CH), 109.68, 111.09, 144.64, 148.47 (thiophene), 131.96, 151.49 (2C=N), 169.74 (C=O) ppm.

Method B: A solution of 0.67 g **7a** (3 mmol) in 20 cm³ triethyl orthoformate was boiled under reflux for 4 h. The reaction mixture showed two spots on TLC plate using 2% CH₂Cl₂/MeOH as eluent. A solid product was precipitated on hot and filtered off as white powder (**14a**). Evaporating of the solvent from the mother liquor, washing the solid residue, and crystallization from methylene chloride afforded pale green crystals. Yield 0.38 g (53%).

General procedure for the synthesis of compounds 10a–10h

A solution of 10 mmol **7a** and 10 mmol appropriate aromatic aldehyde in 30 cm³ ethanol containing a few drops of glacial acetic acid, was boiled under reflux for 3 h. The product that separated on cooling was filtered off, dried, and crystallized from ethanol.

4-Methoxybenzaldehyde (5-isopropyl-4-oxo-3,4-dihydro-thieno[2,3-d]pyrimidine-2-yl)hydrazone (10a, C₁₇H₁₈N₄O₂S)

From 2.24 g **7a** (10 mmol) and 1.36 g *p*-anisaldehyde (10 mmol) as described before. Yield 2.56 g (75%) as yellow crystals; mp 208–211°C; IR (KBr): $\bar{\nu}$ = 1591 (C=C, C=N), 1662 (C=O), 3164, 3353 (NH) cm⁻¹; ¹H NMR (DMSO-d₆): δ = 1.10 (d, 6H, 2CH₃), 3.40 (m, 1H, CH), 3.67 (s, 3H, OCH₃), 6.54 (s, 1H, CH), 6.84 (d, *J* = 8.5 Hz, 2H, *Ar*-H), 7.74 (d, *J* = 8.4 Hz, 2H, *Ar*-H), 7.86 (s, 1H, N=CH), 11.07, 11.42 (2s, 2H, 2NH) ppm; ¹³C NMR (DMSO-d₆): δ = 22.79 (2Me), 28.27 (CH), 55.19 (OMe), 109.08, 114.59, 145.39, 150.10 (thiophene), 113.92, 126.85, 128.96, 143.05 (*Ar*-C), 158.22, 160.43 (2C=N), 167.95 (C=O) ppm.

4-(Dimethylamino)benzaldehyde (5-isopropyl-4-oxo-3,4-dihydrothieno[2,3-d]pyrimidine-2-yl)hydrazone (10b, C₁₈H₂₁N₅O₅)

From **7a** and 1.49 g 4-(dimethylamino)benzaldehyde (10 mmol). Yield 2.84 g (80%) as yellow crystals; mp 247–249°C; IR (KBr): $\bar{\nu}$ = 1590 (C=C, C=N), 1661 (C=O), 3227,

3365 (NH) cm⁻¹; ¹H NMR (DMSO-d₆): δ = 1.21 (d, 6H, 2CH₃), 2.97 (s, 6H, 2CH₃), 3.53 (m, 1H, CH), 6.66 (s, 1H, CH), 6.73 (d, *J* = 9.8 Hz, 2H, *Ar*-H), 7.71 (d, *J* = 9.0 Hz, 2H, *Ar*-H), 7.93 (s, 1H, N=CH), 10.97, 11.42 (2s, 2H, 2NH) ppm; ¹³C NMR (DMSO-d₆): δ = 22.50 (2Me), 27.98 (CH), 39.44 (2CH₃), 108.46, 113.97, 143.86, 145.08 (thiophene), 111.23, 121.33, 128.34, 149.79 (*Ar*-C), 150.87, 157.84 (2C=N), 167.88 (C=O) ppm.

Benzaldehyde (5-isopropyl-4-oxo-3,4-dihydrothieno[2,3-d]pyrimidine-2-yl)hydrazone (10c, C₁₆H₁₆N₄O₅)

From **7a** and 1.06 g benzaldehyde (10 mmol). Yield 2.34 g (75%) as yellow crystals; mp 250–252°C; IR (KBr): $\bar{\nu}$ = 1610 (C=C, C=N), 1656 (C=O), 3153 (NH) cm⁻¹; ¹H NMR (DMSO-d₆): δ = 1.24 (d, 6H, 2CH₃), 3.55 (m, 1H, CH), 6.72 (s, 1H, CH), 7.40, 7.95 (m, 5H, *Ar*-H), 8.06 (s, 1H, N=CH), 11.17, 11.60 (2s, 2H, 2NH) ppm; ¹³C NMR (DMSO-d₆): δ = 22.78 (2CH₃), 28.26 (CH), 109.37, 114.85, 143.08, 145.40 (thiophene), 127.32, 128.40, 129.46, 134.17 (*Ar*-C), 150.03, 158.21 (2C=N), 167.76 (C=O) ppm.

4-Fluorobenzaldehyde (5-isopropyl-4-oxo-3,4-dihydro-thieno[2,3-d]pyrimidine-2-yl)hydrazone (10d, C₁₆H₁₅FN₄O₅)

From **7a** and 1.24 g 4-fluorobenzaldehyde (10 mmol). Yield 2.44 g (74%) as colorless crystals; mp 269–271°C; IR (KBr): $\bar{\nu}$ = 1608 (C=C, C=N), 1663 (C=O), 3282 (NH) cm⁻¹; ¹H NMR (DMSO-d₆): δ = 1.09 (d, 6H, 2CH₃), 3.40 (m, 1H, CH), 6.55 (s, 1H, CH), 7.10 (d, *J* = 8.7 Hz, 2H, *Ar*-H), 7.87 (d, *J* = 2.1 Hz, 2H, *Ar*-H), 7.90 (s, 1H, N=CH), 11.27, 11.54 (2s, 2H, 2NH) ppm; ¹³C NMR (DMSO-d₆): δ = 22.78 (2CH₃), 28.26 (CH), 109.33, 114.85, 145.40, 150.06 (thiophene), 115.24, 129.59, 130.87, 141.88 (*Ar*-C), 158.28, 161.17 (2C=N), 167.76 (C=O) ppm.

