

Synthesis of novel pyranopyridothienopyrimidines derivatives based on fused thieno[3,2-*d*][1,3]oxazin-4-one

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Received mm-dd-yyyy

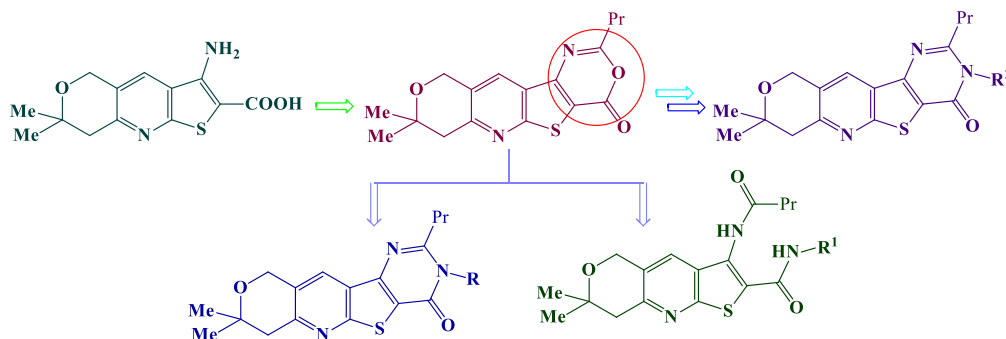
Accepted mm-dd-yyyy

Published on line mm-dd-yyyy

Dates to be inserted by editorial office

Abstract

This study details the development of an effective synthetic method and proposes a reaction mechanism for the preparation of fused thieno[3,2-*d*][1,3]oxazine from the corresponding amino acid. Investigation into the nature of primary amine properties on reactions with condensed thieno[3,2-*d*]oxazine revealed their role in forming either fused thieno[3,2-*e*]pyridines or thieno[3,2-*d*]pyrimidines. Furthermore, synthesis reaction mechanisms for both tri- and tetracyclic systems were provided. Notably, regioselective alkylation of condensed thieno[3,2-*d*]pyrimidin-(3*H*)-one led to the synthesis novel *N*-alkyl derivatives.



Keywords: Synthesis; pyrano[4,3-*d*]thieno[3,2-*e*]pyridine; thieno[3,2-*d*][1,3]oxazin; thieno[3,2-*d*]pyrimidine; *N*-alkylation

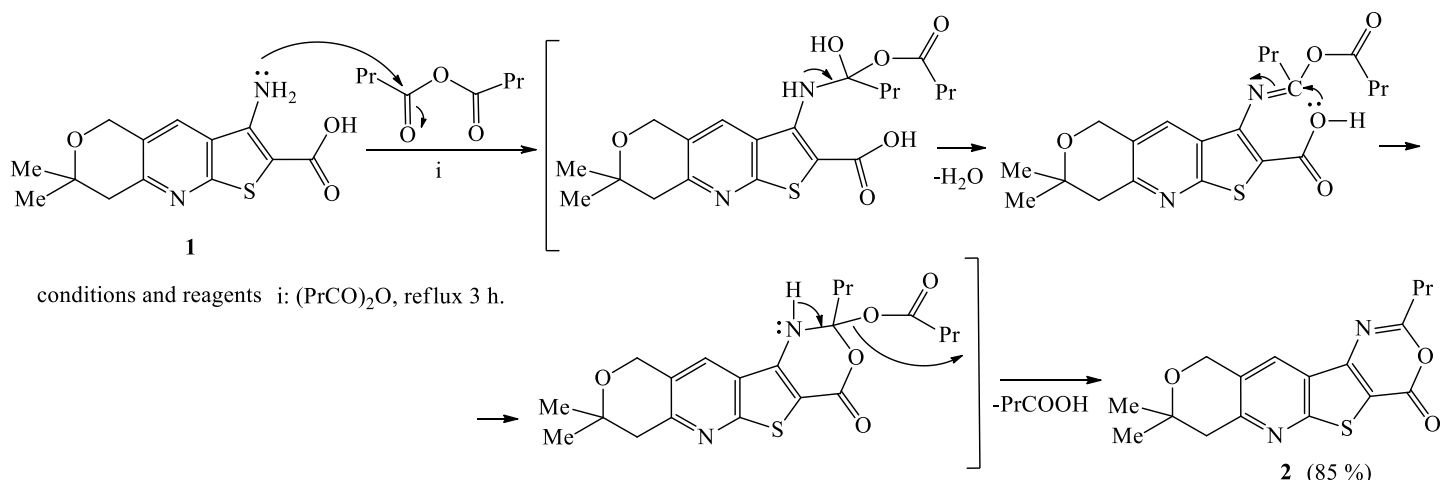
Introduction

Rooted in organic synthesis and medicinal chemistry, heterocyclic compounds are a fundamental aspect of organic chemistry. They are characterized by cyclic structures composed of atoms from at least two different elements, commonly featuring carbon alongside a heteroatom, where oxygen, nitrogen, and sulfur are the most prevalent. Depending on the heteroatom(s) present in their ring structures, heterocycles exhibit diverse chemical and biological properties [1, 2]. Heteroatoms play a crucial role in numerous active pharmaceutical ingredients and excipients. Many nitrogen-containing heterocyclic compounds are pivotal in the advancement of drug design and discovery. Among these, the six-membered heteroaromatic pyridine core is widespread and occurs naturally in sources like alkaloids, vitamins, and coenzymes [3, 4]. From the biological activity point of view the systems containing fused pyridine are of greater interest than the corresponding monocyclic compounds. From the condensed pyridines thieno[2,3-*b*]pyridines exhibit a broad spectrum of biological activity [5, 6]. Another notable six-membered heterocycle containing two nitrogen atoms is pyrimidine, essential as a component found in ribonucleic and deoxyribonucleic acids [7]. Additionally, synthetic analogs of pyrimidines play a significant role in various biological processes [8]. From this perspective, thienopyrimidines are intriguing due to their composition of π -excessive thiophene and π -deficient pyrimidine rings. This composition allows for the exploration of interactions between heterocycles and heteroatoms, influencing reactivity and biological activity, including antimicrobial [9, 10], anti-inflammatory [11, 12], antiviral [13], antioxidant [14], and antitumor [15, 16] effects. Additionally, combining thienopyrimidine with pyridine nuclei to form pyridothienopyrimidine derivatives has been shown to possess antimicrobial, anticancer [17, 18], and neurotropic [19-21] properties. Therefore, the synthesis of new fused thienopyridines and pyridothienopyrimidines holds current and future significance in advancing both heterocyclic chemistry and the discovery of potential new drugs.

The current study is a continuation of our research on the synthesis of fused tri- and tetracyclic systems containing thieno[3,2-*e*]pyridine and pyrido[3',2':4,5]thieno[3,2-*d*]pyrimidine ring.

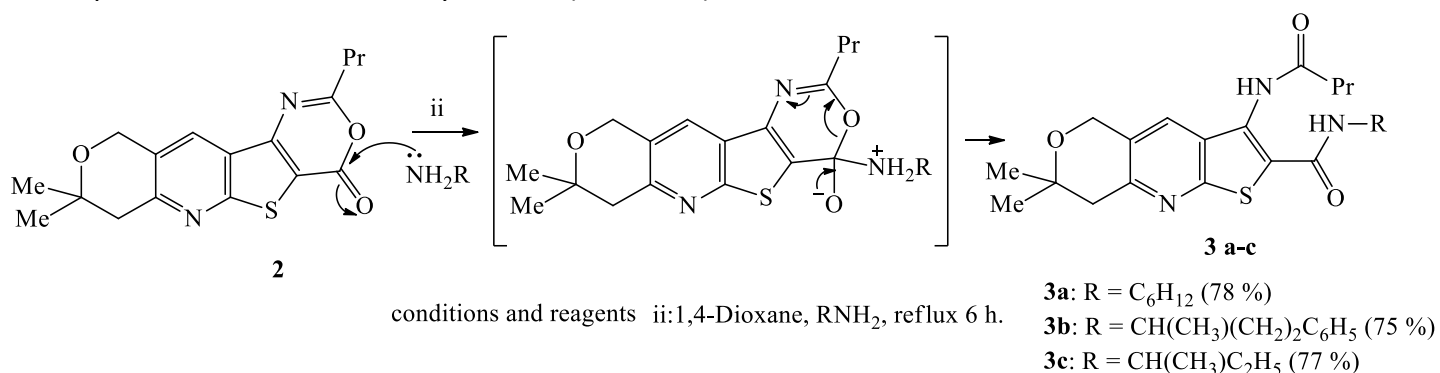
Results and Discussion

Our approach to the synthesis of the fused thieno[3,2-*e*]pyridine and pyrido[3',2':4,5]thieno[3,2-*d*]pyrimidine started from 3-amino-7,7-dimethyl-7,8-dihydro-5*H*-pyrano[4,3-*b*]thieno[3,2-*e*]pyridine-2-carboxylic acid (**1**) [22]. Method for synthesis 8,8-dimethyl-2-propyl-7,10-dihydro-4*H*,8*H*-pyrano[3'',4''':5',6']-pyrido[3',2':4,5]thieno[3,2-*d*][1,3]oxazin-4-one (**2**) was developed (Scheme 1). The reaction between compound **1** and butanoic anhydride was carried out under reflux conditions. The reaction mechanism proceeds through several steps. Firstly, the amino group of the thiophene ring nucleophilically attacks one of the keto functional groups of butanoic anhydride and eliminates water. Next, a lone pair of electrons on the oxygen atom in carboxylic acid hydroxyl functional group acts as a nucleophile, eliminated butyric acid and formed oxazine ring. As a result of reaction, 8,8-dimethyl-2-propyl-7,10-dihydro-4*H*,8*H*-pyrano[3'',4''':5',6']-pyrido[3',2':4,5]thieno[3,2-*d*][1,3]oxazin-4-one (**2**) was synthesized and confirmed by physicochemical methods. In the IR spectrum of the obtained compound **2**, absorption bands characteristic of the C=O group attached to the oxazine ring appear at 1758 cm⁻¹, while absorption bands characteristic of amino (NH₂) and acid (COOH) groups are absent. In the ¹³C NMR spectrum, the characteristic signal of the C=O group of oxazine ring was recorded at 167.2 ppm, which also confirms the structure of the synthesized compound.



