

Thieno[2,3-*d*]pyrimidin-4-ones. Part 2.*

Condensation of 2,3-Disubstituted thieno[2,3-*d*]pyrimidin-4-ones with Aldehydes

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Authors' contributions

This work was carried out in collaboration between the authors. Authors KAB and BZE carried out the synthesis. Author BZE designed the scheme and the protocol for synthetic pathway and wrote the first draft. Author BZE managed the analysis of the study and spectroscopic evaluation. Author KMS did the collation of the data and editing of the write-up. All authors read and approved the final manuscript.

ABSTRACT

The reactions of 2,3-tri-, -tetramethylene-7,8-dihydro-6H-thieno[2,3-*d*]pyrrolo[1,2-*a*]pyrimidine-4-ones (**1a,b**) and 2,3-dimethyl-, -tri-, -tetra-, -pentamethylene-6,7,8,9-tetrahydropyrido[1,2-*a*]thieno[2,3-*d*]pyrimidine-4-ones (**4a-d**), containing active methylene groups in positions 8 or 9, with aromatic aldehydes under acidic and alkaline conditions go depending on reaction conditions and nature of aromatic aldehydes with the formation of new (±)-(4-nitrophenyl)(2,3-tri, tetramethylene-7,8-dihydropyrrolo[1,2-*a*]thieno[2,3-*d*]pyrimidine-4-one-8-yl)methanols (**2, 3**), 9-arylidene derivatives (**5a-e-8a-e**) and (±)-(4-nitrophenyl)(2,3-tetramethylene-6,7,8,9-tetrahydropyrido[1,2-*a*]thieno[2,3-*d*]pyrimidine-4-one-9-yl)methanol (**9**). If aldehydes with electron-withdrawing (nitro) group are used, the reaction can be stopped at a stage where the products of electrophilic additions products are racemates, i.e. containing asymmetric carbon atom in position 8 or 9, and if aromatic aldehydes with electron-donating substituent are used 9-arylidene derivatives are formed exclusively.

*Keywords: condensed thieno[2,3-*d*]pyrimidin-4-ones, electrophilic addition products, 9-arylidene derivatives, aldehydes, condensation*

1. INTRODUCTION

Thiophene and pyrimidine derivatives have been shown to possess a variety of pharmacological activities like antibacterial [2-4], anti-microbial [5-7], antitumor [8], anti-inflammatory [2, 9-11], analgetic [2,10,11], ulcerogenic [2,10], cytotoxic [12-14], and chemotherapeutic [15] activities. Condensed thieno[2,3-*d*]pyrimidin-4-ones are of interest from the theoretical and practical points of view. Condensation of aldehydes with organic compounds, containing activated methylene groups are widely used in organic and bioorganic chemistry. Aldehydes are used in reactions to form new heterocyclic systems [16-22] and electrophilic addition products containing asymmetric carbon atom [23, 24], in Knoevenagel reactions [25, 26], in formation of ylidene derivatives to obtain dehydration of addition products [27-32], in Claisen-Schmidt condensation reactions [33] and in formation of Schiff bases [34]. These reactions are catalyzed with acids as well as with bases (inorganic and organic), and are classified as acid/base-catalyzed reactions. This work was carried out with the purpose of studying condensation of starting compounds with aldehydes, determination of factors influencing the course and direction of reactions. The interaction of thienopyrimidine-4-ones condensed with hydrogenated piperidine ring with aromatic and heterocyclic aldehydes were not investigated.

*Part 1. See literature [1]

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2. MATERIALS AND METHODS

2.1 General Conditions

¹H-NMR spectra were recorded in CDCl₃ and DMSO-d₆ on Unityplus 400 spectrometer operating at 400 MHz. Hexamethyldisilane (HMDS) was used as internal standard, chemical shifts δ of ¹H were recorded in ppm. Mass spectra were acquired on a high-res DFS spectrometer. Mps were measured on a Boetius and MEL-TEMP apparatus manufactured by Barnstead International (USA) and were uncorrected.

IR spectra were recorded on IR Fury System 2000 (Perkin-Elmer) as KBr pellets.

The reaction progress was monitored by TLC on Sorbfil and Whatman UV-254 precoated aluminum plates using C₆H₆/CH₃OH (3:1 and 5:1) solvent system and developed plates were visualized under UV lamp and/or iodine tank where necessary. Solvents were purified by standard procedures. Organic solutions were dried over anhydrous Na₂SO₄ and concentrated with a RVO-64 ROT VAC Evaporator at reduced pressure.

2.2 Synthesis

2,3-Tri- (**1a**), -tetramethylene-7,8-dihydropyrrolo[1,2-a]thieno[2,3-d]pyrimidine-4-ones (**1b**) and 2,3-dimethyl- (**4a**), -tri- (**4b**), -tetra- (**4c**) and 2,3-pentamethylene-6,7,8,9-tetrahydropyrido[1,2-a]thieno[2,3-d]pyrimidine-4-ones (**4d**) were synthesized according to method described by Elmuradov et al. [1].

2.2.1 General procedure for synthesis (±)-(4-nitrophenyl)(2,3-tri-, tetramethylene-7,8-dihydropyrrolo[1,2-a]thieno[2,3-d]pyrimidine-4-one-8-yl)methanols (**2**, **3**)

To a 0.6 mmol of NaOH dissolved in 10.0 mL ethanol were added 2.0 mmol of corresponding thieno[2,3-d]pyrimidine-4-ones (**1a** or **1b**) and 2.0 mmol of 4-nitrobenzaldehyde. Reaction mixture was boiled in water bath at 85-90°C for 0.5-4 h. The solvent was distilled off and the residue was recrystallized from benzene and the desired compounds (**2** or **3**) were obtained in moderate yields.