2-Fluraldehyde (5-isopropyl-4-oxo-3,4-dihydrothieno[2,3-d]pyrimidine-2-yl)hydrazone (10e, C₁₄H₁₄N₄O₂S)

From **7a** and 0.96 g 2-furaldehyde (10 mmol). Yield 2.02 g (67%) as pale brown crystals; mp 246–248°C; IR (KBr): $\bar{\nu}$ = 1612 (C=C, C=N), 1654 (C=O), 3396, 3569 (NH) cm⁻¹; ¹H NMR (DMSO-d₆): δ = 1.24 (d, 6H, 2CH₃), 3.53 (m, 1H, CH), 6.64 (s, 1H, CH), 6.72 (s, 1H, *Ar*-H), 7.10 (d, 1H, *Ar*-H), 7.82 (s, 1H, *Ar*-H), 7.98 (s, 1H, N=CH), 10.64, 11.70 (2s, 2H, 2NH) ppm; ¹³C NMR (DMSO-d₆): δ = 22.77 (2CH₃), 28.26 (CH), 109.60, 114.90, 145.36, 149.95 (thiophene), 111.94, 112.19, 133.18, 144.60 (Furan), 150.00, 157.75 (2C=N), 167.75 (C=O) ppm.

4-Bromobenzaldehyde (5-isopropyl-4-oxo-3,4-dihydrothieno[2,3-d]pyrimidine-2-yl)hydrazone (10f, C₁₆H₁₅BrN₄O₅)

From **7a** and 1.85 g 4-bromobenzaldehyde (10 mmol). Yield 3.04 g (78%) as yellow crystals; mp 295–297°C; IR (KBr): $\bar{\nu}$ = 1599 (C=C, C=N), 1662 (C=O), 3156, 3347 (NH) cm⁻¹; ¹H NMR (DMSO-d₆): δ = 1.24 (d, 6H, 2CH₃), 3.55 (m, 1H, CH), 6.72 (s, 1H, CH), 7.62 (d, *J* = 8.4 Hz, 2H, *Ar*-H), 7.93 (d, *J* = 8.6 Hz, 2H, *Ar*-H), 8.02 (s, 1H, N=CH), 11.46, 11.76 (2s, 2H, 2NH); ¹³C NMR (DMSO-d₆): δ = 22.79 (2CH₃), 28.26 (CH), 109.49, 114.98, 141.75, 145.41

(thiophene), 122.68, 129.24, 131.34, 133.53 (*Ar*-C), 149.96, 158.28 (2C=N), 167.65 (C=O) ppm.

4-Hydroxybenzaldehyde (5-isopropyl-4-oxo-3,4-dihydro-thieno[2,3-d]pyrimidine-2-yl)hydrazone (10g, C₁₆H₁₆N₄O₂S)

From **7a** and 1.22 g 4-hydroxybenzaldehyde (10 mmol). Yield 2.42 (74%) as colorless crystals; mp 277–279°C; ¹H NMR (*DMSO*-d₆): δ = 1.24 (d, 6H, 2CH₃), 3.55 (m, 1H, CH), 6.67 (s, 1H, CH), 6.83 (d, *J* = 8.7 Hz, 2H, *Ar*-H), 7.76 (d, *J* = 8.7 Hz, 2H, *Ar*-H), 7.97 (s, 1H, N=CH), 9.85 (bs, 1H, OH), 11.11, 11.53 (2s, 2H, 2NH) ppm; ¹³C NMR (*DMSO*-d₆): δ = 22.78 (2CH₃), 28.27 (CH), 108.94, 114.48, 145.39, 150.11 (thiophene), 115.33, 125.36, 129.09, 143.52 (*Ar*-C), 158.17, 159.00 (2C=N), 168.03 (C=O) ppm.

3,4-Dihydroxybenzaldehyde (5-isopropyl-4-oxo-3,4-dihydro-thieno[2,3-d]pyrimidine-2-yl)hydrazone (10h, C₁₆H₁₆N₄O₃S)

From **7a** and 1.38 g 3,4-dihydroxybenzaldehyde (10 mmol). Yield 2.44 (71%) as colorless crystals; mp 273–275°C; IR (KBr): $\bar{\nu}$ = 1578 (C=C, C=N), 1632 (C=O), 3318, 3413 (NH), 3651 (OH) cm⁻¹; ¹H NMR (*DMSO*-d₆): δ = 1.24 (d, 6H, 2CH₃), 3.54 (m, 1H, CH), 6.68 (s, 1H, CH), 6.79, 7.10 (2d, 2H, *Ar*-H), 7.40 (s, 1H, *Ar*-H), 7.90 (s, 1H, N=CH), 9.10, 9.40 (2bs, 2H, 2OH), 10.89, 11.46 (2s, 2H, 2NH) ppm; ¹³C NMR (*DMSO*-d₆): δ = 22.79 (2Me), 28.27 (CH), 109.01, 114.48, 145.46, 147.53 (thiophene), 113.65, 115.30, 120.28, 125.68, 143.94, 145.36 (*Ar*-C), 150.04, 158.03 (2C=N), 168.08 (C=O) ppm.

General procedure for the synthesis of compounds 11a–11h

A solution of 0.4 g ferric chloride in 5 cm³ ethanol was added dropwise to a boiling solution of 2 mmol aldehyde hydrazones **10a–10h** in 50 cm³ ethanol. Heating was continued for 30 min and the mixture was then kept overnight at room temperature. Evaporation of the solvent under reduced pressure, washing the residue with water, and drying afforded a solid product which could be crystallized from ethanol.