Scheme 1. Synthesis and mechanism of 8,8-dimethyl-2-propyl-7,10-dihydro-4*H*,8*H*-pyrano[3',4'':5',6']pyrido[3',2':4,5]thieno[3,2-*d*][1,3]oxazin-4-one (**2**)

8,8-Dimethyl-2-propyl-7,10-dihydro-4*H*,8*H*-pyrano[3',4'':5',6']pyrido[3',2':4,5]thieno[3,2-*d*][1,3]oxazin-4-one (**2**), served as a key intermediate in studying its reactivity with various primary amines. Based on the analysis of the data obtained from the studies, it was found that the interaction between oxazine (compound **2**) and amines shows ambiguous behavior. Thus, compound **2** has been used to synthesize fused thieno[3,2-*e*]pyridine derivatives (**3a-c**) by reacting it with cyclohexanamine, 4-phenylbutan-2-amine, or butan-2-amine. The reaction mechanism involves oxazine ring opening under basic conditions, followed by amination via nucleophilic attack on the carbonyl carbon (Scheme 2).

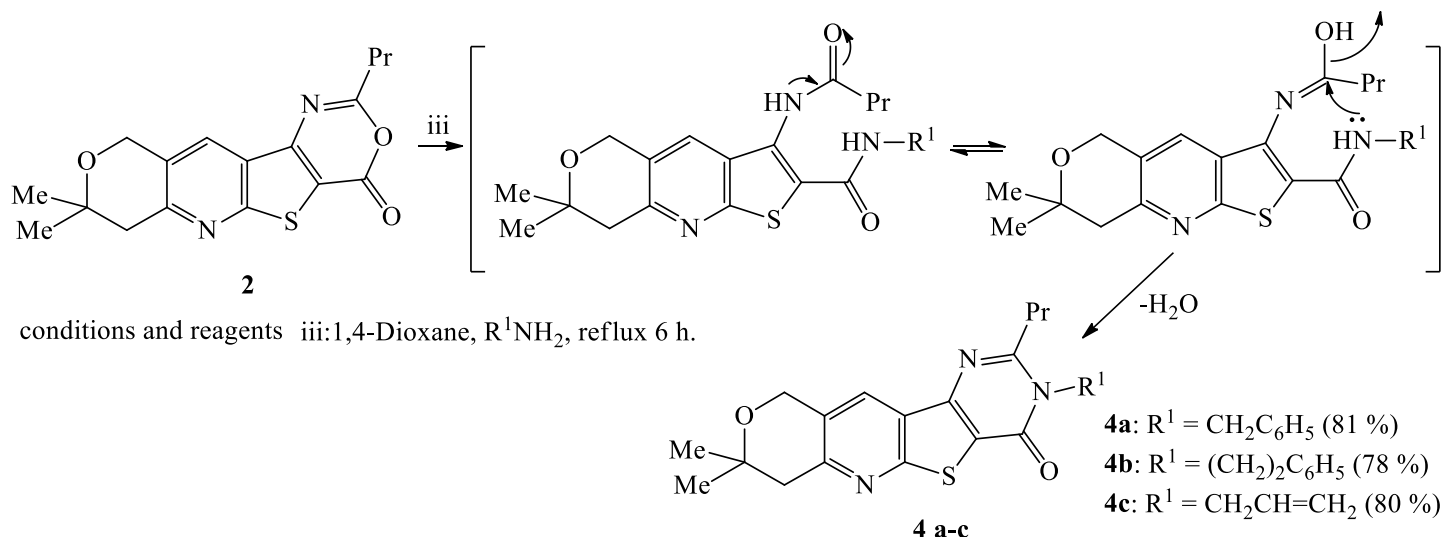


Scheme 2. Synthesis and mechanism of 3-(butyrylamino)-*N*-alkyl-pyrano[4,3-*b*]thieno[3,2-*e*]pyridine-2-carboxamide derivatives (**3a-c**).

The structure and purity of 3-(butyrylamino)-*N*-alkyl-pyrano[4,3-*b*]thieno[3,2-*e*]pyridine-2-carboxamide derivatives (**3a-c**) was confirmed by physicochemical methods. In the IR-spectrum of the obtained compounds **3a-c** are absorption bands characteristic of secondary amines (NH) and carboxyl (C=O) groups at 3234-3269 cm⁻¹ and 1614-1666 cm⁻¹, respectively. In the ¹H NMR spectra of compounds **3a-c** the typical signal of the NH functional group protons are observed at 7.77-7.92 and 10.40-10.47 ppm. In addition, in the ¹³C NMR spectrum, the characteristic signal of the C=O groups was recorded at 160.9-161.4 and 170.9-171.1 ppm.

We were unable to isolate pyrano[4,3-*b*]thieno[3,2-*e*]pyridine derivatives in the case of benzylamine, 2-phenylethanamine, or allylamine. Instead, thieno[3,2-*d*]pyrimidines (**4a-c**) were obtained. The reaction is

assumed to proceed via the same mechanism, but depending on the nature of the amine, cyclization also occur, leading to the elimination of water and formation of the corresponding fused thieno[3,2-*d*]pyrimidine derivatives (**4a-c**) (Scheme 3).

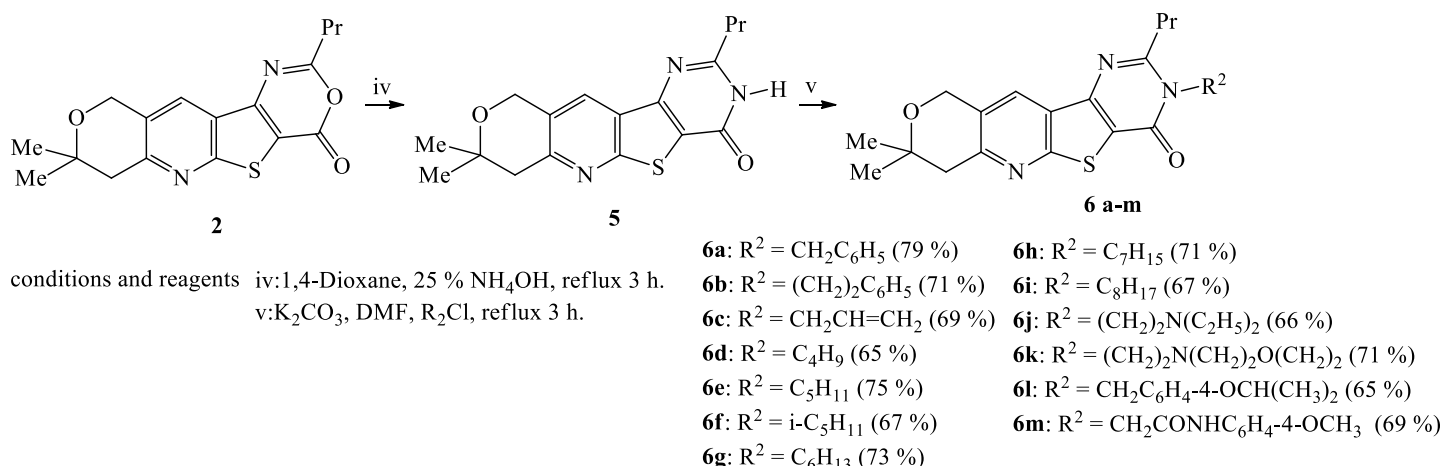


Scheme 3. Synthesis of pyrano[3'',4''':5',6']pyrido[3',2':4,5]thieno[3,2-*d*]pyrimidin-4-one (**4a-c**).

In the IR spectra of the obtained compounds **4a-c**, absorption bands characteristic of the carbonyl group of the pyrimidine ring appears at 1668-1674 cm⁻¹, while absorption bands indicative of NH groups are absent. These observations suggest the formation of intermediate thieno[3,2-*e*]pyridines followed by their cyclization to form corresponding pyrido[3',2':4,5]thieno[3,2-*d*]pyrimidines (compounds **4a-c**).

8,8-Dimethyl-2-propyl-7,10-dihydro-4*H*,8*H*-pyrano[3,4'':5',6']pyrido[3',2':4,5]thieno[3,2-*d*][1,3]oxazin-4-one (**2**) was a convenient substrate for the transition to the 8,8-dimethyl-2-propyl-7,10-dihydro-8*H*-pyrano[3'',4''':5',6']pyrido[3',2':4,5]thieno[3,2-*d*]pyrimidin-4(3*H*)-one (**5**). The reaction was conducted in a 25% aqueous ammonia solution in dioxane under reflux conditions (Scheme 4).