2.2.1.1 (±)-(4-Nitrophenyl)(2,3-trimethylene-7,8-dihydropyrrolo[1,2-a]thieno[2,3-d]pyrimidine-4-one-8-yl)methanol (**2**)

Yield: 0.34 g (45%), mp 221-223°C (benzene), *R*_f=0.79 (C₆H₆/CH₃OH, 5:1, at RT). ¹H-NMR (DMSO-d₆) δ : 1.86-1.77 (1H, m, 7-Ha), 2.14-2.06 (1H, m, 7-Hb), 2.37-2.30 (2H, m, 2-CH₂-CH₂), 2.87 (4H, t, *J*=7.0 Hz, 2-CH₂, 3-CH₂), 3.63 (1H, m, 8-H), 3.85-3.78 (1H, m, 6-Ha), 4.0-3.93 (1H, m, 6-Hb), 5.4 (1H, d, *J*=4.8 Hz, CH(OH)), 5.91 (1H, s, OH), 7.68 (2H, d, *J*=8.8 Hz, H_{Ar}-2',6'), 8.18 (2H, d, *J*=8.8 Hz, H_{Ar}-3',5'). IR (KBr) cm⁻¹: 3378 (OH), 1650 (C=O), 1540 (C=N), 1519 (NO₂), 1475 (C-N). MS-EI in *m/z* (rel. %): 384 ([*M*+1]⁺, 2.1), 383 ([*M*]⁺, 11.2), 365 ([*M*-H₂O]⁺, 3.5), 231 ([*M*-CH(OH)-C₆H₄-NO₂]⁺, 100). Anal. calcd. for C₁₉H₁₇N₃O₄S (383.23): C, 59.53; H, 4.44; N, 10.96. Found: C, 59.60; H, 4.40; N, 11.05.

2.2.1.2 (±)-(4-Nitrophenyl)(2,3-tetramethylene-7,8-dihydropyrrolo[1,2-a]thieno[2,3-d]pyrimidine-4-one-8-yl)methanol (**3**)

Yield: 0.38 g (48%), mp 210-212°C (benzene), *R*_f=0.52 (C₆H₆/CH₃OH, 5:1, at RT). ¹H-NMR (DMSO-d₆) δ : 1.77-1.70 (4H, m, 3-CH₂-(CH₂)₂), 1.85-1.78 (1H, m, 7-Ha), 2.11-2.05 (1H, m, 7-Hb), 2.69 (2H, t, *J*=5.9 Hz, 2-CH₂), 2.83 (2H, t, *J*=6.1 Hz, 3-CH₂), 3.62 (1H, m, 8-H), 3.83-3.77 (1H, m, 6-Ha), 3.98-3.91 (1H, m, 6-Hb), 5.37 (1H, d, *J*=4.6 Hz, CH(OH)), 5.90 (1H, s, OH), 7.68 (2H, d, *J*=8.6 Hz, H_{Ar}-2',6'), 8.18 (2H, d, *J*=8.6 Hz, H_{Ar}-3',5'). IR (KBr) cm⁻¹: 3320 (OH), 1671 (C=O), 1557 (C=N), 1517 (NO₂), 1481 (C-N). MS-EI in *m/z* (rel. %): 397 ([*M*]⁺, 42), 245 ([*M*-CH(OH)-C₆H₄-NO₂]⁺, 100), 151 (35). Anal. calcd. for C₂₀H₁₉N₃O₄S (397.19): C, 60.42; H, 4.78; N, 10.57. Found: C, 60.50; H, 4.70; N, 10.65.

2.2.2 General procedure for synthesis 2,3-disubstituted 9-arylidene(furfurilidene-2)-6,7,8,9-tetrahydropyrido[1,2-a]thieno[2,3-d]pyrimidine-4-ones (5a-e - 8a-e)

To a 0.6 mmol of NaOH dissolved in 10.0 mL n-propanol were added 2.0 mmol of corresponding thieno[2,3-d]pyrimidine-4-ones (**4a-d**) and 2.0 mmol of aldehyde. Reaction mixture was boiled in oil bath at 105-110°C for 7-8 h. The precipitate was filtered, washed with cyclohexane and dried. The residue was recrystallized from corresponding solvent and the condensation products (**5a-e - 8a-e**) were obtained in moderate to excellent yields.

2.2.2.1 2,3-Dimethyl-9-benzylidene-6,7,8,9-tetrahydropyrido[1,2-a]thieno[2,3-d]pyrimidine-4-one (5a)

Yield: 0.425 g (66%), mp 180-182°C (benzene), $R_f=0.88$ (C_6H_6/CH_3OH , 5:1, at RT). ^1H -NMR ($CDCl_3$) δ : 1.94-1.92 (2H, m, 7-CH₂), 2.30 (3H, s, 2-CH₃), 2.43 (3H, s, 3-CH₃), 2.89 (2H, t, $J=6.7$ Hz, 8-CH₂), 3.95 (2H, t, $J=6.0$ Hz, 6-CH₂), 7.40-7.20 (5H, m, $H_{Ph-2,3,4,5,6}$), 8.08 (1H, s, CHPh). IR (KBr) cm^{-1} : 1671 (C=O), 1551 (C=N), 1490 (C-N).

2.2.2.2 2,3-Dimethyl-9-(4-dimethylaminobenzylidene)-6,7,8,9-tetrahydropyrido[1,2-a]thieno[2,3-d]pyrimidine-4-one (5b)

Yield: 0.4 g (55%), mp 201-203°C (benzene), $R_f=0.87$ (C_6H_6/CH_3OH , 5:1, at RT). ^1H -NMR ($CDCl_3$) δ : 1.96-1.91 (2H, m, 7-CH₂), 2.32 (3H, s, 2-CH₃), 2.42 (3H, s, 3-CH₃), 2.88 (2H, t, $J=5.0$ Hz, 8-CH₂), 2.96 (6H, s, $N(CH_3)_2$), 4.04 (2H, t, $J=5.7$ Hz, 6-CH₂), 6.65 (2H, d, $J=8.8$ Hz, $H_{Ar-3',5'}$), 7.36 (2H, d, $J=8.8$ Hz, $H_{Ar-2',6'}$), 7.97 (1H, s, CHAr). IR (KBr) cm^{-1} : 1652 (C=O), 1591 (C=N), 1497 (C-N).