6-Isopropyl-3-(4-methoxyphenyl)thieno[2,3-d][1,2,4]triazolo[4,3-a]pyrimidin-5(1H)-one (11a, C₁₇H₁₆N₄O₂S)

From 0.68 g **10a** (2 mmol) and FeCl₃ as described before. Yield 0.47 g (70%) as colorless crystals; mp 223–225°C; IR (KBr): $\bar{\nu}$ = 1624 (C=C, C=N), 1713 (C=O) cm⁻¹; ¹H NMR (*DMSO*-d₆): δ = 1.22 (d, 6H, 2CH₃), 3.53 (m, 1H, CH), 3.85 (s, 3H, OCH₃), 6.77 (s, 1H, CH), 7.07, 7.66 (2d, 4H, *Ar*-H), 14.15 (s, 1H, NH) ppm; ¹³C NMR (*DMSO*-d₆): δ = 22.80 (2Me), 28.38 (CH), 55.24 (OCH₃), 109.38, 111.47, 144.40, 145.07 (thiophene), 112.84, 119.51, 124.22, 131.88 (*Ar*-C), 149.63, 152.78 (C=N), 160.42 (C=O) ppm.

3-[4-(Dimethylamino)phenyl]-6-isopropylthieno[2,3-d][1,2,4]triazolo[4,3-a]pyrimidin-5(1H)-one (11b, C₁₈H₁₉N₅OS)

From 0.71 g **10b** (2 mmol) and FeCl₃. Yield (0.44 g, 63%) as green crystals; mp 215–217°C; IR (KBr): $\bar{\nu}$ = 1611 (C=C, C=N), 1708 (C=O) cm⁻¹; ¹H NMR (*DMSO*-d₆): δ = 1.21 (d, 6H, 2CH₃), 3.00 (s, 6H, N(CH₃)₂), 3.54 (m, 1H, CH),

6.74 (s, 1H, CH), 6.76, 7.56 (m, 4H, *Ar*-H), 14.00 (s, 1H, NH) ppm; ¹³C NMR (*DMSO*-d₆): δ = 22.79 (2CH₃), 28.37 (CH), 39.76 (2NCH₃), 109.17, 111.36, 145.06, 145.18 (thiophene), 110.44, 114.03, 131.24, 149.64 (*Ar*-C), 150.99, 152.85 (2C=N), 168.82 (C=O) ppm.

6-Isopropyl-3-phenylthieno[2,3-d][1,2,4]triazolo[4,3-a]pyrimidin-5(1H)-one (11c, C₁₆H₁₄N₄OS)

From 0.62 g **10c** (2 mmol) and FeCl₃. Yield 0.37 g (60%) as brown powder; mp 180–182°C; IR (KBr): $\bar{\nu}$ = 1626 (C=C, C=N), 1709 (C=O) cm⁻¹; ¹H NMR (*DMSO*-d₆): δ = 1.09 (d, 6H, 2CH₃), 3.40 (bm, 1H, CH), 6.55 (s, 1H, CH), 7.10, 7.90 (m, 5H, *Ar*-H), 12.55 (bs, 1H, NH) ppm; *m/z* = 310 (M⁺).

3-(4-Fluorophenyl)-6-isopropylthieno[2,3-d][1,2,4]triazolo[4,3-a]pyrimidin-5(1H)-one (11d, C₁₆H₁₃F N₄OS)

From 0.66 g **10d** (2 mmol) and FeCl₃. Yield 0.42 g (65%) as brownish yellow powder; mp 215–217°C; IR (KBr): $\bar{\nu}$ = 1613 (C=C, C=N), 1709 (C=O) cm⁻¹; ¹H NMR (*DMSO*-d₆): δ = 1.20 (d, 6H, 2CH₃), 3.69 (m, 1H, CH), 6.76 (s, 1H, CH), 7.34, 7.80 (m, 4H, *Ar*-H), 12.75 (bs, 1H, NH) ppm.

3-(2-Furyl)-6-isopropylthieno[2,3-d][1,2,4]triazolo[4,3-a]pyrimidin-5(1H)-one (11e, C₁₄H₁₂N₄O₂S)

From 0.60 g **10e** (2 mmol) and FeCl₃. Yield 0.34 g (67%) as brown crystals; mp 235–237°C; IR (KBr): $\bar{\nu}$ = 1624 (C=C, C=N), 1712 (C=O) cm⁻¹; ¹H NMR (*DMSO*-d₆): δ = 1.25 (d, 6H, 2CH₃), 3.58 (m, 1H, CH), 6.71 (s, 1H, CH), 6.80 (d, 1H, *Ar*-H), 7.46 (d, 1H, *Ar*-H), 7.95 (s, 1H, *Ar*-H), 14.25 (s, 1H, NH) ppm; *m/z* = 300 (M⁺).

3-(4-Bromophenyl)-6-isopropylthieno[2,3-d][1,2,4]triazolo[4,3-a]pyrimidin-5(1H)-one (11f, C₁₆H₁₃BrN₄OS)

From 0.78 g **10f** (2 mmol) and FeCl₃. Yield 0.50 g (65%) as pale yellow crystals; mp 228–230°C; IR (KBr): $\bar{\nu}$ = 1622 (C=C, C=N), 1710 (C=O) cm⁻¹; ¹H NMR (*DMSO*-d₆): δ = 1.21 (d, 6H, 2CH₃), 3.68 (bm, 1H, CH), 6.78 (bs, 1H, CH), 7.00, 7.70 (m, 4H, *Ar*-H), 12.80 (bs, 1H, NH) ppm; ¹³C NMR (*DMSO*-d₆): δ = 22.37 (2CH₃), 27.85 (CH), 108.98, 113.21, 142.91, 145.29 (thiophene), 123.05, 126.03, 129.95, 131.87 (*Ar*-C), 149.40, 151.94 (2C=N), 167.50 (C=O) ppm.

3-(4-Hydroxyphenyl)-6-isopropylthieno[2,3-d][1,2,4]triazolo[4,3-a]pyrimidin-5(1H)-one (11g, C₁₆H₁₄N₄O₂S)

From 0.66 g **10g** (2 mmol) and FeCl₃. Yield 0.39 g (60%) as white powder; mp 248–250°C; IR (KBr): $\bar{\nu}$ = 1614 (C=C, C=N), 1685 (C=O), 3107 (NH), 3326 (OH) cm⁻¹; ¹H NMR (*DMSO*-d₆): δ = 1.20 (d, 6H, 2CH₃), 3.51 (m, 1H, CH), 6.61 (s, 1H, CH), 6.83, 7.60 (m, 4H, *Ar*-H), 9.90 (bs, 1H, OH), 14.00 (bs, 1H, NH) ppm; ¹³C NMR (*DMSO*-d₆): δ = 22.69 (2CH₃), 28.23 (CH), 108.85, 111.06, 144.89, 150.11 (thiophene), 114.05, 118.00, 131.77, 143.50 (*Ar*-C), 152.50, 158.75 (2C=N), 168.59 (C=O) ppm; *m/z* = 326 (M⁺).