In the ¹H NMR spectra of compound **5** the typical signal of the NH functional group proton of pyrimidine ring is observed as a broad singlet at 12.61 ppm. Additionally, in the IR spectra, the characteristic absorption bands for CO and NH groups were recorded at 1669 cm⁻¹ and 3320 cm⁻¹, respectively.



Scheme 4. Synthesis of pyrano[3'',4''':5',6']pyrido[3',2':4,5]thieno[3,2-*d*]pyrimidin-4-one (**5, 6a-m**).

To further our investigation into obtaining new derivatives of pyrido[3',2':4,5]thieno[3,2-*d*]pyrimidine, an alkylation reaction with various alkyl chlorides was carried out in the presence of potassium carbonate in DMF, under stirring and refluxing conditions. The reaction proceeded regioselectively, resulting in *N*-alkyl derivatives of the target compounds by high yields (**6a-m**) (Scheme 4). It should be noted that compounds **4a-c** were synthesized both from fused thieno[3,2-*d*][1,3]oxazin-4-one (**2**) and from compound **5** (compounds **6a-c**) as well. The physicochemical data for compounds **4a-c** are identical to those of compounds **6a-c**. These two methods confirm the validity of our assumption regarding the mechanism of obtaining thienopyrimidines starting from oxazine **2**.

Conclusions

An effective method was developed for synthesizing fused thieno[3,2-*d*][1,3]oxazine from the corresponding amino acid. The reaction mechanism of formation fused thieno[3,2-*d*][1,3]oxazine was proposed. Furthermore, the influence of the character of primary amines on the outcome of the reaction with condensed thieno[3,2-*d*]oxazine has been established, resulting in the formation of fused thieno[3,2-*e*]pyridines or thieno[3,2-*d*]pyrimidines. The synthesis mechanisms for both tri- and tetracyclic systems were provided. Moreover, new *N*-alkyl derivatives of condensed thieno[3,2-*d*]pyrimidin-(3*H*)-ones were synthesized with high yields.

Experimental Section

General. All chemicals and solvents were of commercially high purity grade purchased from Sigma-Aldrich (Saint Louis, MO, USA). Melting points (mp) were determined on a Boetius microtable. They are expressed in degrees centigrade (°C). ¹H NMR and ¹³C NMR spectra were recorded in DMSO-*d*₆/CCl₄, 1/3, *v/v* solution (300 MHz for ¹H and 75.462 MHz for ¹³C) on a Varian mercury spectrometer (Varian Inc., Palo Alto, CA, USA). Chemical shifts are reported as δ (parts per million) relative to TMS (tetramethylsilane) as the internal standard. IR spectra were recorded on Nicolet Avatar 330-FTIR spectrophotometer (Thermo Nicolet, Foster, CA, USA) and the reported wave numbers are given in cm⁻¹. Mass spectra were recorded on XEVO G3 QToF spectrometers (Waters Corporation Company, Milford, Massachusetts). Elemental analyses were performed on a Euro EA 3000 Elemental Analyzer (EuroVector, Pavia, Italy).

Synthesis of 8,8-dimethyl-2-propyl-7,10-dihydro-4*H*,8*H*-pyrano[3'',4'':5',6']pyrido[3',2':4,5]thieno[3,2-*d*][1,3]oxazin-4-one (2**).** A mixture of compound **1** (2.78 g, 10 mmol) and butyric anhydride (10 ml) was refluxed for 3 hours. The formed precipitate was filtered off, washed with water and recrystallized from ethanol to give the product as a pure light yellow solid (2.81 g, 85%). mp: 255–256 °C. IR (ν /cm⁻¹): 1758 (C=O). ¹H NMR (300 MHz, DMSO-*d*₆/CCl₄, 1/3): δ _H 1.10 (t, *J* 7.4 Hz, 3H, CH₂CH₃), 1.33 (s, 6H, C(CH₃)₂), 1.90 (sextet, *J* 7.4 Hz, 2H, CH₂CH₃), 2.77 (t, *J* 7.4 Hz, 2H, CH₂CH₂CH₃), 2.98 (s, 2H, 7-CH₂), 4.91 (s, 2H, 10-CH₂), 8.18 (s, 1H, 2-CH). ¹³C NMR (75.465 MHz, DMSO-*d*₆/CCl₄, 1/3) δ _C 13.1 (CH₃), 18.9 (CH₂), 26.1 (2CH₃), 35.6 (7-CH₂), 43.0 (CH₂), 61.1 (10-CH₂), 70.7 (C⁸), 114.9 (11-CH), 124.8 (C), 127.0 (C), 127.1 (C), 149.3 (C), 154.3 (C), 157.1 (C), 160.4 (C), 167.2 (CO). TOF MS ES+ [MH]⁺ *m/z* 331.1130 (calcd for C₁₇H₁₈N₂O₃S, 331.1116). Anal. Calcd for C₁₇H₁₈N₂O₃S (330.41): C, 61.80; H, 5.49; N, 8.48; S, 9.71. Found: C, 61.75; H, 5.42; N, 8.54; S, 9.77.

General procedure for the synthesis of compounds (3a-c). A mixture of compound **2** (0.99 g, 3.0 mmol), corresponding primary amine (3.0 mmol) and dioxane (5 mL) was refluxed for 6 hours. Dioxane was distilled off, the residue was treated with water (10 mL). The precipitated crystals were filtered off, washed with ether and recrystallized from ethanol.

3-(Butyrylamino)-*N*-cyclohexyl-7,7-dimethyl-7,8-dihydro-5*H*-pyrano[4,3-*b*]thieno[3,2-*e*]pyridine-2-carboxamide (3a). Reaction of compound **2** (0.99 g, 3.0 mmol) and cyclohexanamine (0.30 g, 3.0 mmol) according to general procedure afforded 1.0 g (78%) of product **3a** isolated as a white solid: mp 192–193 °C. IR (ν/cm^{-1}): 3258 (2NH), 1666 (CO), 1614 (CO). ^1H NMR (300 MHz, DMSO- d_6 /CCl $_4$, 1/3): δ_{H} 1.05 (t, J 7.3 Hz, 3H, CH $_2$ CH $_3$), 1.32 (s, 6H, C(CH $_3$) $_2$), 1.15-1.97 (m, 12H, CH $_2$ CH $_3$ and 5CH $_2$ cyclohexyl), 2.41 (t, J 7.2 Hz, 2H, CH $_2$ CH $_2$ CH $_3$), 2.91 (s, 2H, 8-CH $_2$), 3.71-3.85 (m, 1H, NHCH $_{\text{cyclohexyl}}$), 4.85 (s, 2H, 5-CH $_2$), 7.78 (br. d, J 8.0 Hz, 1H, NHCH $_{\text{cyclohexyl}}$), 7.88 (c, 1H, 4-CH), 10.40 (br. s, 1H, NH). ^{13}C NMR (75.465 MHz, DMSO- d_6 /CCl $_4$, 1/3) δ_{C} 13.4 (CH $_3$), 18.2 (CH $_2$), 24.6 (2CH $_2$ cyclohexyl), 25.0 (CH $_2$ cyclohexyl), 26.2 (2CH $_3$), 31.9 (2CH $_2$ cyclohexyl), 37.8 (8-CH $_2$), 42.7 (CH $_2$), 48.3 (CH $_{\text{cyclohexyl}}$), 61.4 (5-CH $_2$), 70.8 (C 7), 125.0 (C), 126.7 (C), 128.1 (C), 128.2 (4-CH), 130.1 (C), 153.2 (C), 155.9 (C), 160.9 (CO), 171.0 (CO). Anal. Calcd for C $_{23}$ H $_{31}$ N $_3$ O $_3$ S (429.58): C, 64.31; H, 7.27; N, 9.78; S, 7.46. Found: C, 64.35; H 7.38; N, 9.69; S, 7.51.