2.2.2.3 2,3-Dimethyl-9-(3,4-dimethoxybenzylidene)-6,7,8,9-tetrahydropyrido[1,2-a]thieno[2,3-d]pyrimidine-4-one (5c)

Yield: 0.5 g (65%), mp 205-207°C (methanol), $R_f=0.83$ (C_6H_6/CH_3OH , 5:1, at RT). ^1H -NMR ($CDCl_3$) δ : 1.97-1.92 (2H, m, 7-CH₂), 2.33 (3H, s, 2-CH₃), 2.43 (3H, s, 3-CH₃), 2.88 (2H, td, $J_1=6.5$ Hz, $J_2=2.0$ Hz, 8-CH₂), 3.85 (3H, s, 3'-OCH₃), 3.87 (3H, s, 4'-OCH₃), 4.06 (2H, t, $J=5.8$ Hz, 6-CH₂), 6.84 (1H, d, $J=8.4$ Hz, $H_{Ar-5'}$), 6.93 (1H, d, $J=2.0$ Hz, $H_{Ar-2'}$), 7.02 (1H, dd, $J=8.5$ Hz, $J=2.0$ Hz, $H_{Ar-6'}$), 8.00 (1H, t, $J=2.0$ Hz, CHAr). IR (KBr) cm^{-1} : 1672 (C=O), 1573 (C=N), 1490 (C-N).

2.2.2.4 2,3-Dimethyl-9-(3,4-methylenedioxybenzylidene)-6,7,8,9-tetrahydropyrido[1,2-a]thieno[2,3-d]pyrimidine-4-one (5d)

Yield: 0.44 g (60%), mp 167-169°C (methanol), $R_f=0.90$ (C_6H_6/CH_3OH , 5:1, at RT). ^1H -NMR ($CDCl_3$) δ : 1.96-1.92 (2H, m, 7-CH₂), 2.33 (3H, s, 2-CH₃), 2.43 (3H, s, 3-CH₃), 2.84 (2H, td, $J_1=6.7$ Hz, $J_2=2.2$ Hz, 8-CH₂), 4.05 (2H, t, $J=6.0$ Hz, 6-CH₂), 5.95 (2H, s, O-CH₂), 6.79 (1H, d, $J=6.7$ Hz, $H_{Ar-5'}$), 6.92 (2H, dd, $J_1=6.7$ Hz, $J_2=1.8$ Hz, $H_{Ar-2',6'}$), 7.95 (1H, t, $J=2.2$ Hz, CHAr). IR (KBr) cm^{-1} : 1668 (C=O), 1558 (C=N), 1490 (C-N).

2.2.2.5 2,3-Dimethyl-9-(furfurylidene-2)-6,7,8,9-tetrahydropyrido[1,2-a]thieno[2,3-d]pyrimidine-4-one (5e)

Yield: 0.52 g (84%), mp 176-178°C (benzene), $R_f=0.82$ (C_6H_6/CH_3OH , 3:1, at RT). ^1H -NMR ($CDCl_3$) δ : 1.99-1.94 (2H, m, 7-CH₂), 2.32 (3H, s, 2-CH₃), 2.42 (3H, s, 3-CH₃), 2.97 (2H, td, $J_1=6.7$ Hz, $J_2=2.2$ Hz, 8-CH₂), 4.07 (2H, t, $J=6.0$ Hz, 6-CH₂), 6.45 (1H, tt, $J_1=3.5$ Hz, $J_2=2.0$ Hz, $H_{Het-4'}$), 6.56 (1H, d, $J=3.5$ Hz, $H_{Het-3'}$), 7.48 (1H, d, $J=2.0$ Hz, $H_{Het-5'}$), 7.83 (1H, t, $J=2.2$ Hz, CHHet). IR (KBr) cm^{-1} : 1669 (C=O), 1557 (C=N), 1488 (C-N).

2.2.2.6 2,3-Trimethylene-9-benzylidene-6,7,8,9-tetrahydropyrido[1,2-a]thieno[2,3-d]pyrimidine-4-one (6a)

Yield: 0.43 g (65%), mp 196-198⁰C (methanol), R_f =0.80 (C₆H₆/CH₃OH, 3:1, at RT). ¹H-NMR (CDCl₃) δ : 1.97-1.92 (2H, m, 3-CH₂-CH₂), 2.43-2.38 (2H, m, 7-CH₂), 2.87 (2H, t, J =6.7 Hz, 2-CH₂), 2.90 (2H, t, J =7.3 Hz, 3-CH₂), 3.03 (2H, td, J =7.0 Hz, J =2.0 Hz, 8-CH₂), 4.08 (2H, t, J =6.0 Hz, 6-CH₂), 7.40-7.27 (5H, m, H_{Ph}-2',3',4',5',6'), 8.08 (1H, t, J =2.0 Hz, CHPh). IR (KBr) cm⁻¹: 1678 (C=O), 1591 (C=N), 1492 (C-N).

2.2.2.7 2,3-Trimethylene-9-(4-dimethylaminobenzylidene)-6,7,8,9-tetrahydropyrido[1,2-a]thieno[2,3-d]pyrimidine-4-one (6b)

Yield: 0.44 g (58%), mp 216-218⁰C (benzene), R_f =0.85 (C₆H₆/CH₃OH, 5:1, at RT). ¹H-NMR (CDCl₃) δ : 1.96-1.91 (2H, m, 3-CH₂-CH₂), 2.42-2.36 (2H, m, 7-CH₂), 2.87 (2H, t, J =7.3 Hz, 2-CH₂), 2.90 (2H, t, J =6.3 Hz, 3-CH₂), 2.96 (6H, s, N(CH₃)₂), 3.01 (2H, td, J_1 =7.3 Hz, J_2 =2.0 Hz, 8-CH₂), 4.07 (2H, t, J =6.0 Hz, 6-CH₂), 6.66 (2H, d, J =9.0 Hz, H_{Ar}-3',5'), 7.37 (2H, d, J =9.0 Hz, H_{Ar}-2',6'), 7.98 (1H, t, J =2.0 Hz, CHAr). IR (KBr) cm⁻¹: 1658 (C=O), 1591 (C=N), 1469 (C-N).