3-(3,4-Dihydroxyphenyl)-6-isopropylthieno[2,3-d][1,2,4]-triazolo[4,3-a]pyrimidin-5(1H)-one (11h, C₁₆H₁₂N₄O₃S)

From 0.69 g **11h** (2 mmol) and FeCl₃. Yield 0.42 g (61%) as brown powder; mp >300°C; IR (KBr): $\bar{\nu}$ = 1609 (C=C, C=N), 1694 (C=O), 3350 (OH) cm⁻¹.

General procedure for the synthesis of compounds 12a–12c

A solution of 0.22 g **7a** (1 mmol) and an excess of isothiocyanate (2.5 mmol) in 10 cm³ ethanol was boiled under reflux for 4 h. The product that separated on cooling was filtered off, and recrystallized from ethanol.

2-(5-Isopropyl-4-oxo-3,4-dihydrothieno[2,3-d]pyrimidin-2-yl)-N-phenylhydrazine carbothioamide (12a, C₁₆H₁₇N₅OS₂)

From **7a** and 0.30 g phenyl isothiocyanate (2.5 mmol). Yield 0.27 g (75%) as colorless crystals; mp 270–272°C; IR (KBr): $\bar{\nu}$ = 1608 (C=C, C=N), 1659 (C=O), 3170, 3280 (NH) cm⁻¹; ¹H NMR (DMSO-d₆): δ = 1.22 (d, 6H, 2CH₃), 3.49 (m, 1H, CH), 6.74 (s, 1H, CH), 7.14 (m, 1H, Ar-H), 7.32 (m, 2H, Ar-H), 7.35 (m, 2H, Ar-H), 8.66, 9.58, 9.85, 11.15 (4s, 4H, 4NH) ppm; ¹³C NMR (DMSO-d₆): δ = 22.80 (2CH₃), 28.27 (CH), 109.94, 115.24, 145.19, 152.34 (thiophene), 124.84, 128.04, 139.05 (Ar-C), 158.29 (C=N), 167.78 (C=O), 181.61 (C=S) ppm.

2-(5-Isopropyl-4-oxo-3,4-dihydrothieno[2,3-d]pyrimidin-2-yl)-N-methylhydrazine carbothioamide (12b, C₁₁H₁₅N₅OS₂)

From **7a** and 0.18 g methyl isothiocyanate (2.5 mmol). Yield 0.22 g (74%) as pale yellow crystals; mp 202–204°C; IR (KBr) $\bar{\nu}$ = 1609 (C=C, C=N), 1664 (C=O), 3168, 3304 (NH) cm⁻¹; ¹H NMR (DMSO-d₆): δ = 1.21 (d, 6H, 2CH₃), 2.88 (d, 3H, NCH₃), 3.50 (m, 1H, CH), 6.73 (s, 1H, CH), 8.13 (m, 1H, NH), 8.47, 9.21, 11.00 (3s, 3H, 3NH) ppm; ¹³C NMR (DMSO-d₆): δ = 22.73 (2CH₃), 28.20 (CH), 30.82 (N-CH₃), 109.79, 115.21, 145.10, 152.50 (thiophene), 157.85 (C=N), 167.88 (C=O), 182.50 (C=S) ppm.

N-Allyl-2-(5-isopropyl-4-oxo-3,4-dihydrothieno[2,3-d]pyrimidin-2-yl)hydrazine carbothioamid (12c, C₁₃H₁₇N₅OS₂)

From **7a** and 0.25 g allyl isothiocyanate (2.5 mmol). Yield 0.23 g (71%) as yellow crystals; mp 170–172°C; IR (KBr): $\bar{\nu}$ = 1606 (C=C, C=N), 1665 (C=O), 3160, 3289 (NH) cm⁻¹; ¹H NMR (DMSO-d₆): δ = 1.21 (d, 6H, 2CH₃), 3.51 (m, 1H, CH), 4.10 (d, 2H, CH₂), 5.05 (q, 2H, N-CH₂), 5.81 (m, 1H, CH), 6.73 (s, 1H, CH), 8.33, 8.50, 9.30, 11.00 (4s, 4H, 4NH) ppm.

3-Isopropyl-8-mercapto-5-methylthieno[3,2-e][1,2,4]-triazolo-[4,3-a]pyrimidin-4(5H)-one (13, C₁₃H₁₄N₂O₂S₂)

From 2.38 g **7b** (10 mmol) and 0.91 g CS₂ (12 mmol) in 15 cm³ pyridine, Yield 2.04 g (73%); mp 257–259°C; IR (KBr): $\bar{\nu}$ = 1615 (C=C, C=N), 1651 (C=O), 3202 (NH) cm⁻¹; ¹H NMR (DMSO-d₆): δ = 1.24 (d, 6H, 2CH₃), 3.39 (s, 3H, NCH₃), 3.72 (m, 1H, CH), 7.15 (s, 1H, CH), 14.09 (s, 1H, NH) ppm; ¹³C NMR (DMSO-d₆): δ = 23.00 (2CH₃), 27.21 (CH), 27.90 (N-CH₃), 114.69, 116.73, 141.11, 145.30 (thiophene), 156.04 (C=N), 159.39 (C=O), 162.02 (C=S) ppm.

3-Isopropylthieno[3,2-e]triazolo[4,3-a]pyrimidin-4(5H)-one (14a, C₁₀H₁₀N₄O₃S)

A solution of 2.24 g **7a** (10 mmol) in 10 cm³ triethyl orthoformate was heated under reflux for 4 h. A solid was precipitated on hot which was filtered off, washed with methylenechloride, and crystallized from ethanol to give white crystals. Yield 0.38 g (53%); mp 258–260°C; IR (KBr): $\bar{\nu}$ = 1625 (C=C, C=N), 1692 (C=O), 3104 (NH) cm⁻¹; ¹H NMR (DMSO-d₆): δ = 1.25 (d, 6H, 2CH₃), 3.68 (m, 1H, CH), 7.16 (s, 1H, CH), 9.18 (s, 1H, N=CH), 12.71 (bs, 1H, NH) ppm.