3-(Butyrylamino)-7,7-dimethyl-*N*-(1-methyl-3-phenylpropyl)-7,8-dihydro-5*H*-pyrano[4,3-*b*]thieno[3,2-*e*]pyridine-2-carboxamide (3b). Reaction of compound **2** (0.99 g, 3.0 mmol) and 4-phenylbutan-2-amine (0.45 g, 3.0 mmol) according to general procedure afforded 1.08 g (75%) of product **3b** isolated as a cream solid: mp 193–194 °C. IR (ν/cm^{-1}): 3269 (2NH), 1661 (CO), 1626 (CO). ^1H NMR (300 MHz, DMSO- d_6 /CCl $_4$, 1/3): δ_{H} 1.04 (t, J 7.3 Hz, 3H, CH $_2$ CH $_3$), 1.25 (d, J 6.5 Hz, 3H, CHCH $_3$), 1.32 (s, 6H, C(CH $_3$) $_2$), 1.69-1.83 (m, 4H, CH $_2$ CH $_3$ and CHCH $_2$), 2.42 (t, J 7.2 Hz, 2H, CH $_2$ CH $_2$ CH $_3$), 2.57-2.75 (m, 2H, CH $_2$ C $_6$ H $_5$), 2.92 (s, 2H, 8-CH $_2$), 3.99-4.12 (m, 1H, CHCH $_3$), 4.86 (s, 2H, 5-CH $_2$), 7.07-7.26 (m, 5H, 5CH $_{\text{Ar}}$), 7.92 (s, 1H, 4-CH), 7.92 (br. d, J 8.0 Hz, 1H, NHCH), 10.47 (br. s, 1H, NH). ^{13}C NMR (75.465 MHz, DMSO- d_6 /CCl $_4$, 1/3) δ_{C} 13.4 (CH $_3$), 18.2 (CH $_2$), 20.2(CH $_3$), 26.2 (2CH $_3$), 32.0 (CH $_2$), 37.5 (CH $_2$), 37.8 (8-CH $_2$), 42.7 (CH $_2$), 44.8 (CH), 61.4 (5-CH $_2$), 70.8 (C 7), 124.9 (C), 125.0 (CH), 126.6 (C), 127.6 (2CH $_{\text{Ar}}$), 127.8 (2CH $_{\text{Ar}}$), 128.4 (4-CH), 130.7 (C), 138.8 (C), 141.3 (C), 153.2 (C), 155.9 (C), 161.4 (CO), 170.9 (CO). TOF MS ES $^+$ [MH] $^+$ m/z 480.2322 (calcd for C $_{27}$ H $_{33}$ N $_3$ O $_3$ S, 480.2321). Anal. Calcd for C $_{27}$ H $_{33}$ N $_3$ O $_3$ S (479.63): C, 67.61; H, 6.93; N, 8.76; S, 6.69. Found: C, 67.58; H 6.97; N, 8.69; S, 6.73.

***N*-(*Sec*-butyl)-3-(butyrylamino)-7,7-dimethyl-7,8-dihydro-5*H*-pyrano[4,3-*b*]thieno[3,2-*e*]pyridine-2-carboxamide (3c).** Reaction of compound **2** (0.99 g, 3.0 mmol) and butan-2-amine (0.22 g, 3.0 mmol) according to general procedure afforded 0.93 g (77%) of product **3c** isolated as a white solid: mp 178–179 °C. IR (ν/cm^{-1}): 3234 (2NH), 1661 (CO), 1618 (CO). ^1H NMR (300 MHz, DMSO- d_6 /CCl $_4$, 1/3): δ_{H} 0.94 (t, J 7.4 Hz, 3H, CH $_2$ CH $_3$), 1.04 (t, J 7.3 Hz, 3H, CH $_2$ CH $_3$), 1.20 (d, J 6.6 Hz, 3H, CHCH $_3$), 1.31 (s, 6H, C(CH $_3$) $_2$), 1.45-1.65 (m, 2H, CHCH $_2$ CH $_3$), 1.75 (sextet, J 7.4 Hz, 2H, CH $_2$ CH $_2$ CH $_3$), 2.41 (t, J 7.4 Hz, 2H, CH $_2$ CH $_2$ CH $_3$), 2.91 (s, 2H, 8-CH $_2$), 3.87-4.00 (m, 1H, CHCH $_3$), 4.85 (s, 2H, 5-CH $_2$), 7.77 (br. d, J 8.3 Hz, 1H, NHCH), 7.89 (s, 1H, 4-CH), 10.42 (br. s, 1H, NH). ^{13}C NMR (75.465 MHz, DMSO- d_6 /CCl $_4$, 1/3) δ_{C} 10.3 (CH $_3$), 13.5 (CH $_3$), 18.3 (CH $_3$), 19.7(CH $_2$), 26.2 (2CH $_3$), 28.6 (CH $_2$), 37.8 (8-CH $_2$), 42.7 (CH $_2$), 46.6 (CH), 61.5 (5-CH $_2$), 70.9 (C 7), 123.3 (C), 125.1 (C), 126.8 (C), 128.3 (4-CH), 130.2 (C), 153.3 (C), 155.9 (C), 161.3 (CO), 171.1 (CO). Anal. Calcd for C $_{21}$ H $_{29}$ N $_3$ O $_3$ S (403.54): C, 62.50; H, 7.24; N, 10.41; S, 7.95. Found: C, 62.58; H 7.19; N, 10.48; S, 8.10.

General procedure for the synthesis of compounds (4a-c). A mixture of compound **2** (0.99 g, 3.0 mmol), corresponding primary amine (3.0 mmol) and dioxane (5 mL) was refluxed for 6 hours. Dioxane was distilled off, the residue was treated with water (10 mL). The precipitated crystals were filtered off, washed with ether and recrystallized from ethanol.

3-Benzyl-8,8-dimethyl-2-propyl-7,10-dihydro-8*H*-pyrano[3'',4'':5',6']pyrido[3',2':4,5]thieno[3,2-*d*]pyrimidin-4(3*H*)-one (4a). Reaction of compound **2** (0.99 g, 3.0 mmol) and benzylamine (0.31 g, 3.0 mmol) according to

general procedure afforded 1.02 g (81%) of product **4a** isolated as a white solid: mp 210–211 °C. IR (ν/cm^{-1}): 1671 (CO). ^1H NMR (300 MHz, DMSO- d_6 /CCl $_4$, 1/3): δ_{H} 0.99 (t, J 7.3 Hz, 3H, CH $_2$ CH $_3$), 1.33 (s, 6H, C(CH $_3$) $_2$), 1.75–1.88 (m, 2H, CH $_2$ CH $_3$), 2.78 (t, J 7.4 Hz, 2H, CH $_2$ CH $_2$ CH $_3$), 2.98 (s, 2H, 7-CH $_2$), 4.92 (s, 2H, 10-CH $_2$), 5.46 (s, 2H, NCH $_2$), 7.16–7.36 (m, 5H, 5CH $_{\text{Ar}}$), 8.18 (br. s, 1H, 11-CH). ^{13}C NMR (75.465 MHz, DMSO- d_6 /CCl $_4$, 1/3) δ_{C} 13.2 (CH $_3$), 19.4 (CH $_2$), 26.1 (2CH $_3$), 35.7 (7-CH $_2$), 42.9 (CH $_2$), 45.6 (NCH $_2$), 61.2 (10-CH $_2$), 70.9 (C 8), 119.2 (C), 125.9 (2CH $_{\text{Ar}}$), 126.0 (C), 126.1 (C), 126.3 (11-CH), 126.9 (CH $_{\text{Ar}}$), 128.2 (2CH $_{\text{Ar}}$), 135.8 (C), 148.8 (C), 155.5 (C), 157.6 (C), 159.4 (C), 160.2 (CO). TOF MS ES+ [MH] $^+$ m/z 420.1746 (calcd for C $_{24}$ H $_{25}$ N $_3$ O $_2$ S, 420.1746). Anal. Calcd for C $_{24}$ H $_{25}$ N $_3$ O $_2$ S (419.54): C, 68.71; H, 6.01; N, 10.02; S, 7.64. Found: C, 68.80; H 5.89; N, 10.15; S, 7.70.

8,8-Dimethyl-3-(2-phenylethyl)-2-propyl-7,10-dihydro-8H-pyrano[3'',4'':5',6']pyrido[3',2':4,5]thieno[3,2-d]pyrimidin-4(3H)-one (4b). Reaction of compound **2** (0.99 g, 3.0 mmol) and 2-phenylethanamine (0.36 g, 3.0 mmol) according to general procedure afforded 1.01 g (78%) of product **4b** isolated as a white solid: mp 185–186 °C. IR (ν/cm^{-1}): 1668 (CO). ^1H NMR (300 MHz, DMSO- d_6 /CCl $_4$, 1/3): δ_{H} 1.02 (t, J 7.3 Hz, 3H, CH $_2$ CH $_3$), 1.32 (s, 6H, C(CH $_3$) $_2$), 1.75–1.89 (m, 2H, CH $_2$ CH $_3$), 2.70 (t, J 7.4 Hz, 2H, CH $_2$ CH $_2$ CH $_3$), 2.97 (s, 2H, 7-CH $_2$), 2.70 (t, J 7.3 Hz, 2H, CH $_2$ C $_6$ H $_5$), 4.32 (t, J 7.3 Hz, 2H, NCH $_2$), 4.91 (s, 2H, 10-CH $_2$), 7.18–7.34 (m, 5H, 5CH $_{\text{Ar}}$), 8.19 (s, 1H, 11-CH). ^{13}C NMR (75.465 MHz, DMSO- d_6 /CCl $_4$, 1/3) δ_{C} 13.3 (CH $_3$), 19.5 (CH $_2$), 26.1 (2CH $_3$), 33.8 (CH $_2$), 35.4 (7-CH $_2$), 42.9 (CH $_2$), 44.9 (NCH $_2$), 61.2 (10-CH $_2$), 70.8 (C 8), 119.0 (C), 126.1 (C), 126.2 (11-CH), 126.3 (C), 126.6 (CH $_{\text{Ar}}$), 128.1 (2CH $_{\text{Ar}}$), 128.4 (2CH $_{\text{Ar}}$), 137.5 (C), 148.8 (C), 155.6 (C), 157.3 (C), 159.2 (C), 159.9 (CO). Anal. Calcd for C $_{25}$ H $_{27}$ N $_3$ O $_2$ S (433.57): C, 69.26; H, 6.28; N, 9.69; S, 7.40. Found: C, 69.30; H 6.19; N, 9.73; S, 7.45.