2.2.2.8 2,3-Trimethylene-9-(3,4-dimethoxybenzylidene)-6,7,8,9-tetrahydropyrido[1,2-a]thieno[2,3-d]pyrimidine-4-one (6c)

Yield: 0.5 g (63%), mp 204-206⁰C (methanol), R_f =0.82 (C₆H₆/CH₃OH, 5:1, at RT). ¹H-NMR (CDCl₃) δ : 1.98-1.93 (2H, m, 3-CH₂-CH₂), 2.43-2.38 (2H, m, 7-CH₂), 2.88 (2H, t, J =6.7 Hz, 2-CH₂), 2.91 (2H, t, J =6.0 Hz, 3-CH₂), 3.02 (2H, td, J_1 =7.3 Hz, J_2 =2.0 Hz, 8-CH₂), 3.85 (3H, s, 3'-OCH₃), 3.87 (3H, s, 4'-OCH₃), 4.08 (2H, t, J =6.0 Hz, 6-CH₂), 6.85 (1H, d, J =8.3 Hz, H_{Ar}-5'), 6.94 (1H, d, J =2.0 Hz, H_{Ar}-2'), 7.03 (1H, dd, J_1 =8.3 Hz, J_2 =2.0 Hz, H_{Ar}-6'), 8.02 (1H, t, J =2.0 Hz, CHAr). IR (KBr) cm⁻¹: 1666 (C=O), 1576 (C=N), 1469 (C-N).

2.2.2.9 2,3-Trimethylene-9-(3,4-methylenedioxybenzylidene)-6,7,8,9-tetrahydropyrido[1,2-a]thieno[2,3-d]pyrimidine-4-one (6d)

Yield: 0.45 g (60%), mp 203-205⁰C (methanol), R_f =0.81 (C₆H₆/CH₃OH, 5:1, at RT). ¹H-NMR (CDCl₃) δ : 1.97-1.92 (2H, m, 3-CH₂-CH₂), 2.43-2.37 (2H, m, 7-CH₂), 2.85 (2H, t, J =7.0 Hz, 2-CH₂), 2.90 (2H, t, J =5.6 Hz, 3-CH₂), 3.02 (2H, td, J =7.0 Hz, J =1.7 Hz, 8-CH₂), 4.07 (2H, t, J =5.7 Hz, 6-CH₂), 5.95 (2H, s, O-CH₂), 6.80 (2H, dd, J_1 =7.0 Hz, J_2 =1.7 Hz, H_{Ar}-2',6'), 6.92 (1H, d, J =7.0 Hz, H_{Ar}-5'), 7.97 (1H, t, J =1.7 Hz, CHAr). IR (KBr) cm⁻¹: 1669 (C=O), 1558 (C=N), 1487 (C-N).

2.2.2.10 2,3-Trimethylene-9-(furfurylidene-2)-6,7,8,9-tetrahydropyrido[1,2-a]thieno[2,3-d]pyrimidine-4-one (6e)

Yield: 0.52 g (81%), mp 190-191⁰C (benzene), R_f =0.88 (C₆H₆/CH₃OH, 5:1, at RT). ¹H-NMR (CDCl₃) δ : 2.00-1.95 (2H, m, 3-CH₂-CH₂), 2.43-2.38 (2H, m, 7-CH₂), 2.86 (2H, t, J =6.9 Hz, 2-CH₂), 2.96 (2H, t, J =6.7 Hz, 3-CH₂), 3.01 (2H, td, J_1 =7.1 Hz, J_2 =2.2 Hz, 8-CH₂), 4.09 (2H, t, J =5.9 Hz, 6-CH₂), 6.46 (1H, dd, J_1 =3.5 Hz, J_2 =1.7 Hz, H_{Het}-4'), 6.57 (1H, d, J =3.5 Hz, H_{Het}-3'), 7.45 (1H, d, J =1.7 Hz, H_{Het}-5'), 7.84 (1H, t, J =2.2 Hz, CHHet). IR (KBr) cm⁻¹: 1663 (C=O), 1542 (C=N), 1470 (C-N).

2.2.2.11 2,3-Tetramethylene-9-benzylidene-6,7,8,9-tetrahydropyrido[1,2-a]thieno[2,3-d]pyrimidine-4-one (7a)

Yield: 0.5 g (72%), mp 189-190⁰C (methanol), R_f =0.90 (C₆H₆/CH₃OH, 5:1, at RT). ¹H-NMR (CDCl₃) δ : 1.83-1.78 (4H, m, 3-CH₂-(CH₂)₂), 1.96-1.91 (2H, m, 7-CH₂), 2.72 (2H, t, J =6.0 Hz, 2-CH₂), 2.87 (2H, td, J_1 =6.6 Hz, J_2 =2.0 Hz, 8-CH₂), 2.97 (2H, t, J =6.0 Hz, 3-CH₂), 4.05 (2H, t, J =5.9 Hz, 6-CH₂), 7.40-7.27 (5H, m, H_{Ph}-2',3',4',5',6'), 8.06 (1H, t, J =2.0 Hz, CHPh). IR (KBr) cm⁻¹: 1662 (C=O), 1556 (C=N), 1492 (C-N).

2.2.2.12 2,3-Tetramethylene-9-(4-dimethylaminobenzylidene)-6,7,8,9-tetrahydropyrido[1,2-a]thieno[2,3-d]pyrimidine-4-one (7b)

Yield: 0.48 g (62%), mp 198-200°C (benzene), R_f =0.86 (C_6H_6/CH_3OH , 5:1, at RT). ^1H -NMR ($CDCl_3$) δ : 1.84-1.79 (4H, m, 3-CH₂-(CH₂)₂), 1.95-1.90 (2H, m, 7-CH₂), 2.70 (2H, t, J =5.9 Hz, 2-CH₂), 2.88 (2H, td, J_1 =6.6 Hz, J_2 =2.0 Hz, 8-CH₂), 2.96 (6H, s, N(CH₃)₂), 2.97 (2H, t, J =6.0 Hz, 3-CH₂), 4.04 (2H, t, J =5.8 Hz, 6-CH₂), 6.65 (2H, d, J =9.0 Hz, H_{Ar}-3',5'), 7.37 (2H, d, J =9.0 Hz, H_{Ar}-2',6'), 7.97 (1H, t, J =2.0 Hz, CHAr). IR (KBr) cm^{-1} : 1662 (C=O), 1557 (C=N), 1487 (C-N).