3-Isopropyl-5-methylthieno[3,2-e]triazolo[4,3-a]pyrimidin-4-one (14b, C₁₁H₁₂N₄O₃S)

Method A: A solution of 0.24 g **7b** (1 mmol) in 10 cm³ formic acid was heated under reflux for 8 h. The reaction mixture was allowed to cool and poured onto 100 cm³ ice cold water. The separated product was filtered off, washed with water, dried, and crystallized from ethanol as colorless crystals. Yield 0.17 g (70%); mp 160–162°C; IR (KBr): $\bar{\nu}$ = 1600 (C=C, C=N), 1671 (C=O), 3097 (NH) cm⁻¹; ¹H NMR (DMSO-d₆): δ = 1.25 (d, 6H, 2CH₃), 3.56 (s, 3H, NCH₃), 3.69 (m, 1H, CH), 7.17 (s, 1H, CH), 9.21 (s, 1H, N=CH) ppm; ¹³C NMR (DMSO-d₆): δ = 22.82 (2CH₃), 27.78 (CH), 113.78, 116.61, 141.64, 148.23 (thiophene), 135.69, 155.49 (2C=N), 169.74 (C=O).

Method B: A solution of 0.24 g **7b** (1 mmol) in 10 cm³ triethyl orthoformate was boiled under reflux for 4 h. After cooling the reaction mixture was poured into ice water. The separated product was filtered off, washed, dried, and crystallized from ethanol.

General procedure for the synthesis of compounds 15a and 15b

A solution of 2.38 g **7b** (10 mmol) and 10 mmol appropriate aromatic aldehyde in 30 cm³ ethanol containing a few drops of glacial acetic acid, was boiled under reflux for 3 h. The product that separated on cooling was filtered off, dried, and crystallized from ethanol.

4-Methoxybenzaldehyde (5-isopropyl-3-methyl-4-oxo-dihydrothieno[2,3-d]pyrimidin-2-yl) hydrazone (15a, C₁₈H₂₀N₄O₂S)

From **7b** and 1.36 g 4-methoxybenzaldehyde (10 mmol). Yield 2.63 g (74%) as orange crystals; mp 115–117°C; IR (KBr): $\bar{\nu}$ = 1608 (C=C, C=N), 1665 (C=O), 3222 (NH) cm⁻¹; ¹H NMR (DMSO-d₆): δ = 1.20 (d, 6H, 2CH₃), 3.33 (s, 3H, NCH₃), 3.49 (m, 1H, CH), 3.81 (s, 3H, OCH₃), 7.00 (s, 1H, CH), 7.65, 7.87 (2d, 4H, Ar-H), 8.31 (d, 1H, CH), 1.61 (s, 2H, 2NH) ppm.

1,3-Benzodioxole-5-carbaldehyde (5-isopropyl-3-methyl-4-oxo-3,4-dihydrothieno[2,3-d] pyrimidin-2-yl)hydrazone (15b, C₁₈H₁₈N₄O₃S)

From 2.38 g **7b** (10 mmol) and 1.50 g 1,3-benzodioxole-5-carbaldehyde (10 mmol). Yield 2.74 g (74%) as orange crystals; mp 110–112°C; IR (KBr): $\bar{\nu}$ = 1601 (C=C, C=N), 1675 (C=O), 3240 (NH) cm⁻¹.

General procedure for the synthesis of compounds 16a and 16b

A solution of 0.4 g ferric chloride in 5 cm³ ethanol was added dropwise to a boiling solution of 2 mmol aldehyde hydrazone **15** in 30 cm³ ethanol. Heating was continued for 30 min and the mixture was then kept overnight at room temperature. Evaporation of the solvent under reduced pressure, washing with water, and drying afforded a solid product which could be crystallized from ethanol.

3-Isopropyl-8-(4-methoxyphenyl)-5-methylthieno[3,2-e]-[1,2,4]triazolo[4,3-a]pyrimidin-4-one (16a, C₁₈H₁₈N₄O₂S)

From 0.71 g **15a** (2 mmol) and FeCl₃ as described before. Yield 0.51 g (72%) as brown powder; mp 178–180°C; IR (KBr): $\bar{\nu}$ = 1594 (C=C, C=N), 1680 (C=O) cm⁻¹; ¹H NMR (DMSO-d₆): δ = 1.21 (d, 6H, 2CH₃), 3.31 (s, 3H, NCH₃), 3.60 (m, 1H, CH), 3.88 (s, 3H, OCH₃), 7.02 (s, 1H, CH), 7.17, 7.65 (2d, 4H, Ar-H) ppm.

8-(1,3-Benzodioxol-5-yl)-3-isopropyl-5-methylthieno[3,2-e]-[1,2,4]triazolo[4,3-a]pyrimidin-4-one (16b, C₁₈H₁₆N₄O₃S)

From 0.74 g **15b** (2 mmol) and FeCl₃. Yield 0.47 g (64%) as brown powder; mp 175–177°C; IR (KBr): $\bar{\nu}$ = 1596 (C=C, C=N), 1676 (C=O) cm⁻¹; ¹H NMR (DMSO-d₆): δ = 1.21 (d, 6H, 2CH₃), 3.40 (m, 1H, CH), 3.60 (s, 3H, NCH₃), 6.20 (s, 1H, CH), 7.20 (m, 3H, Ar-H) ppm; *m/z* = 368 (M⁺).

General procedure for the synthesis of compounds 17a and 17b

A solution of 0.24 g **7b** (1 mmol) and an excess of isothiocyanate (2.5 mmol) in 10 cm³ ethanol was boiled under reflux for 4 h. The product that separated after cooling was filtered off and recrystallized from ethanol.