3-Allyl-8,8-dimethyl-2-propyl-7,10-dihydro-8H-pyrano[3'',4'':5',6']pyrido[3',2':4,5]thieno[3,2-d]pyrimidin-4(3H)-one (4c). Reaction of compound **2** (0.99 g, 3.0 mmol) and allylamine (0.17 g, 3.0 mmol) according to general procedure afforded 0.89 g (80%) of product **4c** isolated as a white solid: mp 214–215 °C. IR (ν/cm^{-1}): 3098 (CH=CH $_2$), 1674 (CO), 1647 (C=C). ^1H NMR (300 MHz, DMSO- d_6 /CCl $_4$, 1/3): δ_{H} 1.09 (t, J 7.3 Hz, 3H, CH $_2$ CH $_3$), 1.33 (s, 6H, C(CH $_3$) $_2$), 1.86–1.99 (m, 2H, CH $_2$ CH $_3$), 2.85 (t, J 7.4 Hz, 2H, CH $_2$ CH $_2$ CH $_3$), 2.97 (s, 2H, 7-CH $_2$), 4.83 (br. d, J 4.8 Hz, 2H, NCH $_2$), 4.91 (s, 2H, 10-CH $_2$), 5.10 (br. d, J 17.3 Hz, 1H, CH=CH $_2$), 5.24 (br. d, J 10.4 Hz, 1H, CH=CH $_2$), 5.99 (ddt, J 17.3, 10.4, 4.8 Hz, 1H, CH=CH $_2$), 8.17 (s, 1H, 11-CH). ^{13}C NMR (75.465 MHz, DMSO- d_6 /CCl $_4$, 1/3) δ_{C} 13.4 (CH $_3$), 19.5 (CH $_2$), 26.1 (2CH $_3$), 35.3 (7-CH $_2$), 42.9 (CH $_2$), 44.8 (NCH $_2$), 61.2 (10-CH $_2$), 70.8 (C 8), 116.3 (CH=CH $_2$), 118.9 (C), 126.1 (C), 126.4 (C), 126.7 (11-CH), 132.0 (CH=CH $_2$), 148.9 (C), 155.7 (C), 157.2 (C), 159.5 (C), 159.9 (CO). Anal. Calcd for C $_{20}$ H $_{23}$ N $_3$ O $_2$ S (369.48): C, 65.01; H, 6.27; N, 11.37; S, 8.68. Found: C, 64.98; H 6.30; N, 11.42; S, 8.70.

Synthesis of 8,8-dimethyl-2-propyl-7,10-dihydro-8H-pyrano[3'',4'':5',6']pyrido[3',2':4,5]thieno[3,2-d]pyrimidin-4(3H)-one (5). A mixture of compound **2** (3.30 g, 10 mmol), dioxane (30 mL) and 25% aqueous ammonia solution (16 mL) was refluxed for 3 hours. The formed precipitate was filtered off, washed with water and ether, dried and recrystallized from ethanol to give the product as a pure cream solid (0.70 g, 71%). mp: 331–332 °C. IR (ν/cm^{-1}): 3320 (NH), 1669 (C=O). ^1H NMR (300 MHz, DMSO- d_6 /CCl $_4$, 1/3): δ_{H} 1.03 (t, J 7.4 Hz, 3H, CH $_2$ CH $_3$), 1.32 (s, 6H, C(CH $_3$) $_2$), 1.77–1.89 (m, 2H, CH $_2$ CH $_3$), 2.66 (t, J 7.5 Hz, 2H, CH $_2$ CH $_2$ CH $_3$), 2.95 (s, 2H, 7-CH $_2$), 4.90 (s, 2H, 10-CH $_2$), 8.17 (s, 1H, 11-CH), 12.61 (br. s, 1H, NH). ^{13}C NMR (75.465 MHz, DMSO- d_6 /CCl $_4$, 1/3) δ_{C} 13.7 (CH $_3$), 20.4 (CH $_2$), 26.1 (2CH $_3$), 35.9 (7-CH $_2$), 42.9 (CH $_2$), 61.3 (10-CH $_2$), 70.7 (C 8), 119.6 (C), 125.9 (C), 126.2 (C), 126.5 (11-CH), 150.7 (C), 155.2 (C), 158.1 (C), 159.6 (C), 159.9 (CO). TOF MS ES+ [MH] $^+$ m/z 330.1318 (calcd for C $_{17}$ H $_{19}$ N $_3$ O $_2$ S, 330.1276). Anal. Calcd for C $_{17}$ H $_{19}$ N $_3$ O $_2$ S (329.42): C, 61.98; H, 5.81; N, 12.76; S, 9.73. Found: C, 61.89; H 5.86; N, 12.69; S, 9.87.

General procedure for the synthesis of compounds (6a-m). A mixture of compound **5** (0.66 g, 2.0 mmol), K $_2$ CO $_3$ (0.55 g, 4.0 mmol) and DMF (10 mL) refluxed for 1.0 h. After cooling, the appropriate alkylchloride (2.1 mmol) was added, and the reaction mixture was refluxed for 2.0 h. Then in the mixture added ice-water (30 mL), the obtained crystals were filtered off, washed with water, dried, and recrystallized from EtOH.

3-Benzyl-8,8-dimethyl-2-propyl-7,10-dihydro-8H-pyrano[3'',4'':5',6']pyrido[3',2':4,5]thieno[3,2-*d*]pyrimidin-4(3H)-one (6a). Reaction of compound **5** (0.66 g, 2.0 mmol) and benzylchloride (0.27 g, 2.1 mmol) according to general procedure afforded 0.66 g (79%) of product **6a** isolated as a white solid. Physicochemical data of compound **6a** identical with compound **4a**.

8,8-Dimethyl-3-(2-phenylethyl)-2-propyl-7,10-dihydro-8H-pyrano[3'',4'':5',6']pyrido[3',2':4,5]thieno[3,2-*d*]pyrimidin-4(3H)-one (6b). Reaction of compound **5** (0.66 g, 2.0 mmol) and 2-phenylethanchloride (0.29 g, 2.1 mmol) according to general procedure afforded 0.62 g (71%) of product **6b** isolated as a white solid. Physicochemical data of compound **6b** identical with compound **4b**.

3-Allyl-8,8-dimethyl-2-propyl-7,10-dihydro-8H-pyrano[3'',4'':5',6']pyrido[3',2':4,5]thieno[3,2-*d*]pyrimidin-4(3H)-one (6c). Reaction of compound **5** (0.66 g, 2.0 mmol) and allylchloride (0.16 g, 2.1 mmol) according to general procedure afforded 0.51 g (69%) of product **6c** isolated as a white solid. Physicochemical data of compound **6c** identical with compound **4c**.

3-Butyl-8,8-dimethyl-2-propyl-7,10-dihydro-8H-pyrano[3'',4'':5',6']pyrido[3',2':4,5]thieno[3,2-*d*]pyrimidin-4(3H)-one (6d). Reaction of compound **5** (0.66 g, 2.0 mmol) and 1-chlorobutane (0.19 g, 2.1 mmol) according to general procedure afforded 0.50 g (65%) of product **6d** isolated as a white solid: mp 168–169 °C. IR (ν/cm^{-1}): 1665 (CO). ^1H NMR (300 MHz, DMSO- d_6 /CCl $_4$, 1/3): δ_{H} 1.03 (t, *J* 7.3 Hz, 3H, CH $_2$ CH $_3$), 1.12 (t, *J* 7.4 Hz, 3H, CH $_2$ CH $_3$), 1.32 (s, 6H, C(CH $_3$) $_2$), 1.42-1.55 (m, 2H, CH $_2$ CH $_3$), 1.65-1.76 (m, 2H, NCH $_2$ CH $_2$), 1.86-1.99 (m, 2H, CH $_2$ CH $_3$), 2.86 (t, *J* 7.5 Hz, 2H, CH $_2$ CH $_2$ CH $_3$), 2.95 (br. s, 2H, 7-CH $_2$), 4.05-4.13 (m, 2H, NCH $_2$), 4.89 (br. s, 2H, 10-CH $_2$), 8.13 (s, 1H, 11-CH). ^{13}C NMR (75.465 MHz, DMSO- d_6 /CCl $_4$, 1/3) δ_{C} 13.3 (CH $_3$), 13.4 (CH $_3$), 19.6 (CH $_2$), 19.8 (CH $_2$), 26.1 (2CH $_3$), 30.3 (CH $_2$), 35.5 (7-CH $_2$), 42.8 (CH $_2$), 42.9 (CH $_2$), 61.3 (10-CH $_2$), 70.7 (C 8), 119.3 (C), 126.0 (C), 126.1 (C), 126.2 (11-CH), 148.5 (C), 155.3 (C), 157.1 (C), 158.7 (C), 160.0 (CO). Anal. Calcd for C $_{21}$ H $_{27}$ N $_3$ O $_2$ S (385.52): C, 65.42; H, 7.06; N, 10.90; S, 8.32. Found: C, 65.48; H 7.12; N, 10.85; S, 8.40.