2.2.2.13 2,3-Tetramethylene-9-(3,4-dimethoxybenzylidene)-6,7,8,9-tetrahydropyrido[1,2-a]thieno[2,3-d]pyrimidine-4-one (7c)

Yield: 0.55 g (68%), mp 194-196°C (methanol), R_f =0.84 (C_6H_6/CH_3OH , 5:1, at RT). ^1H -NMR ($CDCl_3$) δ : 1.84-1.77 (4H, m, 3-CH₂-(CH₂)₂), 1.95-1.93 (2H, m, 7-CH₂), 2.72 (2H, t, J =5.9 Hz, 2-CH₂), 2.88 (2H, td, J_1 =6.4 Hz, J_2 =2.0 Hz, 8-CH₂), 2.96 (2H, t, J =5.9 Hz, 3-CH₂), 3.85 (3H, s, 3'-OCH₃), 3.87 (3H, s, 4'-OCH₃), 4.05 (2H, t, J =5.8 Hz, 6-CH₂), 6.85 (1H, d, J =8.5 Hz, H_{Ar}-5'), 6.94 (1H, d, J =2.0 Hz, H_{Ar}-2'), 7.03 (1H, dd, J_1 =8.5 Hz, J_2 =2.0 Hz, H_{Ar}-6'), 8.01 (1H, t, J =2.0 Hz, CHAr). IR (KBr) cm^{-1} : 1663 (C=O), 1557 (C=N), 1488 (C-N).

2.2.2.14 2,3-Tetramethylene-9-(3,4-methylenedioxybenzylidene)-6,7,8,9-tetrahydropyrido[1,2-a]thieno[2,3-d]pyrimidine-4-one (7d)

Yield: 0.55 g (70%), mp 190-192°C (methanol), R_f =0.87 (C_6H_6/CH_3OH , 5:1, at RT). ^1H -NMR ($CDCl_3$) δ : 1.83-1.74 (4H, m, 3-CH₂-(CH₂)₂), 1.95-1.91 (2H, m, 7-CH₂), 2.72 (2H, t, J =6.0 Hz, 2-CH₂), 2.84 (2H, td, J_1 =6.4 Hz, J_2 =2.0 Hz, 8-CH₂), 2.96 (2H, t, J =6.0 Hz, 3-CH₂), 4.04 (2H, t, J =5.7 Hz, 6-CH₂), 5.95 (2H, s, O-CH₂), 6.8 (1H, d, J =8.6 Hz, H_{Ar}-5'), 6.92 (2H, dd, J_1 =8.6 Hz, J_2 =1.7 Hz, H_{Ar}-2',6'), 7.96 (1H, t, J =2.0 Hz, CHAr). IR (KBr) cm^{-1} : 1666 (C=O), 1541 (C=N), 1488 (C-N).

2.2.2.15 2,3-Tetramethylene-9-(furfurylidene-2)-6,7,8,9-tetrahydropyrido[1,2-a]thieno[2,3-d]pyrimidine-4-one (7e)

Yield: 0.58 g (86%), mp 210-212°C (benzene), R_f =0.87 (C_6H_6/CH_3OH , 5:1, at RT). ^1H -NMR ($CDCl_3$) δ : 1.83-1.77 (4H, m, 3-CH₂-(CH₂)₂), 1.99-1.94 (2H, m, 7-CH₂), 2.71 (2H, t, J =6.0 Hz, 2-CH₂), 2.90 (2H, td, J_1 =5.9 Hz, J_2 =2.0 Hz, 8-CH₂), 2.97 (2H, t, J =6.3 Hz, 3-CH₂), 4.07 (2H, t, J =5.8 Hz, 6-CH₂), 6.45 (1H, dd, J_1 =3.5 Hz, J_2 =1.8 Hz, H_{Het}-4'), 6.56 (1H, d, J =3.5 Hz, H_{Het}-3'), 7.48 (1H, d, J =1.8 Hz, H_{Het}-5'), 7.83 (1H, t, J =2.0 Hz, CHHet). IR (KBr) cm^{-1} : 1651 (C=O), 1557 (C=N), 1472 (C-N).

2.2.2.16 2,3-Pentamethylene-9-benzylidene-6,7,8,9-tetrahydropyrido[1,2-a]thieno[2,3-d]pyrimidine-4-one (8a)

Yield: 0.556 g (77%), mp 188-190°C (methanol), R_f =0.83 (C_6H_6/CH_3OH , 5:1, at RT). ^1H -NMR ($CDCl_3$) δ : 1.68-1.60 (4H, m, 2-CH₂-(CH₂)₂), 1.86-1.82 (2H, m, 7-CH₂), 1.95-1.91 (2H, m, 3-CH₂-(CH₂)₂), 2.79 (2H, t, J =5.4 Hz, 2-CH₂), 2.86 (2H, td, J_1 =6.6 Hz, J_2 =1.9 Hz, 8-CH₂), 3.30 (2H, t, J =5.7 Hz, 3-CH₂), 4.05 (2H, t, J =5.9 Hz, 6-CH₂), 7.40-7.26 (5H, m, H_{Ph}-2',3',4',5',6'), 8.04 (1H, t, J =1.9 Hz, CHPh). IR (KBr) cm^{-1} : 1667 (C=O), 1546 (C=N), 1484 (C-N).