2-(5-Isopropyl-3-methyl-4-oxo-3,4-dihydrothieno[2,3-d]pyrimidin-2-yl)-N-phenylhydrazine carbothioamide (17a, C₁₇H₁₉N₅OS₂)

From **7b** and 0.34 g phenyl isothiocyanate (2.5 mmol) as described before. Yield 0.27 g (73%) as colorless crystals; mp 264–266°C; ¹H NMR (DMSO-d₆): δ = 1.25 (d, 6H, 2CH₃), 3.39 (s, 3H, NCH₃), 3.71 (m, 1H, CH), 7.15 (s, 1H, CH), 7.18, 7.33, 7.49 (m, 5H, Ar-H), 9.78 (s, 1H, NH), 14.06 (bd, 2H, 2NH) ppm; ¹³C NMR (DMSO-d₆): δ = 22.97 (2CH₃), 27.20 (CH), 27.90 (N-CH₃), 114.66, 116.71, 141.09, 145.29 (thiophene), 123.48, 124.26, 128.29, 139.33 (Ar-C), 156 (C=N), 159.42 (C=O), 179.46 (C=S) ppm.

2-(5-Isopropyl-3-methyl-4-oxo-3,4-dihydrothieno[2,3-d]pyrimidin-2-yl)-N-methylhydrazine carbothioamide (17b, C₁₂H₁₇N₅OS₂)

From **7b** and 0.18 g, methyl isothiocyanate (2.5 mmol). Yield 0.22 g (70%) as colorless crystals; mp 201–203°C; IR (KBr): $\bar{\nu}$ = 1562 (C=C, C=N), 1672 (C=O), 3137, 3325 (NH) cm⁻¹; ¹H NMR (DMSO-d₆): δ = 1.21 (d, 6H, 2CH₃), 2.89 (d, 3H, NHCH₃), 3.40 (s, 3H, NCH₃), 3.54 (m, 1H, CH), 6.75 (s, 1H, CH), 8.14, 9.27, 9.38 (3s, 3H, 3NH) ppm; ¹³C NMR (DMSO-d₆): δ = 22.74 (2CH₃), 27.14 (CH), 28.19, 30.69 (2N-CH₃), 110.18, 113.76, 145.12, 151.46 (thiophene), 157.63 (C=N), 165.96 (C=O), 181.91 (C=S) ppm.

N-Allyl-2-(5-isopropyl-3-methyl-4-oxo-3,4-dihydrothieno[2,3-d]pyrimidin-2-yl)hydrazine carbothioamide (17c, C₁₄H₁₉N₅OS₂)

From **7b** and 0.25 g allyl isothiocyanate (2.5 mmol). Yield 0.24 g (71%) as white crystals; mp 168–170°C; ¹H NMR (DMSO-d₆): δ = 1.22 (d, 6H, 2CH₃), 3.40 (s, 3H, NCH₃), 3.54 (m, 1H, CH), 4.12 (d, 2H, CH₂), 5.03 (q, 2H, N-CH₂), 5.81 (m, 1H, CH), 6.75 (s, 1H, CH), 8.36, 9.31, 9.44 (3s, 3H, 3NH) ppm; ¹³C NMR (DMSO-d₆): δ = 22.74 (2CH₃), 27.16 (CH), 28.19 (N-CH₃), 45.60 (CH₂), 110.17, 114.91, 145.10, 151.41 (thiophene), 113.72 (CH), 134.75 (N-CH₂), 157.68 (C=N), 166.03 (C=O), 181.66 (C=S) ppm.

3-Isopropyl-5-methyl-8-(methylamino)thieno[3,2-e]-[1,2,4]triazolo[4,3-a]pyrimidin-4-one (18, C₁₂H₁₅N₅OS)

A mixture of 0.31 g **17b** (1 mmol) and 0.26 g mercuric oxide (1.2 mmol) in 25 cm³ ethanol was heated under reflux for 2 h. The precipitate formed after cooling was filtered off, washed, and crystallized from ethanol as white crystals. Yield 0.22 g (70%); mp 192–194°C; IR (KBr): $\bar{\nu}$ = 1580 (C=C, C=N), 1674 (C=O), 3255 (NH) cm⁻¹; ¹H NMR (DMSO-d₆): δ = 1.21 (d, 6H, 2CH₃), 2.87 (d, 3H, NHCH₃), 3.46 (s, 3H, NCH₃), 3.72 (m, 1H, CH), 7.16 (s, 1H, CH) ppm; *m/z* = 277 (M⁺).

N-(5-Isopropyl-4-oxo-3,4-dihydrothieno[2,3-d]pyrimidin-2-yl)acetohydrazide (19, C₁₁H₁₄N₄O₂S)

A mixture of 2.24 g **7a** (10 mmol) in 15 cm³ glacial acetic acid was boiled under reflux for 6 h. The reaction mixture was allowed to cool and poured into 100 cm³ water. The separated solid was filtered off, dried, and crystallized from ethanol as pale brown powder. Yield 1.19 g (71%); mp 140–142°C; IR (KBr): $\bar{\nu}$ = 1603 (C=C, C=N), 1661 (C=O), 3255 (NH) cm⁻¹; ¹H NMR (DMSO-d₆): δ = 1.21 (s, 6H, 2CH₃), 1.91 (s, 3H, COCH₃), 3.49 (m, 1H, CH), 6.69 (s, 1H, CH), 8.73, 9.83, 11.27 (3s, 3H, 3NH) ppm; ¹³C NMR (DMSO-d₆): δ = 20.78 (CH₃), 22.76 (2CH₃), 28.22 (CH), 109.24, 113.50, 145.13, 153.14 (thiophene), 158.41 (C=N), 168.09, 169.57 (2C=O) ppm.

2-[2-(Diphenylmethylene)hydrazino]-5-isopropyl-3-methylthieno[2,3-d]pyrimidin-4-one (20, C₂₃H₂₂N₄OS)

From 0.24 g **7b** (1 mmol) and 0.20 g benzophenone (1 mmol) as described for **10** as brown powder. Yield (0.32 g, 79%); mp 45–47°C; IR (KBr): $\bar{\nu}$ = 1652 (C=C, C=N), 1674 (C=O), 3238 (NH) cm⁻¹; ¹H NMR (DMSO-d₆): δ = 1.18 (d, 6H, 2CH₃), 3.29 (s, 3H, NCH₃), 3.56 (m, 1H, CH), 6.62 (s, 1H, CH), 7.58, 7.72 (m, 10H, 2Ph), 14.00 (bs, 1H, NH) ppm.