8,8-Dimethyl-3-pentyl-2-propyl-7,10-dihydro-8H-pyrano[3'',4'':5',6']pyrido[3',2':4,5]thieno[3,2-*d*]pyrimidin-4(3H)-one (6e). Reaction of compound **5** (0.66 g, 2.0 mmol) and 1-chloropentane (0.22 g, 2.1 mmol) according to general procedure afforded 0.60 g (75%) of product **6e** isolated as a white solid: mp 140–141 °C. IR (ν/cm^{-1}): 1671 (CO). ^1H NMR (300 MHz, DMSO- d_6 /CCl $_4$, 1/3): δ_{H} 0.93-1.00 (m, 2H, CH $_2$ CH $_3$), 1.12 (t, *J* 7.3 Hz, 3H, CH $_2$ CH $_3$), 1.32 (s, 6H, C(CH $_3$) $_2$), 1.37-1.50 (m, 4H, CH $_2$ (CH $_2$) $_2$ CH $_3$), 1.65-1.78 (m, 2H, NCH $_2$ CH $_2$), 1.86-1.99 (m, 2H, CH $_2$ CH $_3$), 2.86 (t, *J* 7.4 Hz, 2H, CH $_2$ CH $_2$ CH $_3$), 2.96 (s, 2H, 7-CH $_2$), 4.04-4.13 (m, 2H, NCH $_2$), 4.89 (s, 2H, 10-CH $_2$), 8.13 (s, 1H, 11-CH). ^{13}C NMR (75.465 MHz, DMSO- d_6 /CCl $_4$, 1/3) δ_{C} 13.4 (CH $_3$), 13.5 (CH $_3$), 19.8 (CH $_2$), 21.7 (CH $_2$), 26.1 (2CH $_3$), 27.9 (CH $_2$), 28.4 (CH $_2$), 35.5 (7-CH $_2$), 42.8 (CH $_2$), 43.1 (CH $_2$), 61.3 (10-CH $_2$), 70.7 (C 8), 119.3 (C), 125.9 (C), 126.0 (C), 126.2 (11-CH), 148.5 (C), 155.3 (C), 157.1 (C), 158.6 (C), 160.0 (CO). TOF MS ES+ [MH] $^+$ *m/z* 400.2111 (calcd for C $_{22}$ H $_{29}$ N $_3$ O $_2$ S, 400.2059). Anal. Calcd for C $_{22}$ H $_{29}$ N $_3$ O $_2$ S (399.55): C, 66.13; H, 7.32; N, 10.52; S, 8.03. Found: C, 66.25; H 7.38; N, 10.47; S, 8.20.

8,8-Dimethyl-3-(3-methylbutyl)-2-propyl-7,10-dihydro-8H-pyrano[3'',4'':5',6']pyrido[3',2':4,5]thieno[3,2-*d*]pyrimidin-4(3H)-one (6f). Reaction of compound **5** (0.66 g, 2.0 mmol) and 1-chloro-3-methylbutane (0.22 g, 2.1 mmol) according to general procedure afforded 0.53 g (67%) of product **6f** isolated as a white solid: mp 179–180 °C. IR (ν/cm^{-1}): 1674 (CO). ^1H NMR (300 MHz, DMSO- d_6 /CCl $_4$, 1/3): δ_{H} 1.05 (d, *J* 6.5 Hz, 6H, CH(CH $_3$) $_2$), 1.12 (t, *J* 7.3 Hz, 3H, CH $_2$ CH $_3$), 1.32 (s, 6H, C(CH $_3$) $_2$), 1.55-1.66 (m, 2H, NCH $_2$ CH $_2$), 1.71-1.87 (m, 1H, CH(CH $_3$) $_2$), 1.87-2.00 (m, 2H, CH $_2$ CH $_3$), 2.86 (t, *J* 7.4 Hz, 2H, CH $_2$ CH $_2$ CH $_3$), 2.96 (s, 2H, 7-CH $_2$), 4.07-4.16 (m, 2H, NCH $_2$), 4.90 (s, 2H, 10-CH $_2$), 8.15 (s, 1H, 11-CH). ^{13}C NMR (75.465 MHz, DMSO- d_6 /CCl $_4$, 1/3) δ_{C} 13.4 (CH $_3$), 19.8 (CH $_2$), 22.0 (2CH $_3$), 25.8 (CH), 26.1 (2CH $_3$), 35.5 (7-CH $_2$), 36.9 (CH $_2$), 41.7 (CH $_2$), 42.9 (CH $_2$), 61.3 (10-CH $_2$), 70.8 (C 8), 119.3 (C), 125.9 (C), 126.0 (C), 126.2 (11-CH), 148.5 (C), 155.3 (C), 157.0 (C), 158.6 (C), 160.0 (CO). Anal. Calcd for C $_{22}$ H $_{29}$ N $_3$ O $_2$ S (399.55): C, 66.13; H, 7.32; N, 10.52; S, 8.03. Found: C, 66.50; H 7.29; N, 10.58; S, 8.11.

3-Hexyl-8,8-dimethyl-2-propyl-7,10-dihydro-8H-pyrano[3'',4'':5',6']pyrido[3',2':4,5]thieno[3,2-*d*]pyrimidin-4(3*H*)-one (6g). Reaction of compound **5** (0.66 g, 2.0 mmol) and 1-chlorohexane (0.25 g, 2.1 mmol) according to general procedure afforded 0.6 g (73%) of product **6g** isolated as a white solid: mp 145–146 °C. IR (ν/cm^{-1}): 1671 (CO). ^1H NMR (300 MHz, DMSO- d_6 /CCl $_4$, 1/3): δ_{H} 0.90–0.97 (m, 3H, CH $_2$ CH $_3$), 1.12 (t, J 7.3 Hz, 3H, CH $_2$ CH $_3$), 1.32 (s, 6H, C(CH $_3$) $_2$), 1.28–1.50 (m, 6H, NCH $_2$ (CH $_2$) $_3$), 1.64–1.77 (m, 2H, CH $_2$ CH $_3$), 1.86–1.99 (m, 2H, CH $_2$ CH $_3$), 2.86 (t, J 7.4 Hz, 2H, CH $_2$ CH $_2$ CH $_3$), 2.96 (s, 2H, 7-CH $_2$), 4.05–4.13 (m, 2H, NCH $_2$), 4.90 (s, 2H, 10-CH $_2$), 8.14 (s, 1H, 11-CH). ^{13}C NMR (75.465 MHz, DMSO- d_6 /CCl $_4$, 1/3) δ_{C} 13.4 (CH $_3$), 13.5 (CH $_3$), 19.8 (CH $_2$), 21.8 (CH $_2$), 26.0 (CH $_2$), 26.1 (2CH $_3$), 28.2 (CH $_2$), 30.7 (CH $_2$), 35.5 (7-CH $_2$), 42.9 (CH $_2$), 43.2 (CH $_2$), 61.3 (10-CH $_2$), 70.8 (C 8), 119.3 (C), 125.9 (C), 126.0 (C), 126.2 (11-CH), 148.5 (C), 155.3 (C), 157.1 (C), 158.6 (C), 160.0 (CO). Anal. Calcd for C $_{23}$ H $_{31}$ N $_3$ O $_2$ S (413.58): C, 66.79; H, 7.56; N, 10.16; S, 7.75. Found: C, 66.63; H 7.62; N, 10.24; S, 7.69.

3-Heptyl-8,8-dimethyl-2-propyl-7,10-dihydro-8H-pyrano[3'',4'':5',6']pyrido[3',2':4,5]thieno[3,2-*d*]pyrimidin-4(3*H*)-one (6h). Reaction of compound **5** (0.66 g, 2.0 mmol) and 1-chloroheptane (0.28 g, 2.1 mmol) according to general procedure afforded 0.61 g (71%) of product **6h** isolated as a white solid: mp 143–144 °C. IR (ν/cm^{-1}): 1672 (CO). ^1H NMR (300 MHz, DMSO- d_6 /CCl $_4$, 1/3): δ_{H} 0.88–0.95 (m, 3H, CH $_2$ CH $_3$), 1.12 (t, J 7.3 Hz, 3H, CH $_2$ CH $_3$), 1.32 (s, 6H, C(CH $_3$) $_2$), 1.25–1.50 (m, 8H, (CH $_2$) $_4$ CH $_3$), 1.65–1.77 (m, 2H, NCH $_2$ CH $_2$), 1.86–2.00 (m, 2H, CH $_2$ CH $_3$), 2.86 (t, J 7.4 Hz, 2H, CH $_2$ CH $_2$ CH $_3$), 2.96 (s, 2H, 7-CH $_2$), 4.09 (t, J 7.7 Hz, 2H, NCH $_2$), 4.91 (s, 2H, 10-CH $_2$), 8.15 (s, 1H, 11-CH). ^{13}C NMR (75.465 MHz, DMSO- d_6 /CCl $_4$, 1/3) δ_{C} 13.4 (CH $_3$), 13.6 (CH $_3$), 19.8 (CH $_2$), 21.9 (CH $_2$), 26.1 (2CH $_3$), 26.3 (CH $_2$), 28.2 (2CH $_2$), 31.0 (CH $_2$), 35.6 (7-CH $_2$), 42.9 (CH $_2$), 43.2 (CH $_2$), 61.3 (10-CH $_2$), 70.8 (C 8), 119.4 (C), 125.9 (C), 126.0 (C), 126.2 (11-CH), 148.5 (C), 155.3 (C), 157.1 (C), 158.6 (C), 160.1 (C), 165.5 (CO). Anal. Calcd for C $_{24}$ H $_{33}$ N $_3$ O $_2$ S (427.60): C, 67.41; H, 7.78; N, 9.83; S, 7.50. Found: C, 67.52; H 7.68; N, 9.93; S, 7.58.