2.2.2.17 2,3-Pentamethylene-9-(4-dimethylaminobenzylidene)-6,7,8,9-tetrahydropyrido[1,2-a]thieno[2,3-d]pyrimidine-4-one (8b)

Yield: 0.575 g (71%), mp 186-188°C (benzene), R_f =0.87 (C_6H_6/CH_3OH , 5:1, at RT). ^1H -NMR ($CDCl_3$) δ : 1.67-1.59 (4H, m, 2-CH₂-(CH₂)₂), 1.84-1.81 (2H, m, 7-CH₂), 1.95-1.91 (2H, m, 3-CH₂-(CH₂)₂), 2.77 (2H, t, J =5.4 Hz, 2-CH₂), 2.88 (2H, td, J_1 =5.4 Hz, J_2 =2.0 Hz, 8-CH₂), 2.96 (6H, s, N(CH₃)₂), 3.29 (2H, t, J =5.7 Hz, 3-CH₂), 4.04 (2H, t, J =5.7 Hz, 6-CH₂), 6.65 (2H, d, J =8.9 Hz, H_{Ar}-3',5'), 7.36 (2H, d, J =8.9 Hz, H_{Ar}-2',6'), 7.94 (1H, t, J =2.0 Hz, CHAr). IR (KBr) cm^{-1} : 1674 (C=O), 1548 (C=N), 1479 (C-N).

2.2.2.18 2,3-Pentamethylene-9-(3,4-dimethoxybenzylidene)-6,7,8,9-tetrahydropyrido[1,2-a]thieno[2,3-d]pyrimidine-4-one (8c)

Yield: 0.641 g (76%), mp 167-168⁰C (methanol), *R*_f=0.85 (C₆H₆/CH₃OH, 5:1, at RT). ¹H-NMR (CDCl₃) δ: 1.68-1.61 (4H, m, 2-CH₂-(CH₂)₂), 1.85-1.83 (2H, m, 7-CH₂), 1.95-1.93 (2H, m, 3-CH₂-(CH₂)), 2.78 (2H, t, *J*=5.7 Hz, 2-CH₂), 2.87 (2H, td, *J*₁=6.4 Hz, *J*₂=2.0 Hz, 8-CH₂), 3.30 (2H, t, *J*=5.7 Hz, 3-CH₂), 3.85 (3H, s, 3'-OCH₃), 3.86 (3H, s, 4'-OCH₃), 4.06 (2H, t, *J*=5.9 Hz, 6-CH₂), 6.85 (1H, d, *J*=8.4 Hz, H_{Ar}-5'), 6.94 (1H, d, *J*=2.0 Hz, H_{Ar}-2'), 7.02 (1H, dd, *J*₁=8.4 Hz, *J*₂=2.0 Hz, H_{Ar}-6'), 7.98 (1H, t, *J*=2.0 Hz, CHAr). IR (KBr) cm⁻¹: 1660 (C=O), 1545 (C=N), 1485 (C-N).

2.2.2.19 2,3-Pentamethylene-9-(3,4-methylenedioxybenzylidene)-6,7,8,9-tetrahydropyrido[1,2-a]thieno[2,3-d]pyrimidine-4-one (8d)

Yield: 0.53 g (65%), mp 178-180⁰C (methanol), *R*_f=0.84 (C₆H₆/CH₃OH, 5:1, at RT). ¹H-NMR (CDCl₃) δ: 1.66-1.61 (4H, m, 2-CH₂-(CH₂)₂), 1.84-1.82 (2H, m, 7-CH₂), 1.94-1.91 (2H, m, 3-CH₂-(CH₂)), 2.78 (2H, t, *J*=5.4 Hz, 2-CH₂), 2.83 (2H, td, *J*₁=6.9 Hz, *J*₂=2.0 Hz, 8-CH₂), 3.29 (2H, t, *J*=5.7 Hz, 3-CH₂), 4.04 (2H, t, *J*=5.7 Hz, 6-CH₂), 5.95 (2H, s, O-CH₂), 6.79 (1H, d, *J*=8.5 Hz, H_{Ar}-5'), 6.90 (2H, dd, *J*₁=8.5 Hz, *J*₂=1.9 Hz, H_{Ar}-2',6'), 7.93 (1H, t, *J*=2.0 Hz, CHAr). IR (KBr) cm⁻¹: 1663 (C=O), 1548 (C=N), 1491 (C-N).

2.2.2.20 2,3-Pentamethylene-9-(furfurylidene-2)-6,7,8,9-tetrahydropyrido[1,2-a]thieno[2,3-d]pyrimidine-4-one (8e)

Yield: 0.633 g (90%), mp 170-171⁰C (benzene), *R*_f=0.88 (C₆H₆/CH₃OH, 5:1, at RT). ¹H-NMR (CDCl₃) δ: 1.67-1.61 (4H, m, 2-CH₂-(CH₂)₂), 1.84-1.81 (2H, m, 7-CH₂), 1.97-1.95 (2H, m, 3-CH₂-(CH₂)), 2.78 (2H, t, *J*=5.7 Hz, 2-CH₂), 2.96 (2H, td, *J*₁=6.7 Hz, *J*₂=2.2 Hz, 8-CH₂), 3.29 (2H, t, *J*=5.4 Hz, 3-CH₂), 4.07 (2H, t, *J*=5.7 Hz, 6-CH₂), 6.45 (1H, dd, *J*₁=3.5 Hz, *J*₂=1.7 Hz, H_{Het}-4'), 6.56 (1H, d, *J*=3.5 Hz, H_{Het}-3'), 7.48 (1H, d, *J*=1.7 Hz, H_{Het}-5'), 7.82 (1H, t, *J*=2.2 Hz, CHHet). IR (KBr) cm⁻¹: 1651 (C=O), 1542 (C=N), 1478 (C-N).