2-(3,5-Dimethyl-1-H-pyrazol-1-yl)-5-isopropyl-3-methylthieno[2,3-d]pyrimidin-4(3H)-one (21, C₁₄H₁₈N₄OS)

A mixture of 0.24 g **7b** (1 mmol) and 0.12 g pentane-2,4-dione (1.2 mmol) was heated under reflux for 6 h in 30 cm³ absolute ethanol. The reaction mixture was allowed to cool. The solid product that separated was filtered off and recrystallized from ethanol as pale orange crystals. Yield 0.20 g

(66%); mp 115–117°C; IR (KBr): $\bar{\nu}$ = 1577 (C=C, C=N), 1677 (C=O) cm^{-1} ; ^1H NMR (*DMSO-d*₆): δ = 1.22 (d, 6H, 2CH₃), 2.22, 2.34 (2d, 6H, 2CH₃), 3.32 (s, 3H, NCH₃), 3.68 (m, 1H, CH), 6.16, 7.31 (2s, 2H, 2CH) ppm.

General procedure for the synthesis of compounds 22a–22d
A solution of 1 mmol **7a** or **7b** and an excess of the appropriate isocyanate (2.5 mmol) in 10 cm^3 ethanol was boiled under reflux for 4 h. The product that separated after cooling was filtered off and recrystallized from ethanol.

2-(5-Isopropyl-4-oxo-3,4-dihydrothieno[2,3-d]pyrimidin-2-yl)-N-phenylhydrazine carboxamide (22a, C₁₆H₁₇N₅O₂S)

From **7a** and 0.30 g phenyl isocyanate (2.5 mmol). Yield 0.26 g (75%) as white crystals; mp 218–220°C; IR (KBr): $\bar{\nu}$ = 1548 (C=C, C=N), 1623 (NHCONH), 1670 (C=O), 3321, 3386 (NH) cm^{-1} ; ^1H NMR (*DMSO-d*₆): δ = 1.22 (d, 6H, 2CH₃), 3.50 (m, 1H, CH), 6.69 (s, 1H, CH), 6.96 (m, 1H, Ar-H), 7.75 (m, 2H, Ar-H), 7.46 (m, 2H, Ar-H), 8.15, 8.52, 8.77, 11.12 (4s, 4H, 4NH) ppm; ^{13}C NMR (*DMSO-d*₆): δ = 22.77 (2CH₃), 28.24 (CH), 109.42, 114.79, 145.18, 153.63 (thiophene), 118.41, 121.89, 128.58, 139.55 (Ar-C), 155.49 (C=N), 158.35, 168.06 (2C=O) ppm.

N-(4-Chlorophenyl)-2-(5-isopropyl-4-oxo-3,4-dihydrothieno[2,3-d]pyrimidin-2-yl)hydrazine carboxamide (22b, C₁₆H₁₆ClN₅O₂S)

From **7a** and 0.38 g 4-chlorophenyl isocyanate (2.5 mmol). Yield 0.28 g (76%) as white crystals; mp 200–202°C; ^1H NMR (*DMSO-d*₆): δ = 1.22 (d, 6H, 2CH₃), 3.50 (m, 1H, CH), 6.70 (s, 1H, CH), 7.32, 7.52 (2d, 4H, Ar-H), 8.24, 8.54, 8.94, 11.15 (4s, 4H, 4NH) ppm; ^{13}C NMR (*DMSO-d*₆): δ = 22.76 (2CH₃), 28.23 (CH), 109.41, 114.79, 145.15, 153.53 (thiophene), 119.97, 125.38, 128.37, 138.61 (Ar-C), 155.43 (C=N), 158.32, 167.99 (2C=O) ppm.

2-(5-Isopropyl-4-oxo-3,4-dihydrothieno[2,3-d]pyrimidin-2-yl)-N-(2-methylphenyl)hydrazine carboxamide (22c, C₁₇H₁₉N₅O₂S)

From **7a** and 0.33 g *o*-tolyl isocyanate (2.5 mmol). Yield 0.27 g (76%) of white crystals; mp 166–168°C; IR (KBr): $\bar{\nu}$ = 1607 (C=C, C=N), 1656 (C=O), 3237 (NH) cm^{-1} ; ^1H NMR (*DMSO-d*₆): δ = 1.22 (d, 6H, 2CH₃), 2.22 (s, 3H, CH₃), 3.51 (m, 1H, CH), 6.70 (s, 1H, CH), 7.00 (m, 1H, Ar-H), 7.15 (m, 2H, Ar-H), 7.65 (d, 1H, Ar-H), 8.00, 8.39, 8.54, 11.12 (4s, 4H, 4NH) ppm; ^{13}C NMR (*DMSO-d*₆): δ = 17.68 (CH₃), 22.76 (2CH₃), 28.24 (CH), 109.38, 114.75, 145.16, 153.61 (thiophene), 121.92, 122.99, 123.19, 125.99, 130.08, 137.04 (Ar-C), 155.74 (C=N), 158.34, 168.06 (2C=O) ppm.

2-(5-Isopropyl-3-methyl-4-oxo-3,4-dihydrothieno[2,3-d]pyrimidin-2-yl)-N-phenylhydrazine carboxamide (22d, C₁₇H₁₉N₅O₂S)

A solution of 0.24 g **7b** (1 mmol) and an excess of phenyl isocyanate (0.30 g, 2.5 mmol) in 10 cm^3 ethanol was boiled under reflux for 4 h. The separated product was filtered off and recrystallized from ethanol as colorless crystals. Yield

0.26 g (73%); mp 207–209°C; ^1H NMR (*DMSO-d*₆): δ = 1.22 (d, 6H, 2CH₃), 3.45 (s, 3H, NCH₃), 3.55 (m, 1H, CH), 6.72 (s, 1H, CH), 6.96 (m, 1H, Ar-H), 7.26 (m, 2H, Ar-H), 7.49 (m, 2H, Ar-H), 8.28, 8.81, 9.19 (3s, 3H, 3NH) ppm.