8,8-Dimethyl-3-octyl-2-propyl-7,10-dihydro-8H-pyrano[3'',4'':5',6']pyrido[3',2':4,5]thieno[3,2-*d*]pyrimidin-4(3*H*)-one (6i). Reaction of compound **5** (0.66 g, 2.0 mmol) and 1-chlorooctane (0.31 g, 2.1 mmol) according to general procedure afforded 0.59 g (67%) of product **6i** isolated as a white solid: mp 136–137 °C. IR (ν/cm^{-1}): 1671 (CO). ^1H NMR (300 MHz, DMSO- d_6 /CCl $_4$, 1/3): δ_{H} 0.87–0.93 (m, 3H, CH $_2$ CH $_3$), 1.12 (t, J 7.3 Hz, 3H, CH $_2$ CH $_3$), 1.32 (s, 6H, C(CH $_3$) $_2$), 1.24–1.50 (m, 10H, (CH $_2$) $_5$ CH $_3$), 1.64–1.77 (m, 2H, NCH $_2$ CH $_2$), 1.86–2.00 (m, 2H, CH $_2$ CH $_3$), 2.86 (t, J 7.4 Hz, 2H, CH $_2$ CH $_2$ CH $_3$), 2.96 (s, 2H, 7-CH $_2$), 4.04–4.13 (m, 2H, NCH $_2$), 4.90 (s, 2H, 10-CH $_2$), 8.13 (s, 0.5H, 11-CH), 8.15 (s, 0.5H, 11-CH). ^{13}C NMR (75.465 MHz, DMSO- d_6 /CCl $_4$, 1/3) δ_{C} 13.4 (CH $_3$), 13.6 (CH $_3$), 19.8 (CH $_2$), 21.9 (CH $_2$), 26.1 (2CH $_3$), 26.3 (CH $_2$), 28.2 (CH $_2$), 28.4 (CH $_2$), 28.5 (CH $_2$), 31.1 (CH $_2$), 35.6 (7-CH $_2$), 42.9 (CH $_2$), 43.2 (CH $_2$), 61.3 (10-CH $_2$), 70.8 (C 8), 119.3 (C), 125.9 (C), 126.0 (C), 126.2 (11-CH), 148.5 (C), 155.3 (C), 157.1 (C), 158.6 (C), 160.0 (CO). Anal. Calcd for C $_{25}$ H $_{35}$ N $_3$ O $_2$ S (441.63): C, 67.99; H, 7.99; N, 9.51; S, 7.26. Found: C, 68.10; H 7.85; N, 9.60; S, 7.35.

3-[2-(Diethylamino)ethyl]-8,8-dimethyl-2-propyl-7,10-dihydro-8H-pyrano[3'',4'':5',6']pyrido[3',2':4,5]thieno[3,2-*d*]pyrimidin-4(3*H*)-one (6j). Reaction of compound **5** (0.66 g, 2.0 mmol) and 2-chloro-*N,N*-diethylethanamine (0.28 g, 2.1 mmol) according to general procedure afforded 0.57 g (66%) of product **6j** isolated as a white solid: mp 160–161 °C. IR (ν/cm^{-1}): 1673 (CO). ^1H NMR (300 MHz, DMSO- d_6 /CCl $_4$, 1/3): δ_{H} 0.98 (t, J 7.1 Hz, 6H, N(CH $_2$ CH $_3$) $_2$), 1.11 (t, J 7.3 Hz, 3H, CH $_2$ CH $_3$), 1.32 (s, 6H, C(CH $_3$) $_2$), 1.85–1.99 (m, 2H, CH $_2$ CH $_3$), 0.98 (q, J 7.1 Hz, 4H, N(CH $_2$ CH $_3$) $_2$), 2.72 (t, J 6.6 Hz, 2H, CH $_2$ N(C $_2$ H $_5$) $_2$), 2.95 (t, J 7.4 Hz, 2H, CH $_2$ CH $_2$ CH $_3$), 2.96 (s, 2H, 7-CH $_2$), 4.15 (t, J 6.6 Hz, 2H, NCH $_2$), 4.90 (s, 2H, 10-CH $_2$), 8.18 (s, 1H, 11-CH). ^{13}C NMR (75.465 MHz, DMSO- d_6 /CCl $_4$, 1/3) δ_{C} 11.7 (2CH $_3$), 13.4 (CH $_3$), 19.6 (CH $_2$), 26.1 (2CH $_3$), 35.8 (7-CH $_2$), 42.4 (CH $_2$), 42.9 (CH $_2$), 47.1 (2NCH $_2$), 50.6 (NCH $_2$), 61.3 (10-CH $_2$), 70.8 (C 8), 119.2 (C), 126.0 (C), 126.1 (C), 126.3 (11-CH), 148.6 (C), 155.3 (C), 157.2 (C), 159.2 (C), 160.1 (CO). Anal. Calcd for C $_{23}$ H $_{32}$ N $_4$ O $_2$ S (428.59): C, 64.45; H, 7.53; N, 13.07; S, 7.48. Found: C, 64.49; H 7.68; N, 13.17; S, 7.52.

8,8-Dimethyl-3-(2-morpholin-4-ylethyl)-2-propyl-7,10-dihydro-8H-pyrano[3'',4'':5',6']pyrido[3',2':4,5]thieno[3,2-*d*]pyrimidin-4(3*H*)-one (6k). Reaction of compound **5** (0.66 g, 2.0 mmol) and 4-(2-chloroethyl)morpholine

(0.31 g, 2.1 mmol) according to general procedure afforded 0.63 g (71%) of product **6k** isolated as a white solid: mp 175–176 °C. IR (ν/cm^{-1}): 1659 (CO). ^1H NMR (300 MHz, DMSO- d_6 /CCl $_4$, 1/3): δ_{H} 1.12 (t, J 7.3 Hz, 3H, CH $_2$ CH $_3$), 1.33 (s, 6H, C(CH $_3$) $_2$), 1.87–2.00 (m, 2H, CH $_2$ CH $_3$), 2.48–2.55 (m, 4H, N(CH $_2$) $_2$), 2.65 (t, J 6.8 Hz, 2H, NCH $_2$ CH $_2$), 2.94 (t, J 7.5 Hz, 2H, CH $_2$ CH $_2$ CH $_3$), 2.96 (s, 2H, 7-CH $_2$), 3.57–3.62 (m, 4H, O(CH $_2$) $_2$), 4.24 (t, J 6.8 Hz, 2H, NCH $_2$ CH $_2$), 4.91 (s, 2H, 10-CH $_2$), 8.16 (s, 1H, 11-CH). ^{13}C NMR (75.465 MHz, DMSO- d_6 /CCl $_4$, 1/3) δ_{C} 13.4 (CH $_3$), 19.6 (CH $_2$), 26.1 (2CH $_3$), 35.6 (7-CH $_2$), 40.9 (CH $_2$), 42.9 (CH $_2$), 53.4 (2NCH $_2$), 56.1 (NCH $_2$), 61.3 (10-CH $_2$), 65.9 (2OCH $_2$), 70.8 (C 8), 119.2 (C), 126.0 (C), 126.1 (C), 126.3 (11-CH), 148.6 (C), 155.4 (C), 157.2 (C), 159.1 (C), 160.1 (CO). Anal. Calcd for C $_{23}$ H $_{30}$ N $_4$ O $_3$ S (442.58): C, 62.42; H, 6.83; N, 12.66; S, 7.25. Found: C, 62.50; H, 6.72; N, 12.51; S, 7.34.

3-(4-Isopropoxybenzyl)-8,8-dimethyl-2-propyl-7,10-dihydro-8H-pyrano[3'',4'':5',6']pyrido[3',2':4,5]thieno[3,2-*d*]pyrimidin-4(3H)-one (6l). Reaction of compound **5** (0.66 g, 2.0 mmol) and 1-(chloromethyl)-4-isopropoxybenzene (0.39 g, 2.1 mmol) according to general procedure afforded 0.62 g (65%) of product **6l** isolated as a white solid: mp 219–220 °C. IR (ν/cm^{-1}): 1675 (CO). ^1H NMR (300 MHz, DMSO- d_6 /CCl $_4$, 1/3): δ_{H} 1.01 (t, J 7.3 Hz, 3H, CH $_2$ CH $_3$), 1.30 (d, J 6.0 Hz, 6H, CH(CH $_3$) $_2$), 1.33 (s, 6H, C(CH $_3$) $_2$), 1.76–1.89 (m, 2H, CH $_2$ CH $_3$), 2.81 (t, J 7.5 Hz, 2H, CH $_2$ CH $_2$ CH $_3$), 2.98 (s, 2H, 7-CH $_2$), 4.52 (septet, J 6.0 Hz, 6H, CH(CH $_3$) $_2$), 4.91 (s, 2H, 10-CH $_2$), 5.36 (s, 2H, NCH $_2$), 6.76–6.82 (m, 2H, 2CH $_{\text{Ar}}$), 7.09–7.15 (m, 2H, 2CH $_{\text{Ar}}$), 8.17 (s, 1H, 11-CH). ^{13}C NMR (75.465 MHz, DMSO- d_6 /CCl $_4$, 1/3) δ_{C} 13.3 (CH $_3$), 19.5 (CH $_2$), 21.5 (2CH $_3$), 26.1 (2CH $_3$), 35.7 (7-CH $_2$), 42.9 (CH $_2$), 45.1 (CH $_2$), 61.3 (10-CH $_2$), 68.7 (CH), 70.8 (C 8), 115.2 (2CH $_{\text{Ar}}$), 119.3 (C), 126.0 (C), 126.1 (C), 126.3 (11-CH), 127.2 (C), 127.5 (2CH $_{\text{Ar}}$), 148.8 (C), 155.5 (C), 156.7 (C), 157.7 (C), 159.4 (C), 160.2 (CO). Anal. Calcd for C $_{27}$ H $_{31}$ N $_3$ O $_3$ S (477.62): C, 67.90; H, 6.54; N, 8.80; S, 6.71. Found: C, 67.95; H, 6.48; N, 8.87; S, 6.73.