2.2.2.21 (±)-(4-Nitrophenyl)(2,3-tetramethylene-6,7,8,9-tetrahydropyrido[1,2-a]thieno[2,3-d]pyrimidine-4-one-9-yl)methanol (9)

To a 0.6 mmol of NaOH dissolved in 10.0 mL n-propanol were added 2.0 mmol of 2,3-tetramethylene-6,7,8,9-tetrahydropyrido[1,2-a]thieno[2,3-d]pyrimidine-4-one (**4c**), and 2.0 mmol of 4-nitrobenzaldehyde. Reaction mixture was boiled in oil bath at 105-110⁰C for 1 h. The precipitate was filtered, washed with cyclohexane and dried. The residue was recrystallized from benzene and the electrophilic addition product (**9**) was obtained in moderate yield.

Yield: 0.452 g (55%), mp 160-162⁰C, *R*_f=0.68 (C₆H₆/CH₃OH, 5:1, at RT). ¹H-NMR (DMSO-d₆) δ: 1.76-1.70 (6H, m, 3-CH₂-(CH₂)₂, 7-CH₂), 1.85-1.81 (1H, m, 8-Ha), 1.97-1.93 (1H, m, 8-Hb), 2.66 (2H, t, *J*=6.2 Hz, 2-CH₂), 2.80 (2H, t, *J*=6.3 Hz, 3-CH₂), 2.93-2.90 (1H, m, 9-H), 3.82 (2H, t, *J*=5.9 Hz, 6-CH₂), 5.22 (1H, d, *J*=5.1 Hz, CH(OH)), 5.82 (1H, s, OH), 7.96 (2H, d, *J*=8.8 Hz, H_{Ar}-2',6'), 8.06 (2H, d, *J*=8.8 Hz, H_{Ar}-3',5'). IR (KBr) cm⁻¹: 3324 (OH), 1667 (C=O), 1591 (C=N), 1519 (NO₂), 1480 (C-N). MS-EI in m/z (rel. %): 411 ([M]⁺, 0.5), 393 ([M-H₂O]⁺, 100), 365 ([M-NO₂]⁺, 19.7), 259 ([M-(HO)CHC₆H₄NO₂]⁺, 38). Anal. calcd. for C₂₁H₂₁N₃O₄S (411.23): C, 61.28; H, 5.10; N, 10.21. Found: C, 61.35; H, 5.02; N, 10.32.

3. RESULTS AND DISCUSSION

3.1 Chemistry

Recently we have investigated the condensation of 2,3-tri- and -tetramethylene-7,8-dihydro-6H-thieno[2,3-d]pyrrolo[1,2-a]pyrimidine-4-ones (**1a**, **b**) containing hydrogenated pyrrole ring with various aromatic and heterocyclic aldehydes with electron-donating groups under alkaline (NaOH/EtOH) and acidic (glacial AcOH) conditions and have synthesized corresponding 8-arylidene derivatives [1]. In further investigations compounds **1a**, **b** react with 4-nitrobenzaldehyde containing withdrawing (nitro) group in basic conditions (Scheme 1) and form electrophilic addition products - (±)-(4-nitrophenyl)(2,3-tri-,tetramethylene-7,8-dihydropyrrolo[1,2-a]thieno[2,3-d]pyrimidine-4-one-8-yl)methanols (**2**, **3**):

Scheme 2. Reagents and conditions: (ii) R₂-CHO, AcOH, 117°C, 0.5-6 h
 (iii) R₂-CHO, NaOH, EtOH, 78°C, 2-16 h
 (iv) R₂-CHO, NaOH, n-PrOH, 97°C, 7-8 h

Table 1. Yields and R, R₁, R₂, R₃ in compounds 2-9

No	Starting materials					Product	Yield, %
	Substrate	R	R ₁	R ₂	R ₃		
1	1a		(CH ₂) ₃	H	NO ₂	2	45
2	1b		(CH ₂) ₄	H	NO ₂	3	48
3	4a	CH ₃	CH ₃	H	H	5a	66
4	4a	CH ₃	CH ₃	H	N(CH ₃) ₂	5b	55
5	4a	CH ₃	CH ₃	CH ₃ O	CH ₃ O	5c	65
6	4a	CH ₃	CH ₃		OCH ₂ O	5d	60
7	4a	CH ₃	CH ₃		Furyl-2	5e	84
8	4b		(CH ₂) ₃	H	H	6a	65
9	4b		(CH ₂) ₃	H	N(CH ₃) ₂	6b	58
10	4b		(CH ₂) ₃	CH ₃ O	CH ₃ O	6c	63
11	4b		(CH ₂) ₃		OCH ₂ O	6d	60
12	4b		(CH ₂) ₃		Furyl-2	6e	81
13	4c		(CH ₂) ₄	H	H	7a	72
14	4c		(CH ₂) ₄	H	N(CH ₃) ₂	7b	62
15	4c		(CH ₂) ₄	CH ₃ O	CH ₃ O	7c	68
16	4c		(CH ₂) ₄		OCH ₂ O	7d	70
17	4c		(CH ₂) ₄		Furyl-2	7e	86
18	4d		(CH ₂) ₅	H	H	8a	77
19	4d		(CH ₂) ₅	H	N(CH ₃) ₂	8b	71
20	4d		(CH ₂) ₅	CH ₃ O	CH ₃ O	8c	76
21	4d		(CH ₂) ₅		OCH ₂ O	8d	65
22	4d		(CH ₂) ₅		Furyl-2	8e	90
23	4c		(CH ₂) ₄	H	NO ₂	9	55

It is necessary to emphasize that carrying out reactions with **4a-d**: aldehyde ratios of 1:2, 1:3, 1:4, increasing the duration of condensation to 8-16 hours, and increasing the ratio of **4a-d**: NaOH up to 1:0.5 results only monoarylidene derivatives **5 a-e - 8 a-e**.

The IR spectrum of compounds **5 a-e - 8 a-e** shows absorption bands between 2911-2952 cm⁻¹ for CH₃ and CH₂-groups, 1651-1678 cm⁻¹ for carbonyl (C=O) groups, 1530-1591 cm⁻¹ for C=N bonds, 1469-1494 cm⁻¹ for C-N bonds.