5-Isopropylthieno[2,3-d]pyrimidine-4(3H)-one (23, C₉H₁₀N₂OS)

A solution of 0.69 g **22a** (2 mmol) and 25 cm^3 2 *M* sodium hydroxide was boiled for 1 h, then cooled and neutralized by addition of 2 *M* hydrochloric acid. The precipitate formed was collected, washed, and crystallized from ethanol as white powder. Yield 0.27 g (70%); mp 210–212°C; ^1H NMR (*DMSO-d*₆): δ = 1.27 (s, 6H, 2CH₃), 3.59 (m, 1H, CH), 7.18, 8.05 (2s, 2H, 2CH), 12.39 (bs, 1H, NH) ppm.

Ethyl-2-(5-isopropyl-3-methyl-4-oxo-3,4-dihydrothieno[2,3-d]pyrimidin-2-yl)hydrazine carboxylate (24, C₁₃H₁₈N₄O₃S)

A mixture of 0.24 g **7b** (1 mmol) and 20 cm^3 ethyl chloroformate was heated under reflux for 4 h. The reaction mixture was allowed to cool. Evaporation of the solvent under reduced pressure and washing of the residue with *n*-hexane afforded a solid product, which was collected by filtration as yellow powder. Yield 0.20 g (65%); mp 143–145°C; IR (KBr): $\bar{\nu}$ = 1530 (C=C, C=N), 1669 (NHCO), 1728 (C=O), 3258 (NH) cm^{-1} ; ^1H NMR (*DMSO-d*₆): δ = 1.19 (t, 3H, CH₃), 1.21 (d, 6H, 2CH₃), 3.53 (m, 1H, CH), 4.09 (q, 1H, CH), 6.73 (s, 1H, CH), 9.17, 9.25 (2s, 2H, 2NH) ppm; m/z = 310 (M^+).

Synthesis of compounds 25a and 26a

A solution of 1.12 g **7a** or **7b** (5 mmol) in 10 cm^3 acetic acid was treated with a solution of 0.15 g sodium nitrite in 3 cm^3 H₂O at 5°C. The reaction mixture was allowed to stand at room temperature for 24 h with stirring. The solid product was filtered off and crystallized from ethanol to furnish colorless crystals. Yield 0.82 g (70%), mp 100–102°C.

2-Azido-5-isopropylthieno[2,3-d]pyrimidin-4(3H)-one (25a, C₉H₉N₅OS) (Major product)

IR (KBr): $\bar{\nu}$ = 1573 (C=C, C=N), 1663 (C=O), 2154 (N₃), 3445 (NH) ppm; ^1H NMR (*DMSO-d*₆): δ = 1.26 (d, 6H, 2CH₃), 3.61 (m, 1H, CH), 7.00 (s, 1H, CH), 12.60 (bs, 1H, NH) ppm; ^{13}C NMR (*DMSO-d*₆): δ = 22.67 (2CH₃), 28.23 (CH), 111.20, 113.64, 115.81, 145.32 (thiophene), 147.45 (C=N), 165.00 (C=O) ppm.

6-Isopropyltetrazolo[1,5-a]thieno[3,2-e]pyrimidine-5(4H)-one (26a, C₉H₉N₅OS) (Minor product)

^1H NMR (*DMSO-d*₆): δ = 1.28 (d, 6H, 2CH₃), 4.15 (m, 1H, CH), 7.35 (s, 1H, CH), 13.50 (bs, 1H, NH) ppm; ^{13}C NMR (*DMSO-d*₆): δ = 22.80 (2CH₃), 27.71 (CH), 111.20, 113.64, 115.81, 145.32 (thiophene), 147.45 (C=N), 165.00 (C=O) ppm.

Synthesis of compounds 25b and 26b

From 1.19 g **7b** (5 mmol) in 10 cm^3 acetic acid as described before to give colorless crystals. Yield 1.06 g (73%), mp 130–132°C.

2-Azido-5-isopropyl-3-methylthieno[2,3-d]pyrimidin-4-one
(**25b**, C₁₀H₁₁N₅OS) (*Minor product*)

IR (KBr): $\bar{\nu}$ = 1604 (C=C, C=N), 1676 (C=O), 2205 (N₃), 3120 (NH) cm⁻¹; ¹H NMR (DMSO-d₆): δ = 1.22 (d, 6H, 2CH₃), 3.33 (s, 3H, NCH₃), 3.59 (m, 1H, CH), 7.05 (s, 1H, CH) ppm; ¹³C NMR (DMSO-d₆): δ = 22.76 (Me), 27.79 (CH), 30.04 (N-Me), 113.94, 116.02, 40.57, 147.29 (thiophene), 150.45 (C=N), 156.13 (C=O) ppm.

6-Isopropyl-4-methyletrazolo[1,5-a]thieno[3,2-e]pyrimidin-5-one (**26b**, C₁₀H₁₁N₅OS) (*Major product*)

¹H NMR (DMSO-d₆): δ = 1.26 (d, 6H, 2CH₃), 3.61 (s, 3H, NCH₃), 3.66 (m, 1H, CH), 7.38 (s, 1H, CH) ppm.

2-Amino-5-isopropyl-3-methylthieno[2,3-d]pyrimidine-4-(3H)-one (**28**, C₁₀H₁₃N₃OS)

Zinc dust (0.08 g, 1.2 mmol) was added to a solution of 0.28 g **26b** (1 mmol) in 20 cm³ acetic acid with stirring. The reaction mixture was heated at 80°C for 5 h and then left to cool at room temperature. The solid product that separated was filtered off and crystallized from ethanol to furnish pale brown crystals. Yield 0.08 g (35%); mp 180–182°C; IR (KBr): $\bar{\nu}$ = 1640 (C=C, C=N), 1675 (C=O), 3132 (NH) cm⁻¹; ¹H NMR (DMSO-d₆): δ = 1.18 (d, 6H, 2CH₃), 3.41 (s, 3H, NCH₃), 3.51 (m, 1H, CH), 6.54 (s, 1H, CH), 7.03 (s, 2H, NH₂) ppm.

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