2-(8,8-Dimethyl-4-oxo-2-propyl-7,10-dihydro-8H-pyrano[3'',4'':5',6']pyrido[3',2':4,5]thieno[3,2-*d*]pyrimidin-3(4H)-yl)-*N*-(4-methoxyphenyl)acetamide (6m). Reaction of compound **5** (0.66 g, 2.0 mmol) and 2-chloro-*N*-(4-methoxyphenyl)acetamide (0.42 g, 2.1 mmol) according to general procedure afforded 0.68 g (69%) of product **6m** isolated as a white solid: mp 199–200 °C. IR (ν/cm^{-1}): 3338 (NH), 1682 (CO), 1675 (CO). ^1H NMR (300 MHz, DMSO- d_6 /CCl $_4$, 1/3): δ_{H} 1.11 (t, J 7.4 Hz, 3H, CH $_2$ CH $_3$), 1.33 (s, 6H, C(CH $_3$) $_2$), 1.87–2.00 (m, 2H, CH $_2$ CH $_3$), 2.82–2.88 (m, 2H, CH $_2$ CH $_2$ CH $_3$), 2.97 (s, 2H, 7-CH $_2$), 3.75 (s, 3H, OCH $_3$), 4.92 (s, 2H, 10-CH $_2$), 5.00 (s, 2H, NCH $_2$), 6.77–6.82 (m, 2H, 2CH $_{\text{Ar}}$), 7.48–7.53 (m, 2H, 2CH $_{\text{Ar}}$), 8.22 (s, 1H, 11-CH), 10.16 (br. s, 1H, NH). ^{13}C NMR (75.465 MHz, DMSO- d_6 /CCl $_4$, 1/3) δ_{C} 13.4 (CH $_3$), 19.3 (CH $_2$), 26.1 (2CH $_3$), 35.8 (7-CH $_2$), 42.9 (CH $_2$), 45.9 (CH $_2$), 54.6 (CH $_3$), 61.3 (10-CH $_2$), 70.8 (C 8), 113.3 (2CH), 118.7 (C), 120.3 (2CH), 126.1 (C), 126.2 (C), 126.5 (11-CH), 131.6 (C), 149.0 (C), 155.1 (C), 155.5 (C), 157.5 (C), 159.9 (C), 160.1 (C), 163.6 (CO). Anal. Calcd for C $_{26}$ H $_{28}$ N $_4$ O $_4$ S (492.59): C, 63.40; H, 5.73; N, 11.37; S, 6.51. Found: C, 63.48; H, 5.68; N, 11.42; S, 6.65.

Supplementary Material

NMR ^1H and ^{13}C spectra of products can be found in the supplementary material file.

References

- Dua, R.; Shrivastava, S.; Sonwane, S. K.; Srivastava, S. K. *ABR*, **2011**, *5*, 120–144.
- Eicher, T.; Hauptmann, S.; Speicher, A. *The chemistry of heterocycles: structures, reactions, synthesis, and applications*. John Wiley & Sons, 2013.
<https://doi.org/10.1002/352760183X>

3. Ling, Y., Hao, Z.-Y.; Liang, D.; Zhang, C. L.; Liu, Y. F.; Wang Y. *Drug Des., Devel. Ther.* **2021**, 15, 4289–4338.
<https://doi.org/10.2147/DDDT.S329547>
4. Islam, M. B.; Islam, M. I.; Nath, N.; Emran, T. B.; Rahman, M. R.; Sharma, R.; Matin, M. M. *BioMed res. Inter.* **2023**, 2023, 1-15.
<https://doi.org/10.1155/2023/9967591>
5. Alenazi, N. A.; Alharbi, H.; Qarah, A. F.; Alsoliemy, A.; Abualnaja, M. M.; Karkashan, A.; Abbas, B.; El-Metwaly, N. M. *Arab. J. Chem.* **2023**, 16, 1-15.
<https://doi.org/10.1016/j.arabic.2023.105226>
6. Mohi El-Deen, E. M.; El-Gwaad, A.; Amina, A.; Anwar, M. M. *Egypt. J. Chem.* **2023**, 66, 231-242.
7. Singh, A.; Singh, R. DNA: an important component of life. In *Biochemistry, Biophysics, and Molecular Chemistry*; Apple Academic Press.
<https://doi.org/10.1201/9780429284175-12>
8. Tolba, M.; El-Dean, A.; Ahmed, M.; Hassanien, R.; Sayed, M.; Zaki, R. M.; Mohamed, Sh. K.; Zawam, S. A.; Abdel-Raheem, Sh. A. A. *Curr. Chem. Lett.*, **2022**, 11, 121-138.
<https://doi.org/10.5267/j.ccl.2021.8.002>
9. Ding, R.; Wang, X.; Fu, J.; Chang, Y.; Li, Y.; Liu, Y.; Liu, Y.; Ma, J.; Hu, J. *Eur. J. Med. Chem.* **2022**, 237, 114398-114398.
<https://doi.org/10.1016/j.ejmech.2022.114398>
10. Mahmoud, M. R.; El-Azm, F. S. A.; Ali, A. T.; Ali, Y. M. *Synth. Commun.* **2015**, 45, 982-992.
<https://doi.org/10.1080/00397911.2014.999340>
11. El-Shoukrofy, M. S.; Abd El Razik, H. A.; AboulWafa, O. M.; Bayad, A. E.; El-Ashmawy, I. M. *Bioorg. Chem.* **2019**, 85, 541-557.
<https://doi.org/10.1016/j.bioorg.2019.02.036>
12. Abdelkhalek, A. S.; Kothayer, H.; Rezaq, S.; Orabi, K. Y.; Romero, D. G.; El-Sabbagh, O. I. *Eur. J. Med. Chem.*, **2023**, 256, 1-44.
<https://doi.org/10.1016/j.ejmech.2023.115443>
13. Lagardère, P.; Fersing, C.; Masurier, N.; Lisowski, V. *Pharmaceuticals* **2021**, 15, 1-58.
<https://doi.org/10.3390/ph15010035>
14. Elmongy, E.; Kedr, M.; Abotaleb, N.; Abbas, S. *Egypt. J. Chem.* **2021**, 64, 6857-6867.
<https://doi.org/10.21608/ejchem.2021.23721.2412>
15. Zhang, H.; Lin, G.; Jia, S.; Wu, J.; Zhang, Y.; Tao, Y.; Huang, W.; Song, M.; Ding, K.; Ma, D.; Fan, M. *Bioorg. Chem.* **2024**, 148, 107456-107456.
<https://doi.org/10.1016/j.bioorg.2024.107456>
16. Mohamed, A. T.; Abou-Elregal, M. K.; Youssef, A. S.; Hemdan, M. M.; Samir, S. S.; Abou-Elmagd, W. S. *Synth. Commun.* **2020**, 50, 399-411.
<https://doi.org/10.1080/00397911.2019.1697822>
17. Mohi El-Deen, E. M.; Anwar, M. M.; El-Gwaad, A. A. A.; Karam, E. A.; El-Ashrey, M. K.; Kassab, R. R. *Molecules* **2022**, 27, 1-22.
<https://doi.org/10.3390/molecules27030803>
18. El-Deen, E. M. M.; Anwar, M. M.; Abd El-Gwaad, A. A.; Karam, E. A.; El-Ashrey, M. K.; Kassab, R. R. *Arab. J. Chem.* **2022**, 15, 1-20.
<https://doi.org/10.1016/j.arabic.2022.103751>

19. Dabaeva, V. V.; Baghdasaryan, M. R.; Paronikyan, R. G.; Nazaryan, I. M.; Hakobyan, H. G.; Hunanyan, L. S.; Paronikyan E. G. Dashyan, Sh. Sh. *Russ. J. Bioorg. Chem.* **2022**, 48, 125-134.
<https://doi.org/10.1134/S1068162022010034>
20. Dashyan, Sh. Sh.; Babaev, E. V.; Paronikyan, E. G.; Ayvazyan, A. G.; Paronikyan, R. G.; Hunanyan, L. S. *Molecules* **2022**, 27, 1-23.
21. Dabaeva, V. V.; Bagdasaryan, M. R.; Paronikyan, E. G.; Dashyan, Sh. Sh.; Paronikyan, R. G.; Nazaryan, I. M.; Akopyan, A. G. *Pharm. Chem. J.* **2020**, 54, 707-713.
<https://doi.org/10.1007/s11094-020-02259-y>
22. Dabaeva, V. V.; Noravyan, A. S.; Enokyan, B. D.; *Chem. Heterocycl. Comp.* **1995**, 31, 219-222.
<https://doi.org/10.1007/BF01169683>

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