The chemical shift for 9-CH₂ group protons of compounds **5 a-e - 8 a-e** in ¹H NMR spectrum is absent at 2.88-3.27 ppm (2H, triplet for starting compounds **4a-d**), olefin protons =CHPh (Ar,Het) are displayed as 1H triplet at 7.83-8.08 ppm (J=1.7-2.2 Hz). The analysis of ¹H NMR spectrum shows that condensation goes only on the 9-CH₂ group. Other methylene and methyl groups of compounds **4a-d** do not participate in the reaction. The reaction through the 9-CH₂ group is unambiguously confirmed by single-crystal X-Ray diffraction in the example of 2,3-dimethyl-9-(furfurilidene-2)-6,7,8,9-tetrahydropyrido[1,2-a]thieno[2,3-d]pyrimidine-4-one **5e** (Fig. 2) [35].

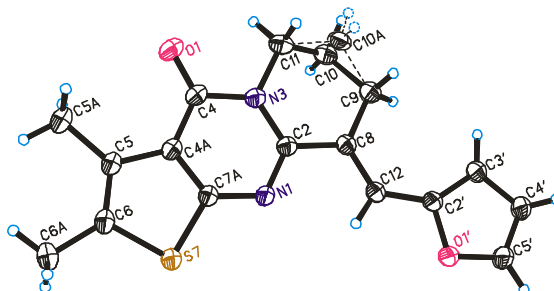
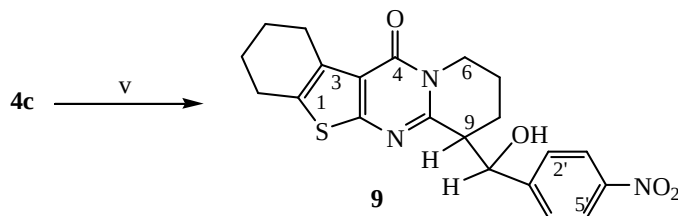


Fig. 2 The structure of 2,3-dimethyl-9-(furfurilidene-2)-6,7,8,9-tetrahydropyrido[1,2-a]thieno[2,3-d]pyrimidine-4-one (**5e**) from a single-crystal X-ray diffraction study.

Condensation of compound **4c** with 4-nitrobenzaldehyde, similar to compounds **1a,b** results in the formation of electrophilic additions product - ($\pm$)-(4-nitrophenyl)(2,3-tetramethylene-6,7,8,9-tetrahydropyrido[1,2-a]thieno[2,3-d]pyrimidine-4-one-9-yl)methanol (**9**) (Table 1, Scheme 3):



Scheme 3. Reagents and conditions: (v) 4-O₂N-C₆H₄-CHO, NaOH, n-C₃H₇OH, 97°C, 1 h

It is expected that the condensation of 2,3-dimethyl-, -tri-, -tetra-, -pentamethylene-6,7,8,9-tetrahydropyrido[1,2-a]thieno[2,3-d]pyrimidine-4-ones **4a-d** with aromatic aldehydes results in the formation of products with 9-arylidene- or 9-aryl-, -hydroxymethyl fragments, depending on the structure of aromatic aldehydes. The condensation reactions under acidic conditions, contrary to tricyclic quinazoline-4-ones [36-38], takes place with more difficulty with the formation of a mixture of products.

In the IR spectrum of compound **9** the absorption bands are observed for hydroxyl group at 3324 cm⁻¹, for methylene groups between 2855-2932 cm⁻¹, for carbonyl group at 1667 cm⁻¹, for C=N bond at 1591 cm⁻¹, for nitrogroup at 1519 cm⁻¹, and for C-N bond at 1480 cm⁻¹.

It is necessary to note that thieno[2,3-d]pyrimidine-4-ones, condensed with azepine ring - 2,3-disubstituted 4,6,7,8,9,10-hexahydroazepino[1,2-a]thieno[2,3-d]pyrimidine-4-ones do not react with aldehydes. So, attempts to carry out reactions with aromatic aldehydes in various conditions: **substrate:aldehydes:NaOH** ratios of 1:1:0.1, 1:2:0.1, 1:2:0.5, 1:4:0.1, 1:4:0.5 in ethanol (78°C), n-propanol (97°C), n-butanol (117°C) **weren't successful**.

4. CONCLUSION

The condensation of 2,3-disubstituted 7,8-dihydro-6H-thieno[2,3-d]pyrrolo[1,2-a]pyrimidine-4-ones (**1a,b**), with aldehydes in ethanol (78°C) under alkaline conditions goes exclusively through 8-CH₂ group forming ($\pm$)-(4-nitrophenyl)(2,3-tri-, -tetramethylene-7,8-dihydropyrrolo[1,2-a]thieno[2,3-d]pyrimidine-4-one-8-yl)methanols (**2, 3**). But interaction of 2,3-disubstituted 6,7,8,9-tetrahydropyrido[1,2-a]thieno[2,3-d]pyrimidine-4-ones (**4a-d**) with aldehydes compared to compounds (**1a,b**) in ethanol (78°C) under alkaline conditions goes slower, but in n-propanol (97°C) goes exclusively through 9-CH₂ groups, forming 9-arylidene(furfurilidene-2)-(**5 a-e - 8 a-e**) and ($\pm$)-(4-nitrophenyl)(2,3-tetramethylene-6,7,8,9-tetrahydropyrido[1,2-a]thieno[2,3-d]pyrimidine-4-one-9-yl)methanol (**9**). It means, that with the increase of number of methylene groups, condensation demands more severe conditions, whereas thieno[2,3-d]pyrimidine-4-ones annulated with azepine ring attempts failed even with heating in n-butanol (117°C).

Additionally, starting compounds (**1a,b, 4a-d**) were individually evaluated for their antiproliferative activities on mammalian cancer cell models. The tested compounds showed weak affection on human cervix adenocarcinoma cells (HeLa) whereas some of the tested compounds exhibited more consistent inhibition of cell growth on murine myeloma cells (P3X) [39]. New compounds (**2,3, 5a-e-8 a-e, 9**), which are synthesized in this work are derivatives of starting compounds **1a,b** and **4a-d**. Further work in this direction will take place in the future.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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