

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

Burkhon Zh. Elmuradov, Khurshed A. Bozorov, Khusnutdin M. Shakhidoyatov

*Institute of the Chemistry of Plant Substances, Academy of Sciences,
Republic of Uzbekistan. 100170, Mirzo Ulugbek str., 77, Tashkent, Uzbekistan.
Fax: (+998-71)-120-64-75; E-mail: b_elmuradov@yahoo.com*

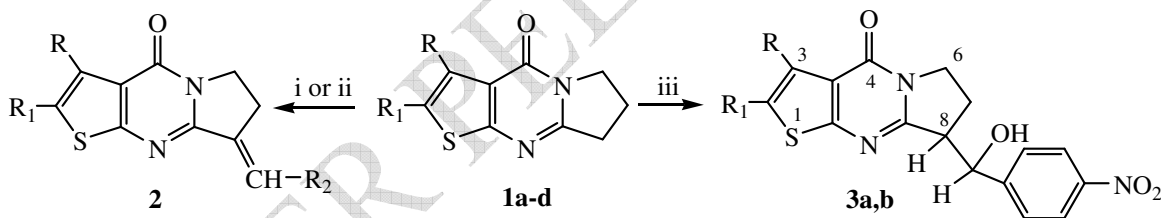
Abstract: The reaction of 2,3-dimethyl-, -tri-, -tetra-, -pentamethylene-6,7,8,9-tetrahydropyrrolo[1,2-*a*]thieno[2,3-*d*]pyrimidine-4-ones, containing active methylene groups in α -position, with aromatic aldehydes under acidic and alkaline conditions goes in depend on reaction condition and nature of aromatic aldehydes with formation of 9-(aryl-, -hydroxymethyl) - or 9-arylidene derivatives. If aldehydes with electron-acceptor (nitro) group are used, the reaction can be stopped at a stage where electrophilic additions products are formed, i.e. containing asymmetric α -carbon atom, and if aromatic aldehydes with electron-donating substituent are used α -arylidene derivatives are formed exclusively.

Key words: condensed thieno[2,3-*d*]pyrimidin-4-ones, CH-acids, electrophilic addition, aldehydes, 9-arylidene derivatives

Thiophene and pyrimidine derivatives have been shown to possess a variety of pharmacological activities like antibacterial,² anti-microbial,³ antitumor,⁴ anti-inflammatory,^{2a,5} analgesics,^{2a,5b,c} ulcerogenic,^{2a,5b} cytotoxic,⁶ and chemotherapeutic⁷ activities.

Condensed thieno[2,3-*d*]pyrimidin-4-ones are of interest from the theoretical and practical points of view. However, the interaction of thienopyrimidinones, condensed with hydrogenated piperidine ring with electrophilic reagents is not investigated.

Recently,¹ we have investigated the condensation of 2,3-dimethyl-, -tri-, -tetra-, -pentamethylene-7,8-dihydro-6H-thieno[2,3-*d*]pyrrolo[1,2-*a*]pyrimidine-4-ones containing hydrogenated pyrrole ring (**1a-d**) with various aromatic and heterocyclic aldehydes under alkaline and acidic conditions, and have synthesized corresponding 8-arylidene derivatives **2**:



Scheme 1. Reagents and conditions: (i) $R_2\text{-CHO}$, AcOH, 117°C, 0.5-6 h
(ii) $R_2\text{-CHO}$, NaOH, EtOH, 78°C, 7-8 h
(iii) 4-O₂N-C₆H₄-CHO, NaOH, EtOH, 78°C, 1-3 h

The boiling of equimolar quantities of reagents in glacial acetic acid for 0.5-3 h results in formation of 8-arylidene derivatives in low yield (20-30%). The increase of reaction duration to 6 hours results in decrease in the yield of condensation products.

The reaction of **1a-d** with benzaldehyde and substituted benzaldehydes with electron-donating groups under alkaline conditions and at lower temperatures results in good yields (61-94%) for compound **2**.¹

Compounds **1a-d** react with 4-nitrobenzaldehyde in basic conditions (Scheme 1, iii), and form 2,3-tri-, -tetramethylene-8-(4-nitrophenyl-, hydroxymethyl)-7,8-dihydropyrrolo[1,2-*a*]thieno[2,3-*d*]pyrimidine-4-ones, intermediate products of electrophilic additions (**3a, b**).

In ¹H NMR (400 MHz, DMSO-*d*₆) spectrum of compound **3a** two protons of β -CH₂ group give separate one-proton (1H) multiplets at 1.77-1.86 ppm (β -CH₂-a) and 2.06-2.14 ppm (β -CH₂-b). Protons of γ -CH₂ give separate multiplets at 3.78-3.85 ppm (γ -CH₂-a) and 3.93-4.0 ppm (γ -CH₂-b). The α -CH- proton gives 1H triplet of doublets at 3.63 ppm, the other hydrogen in (HO)-C-(H) gives 1H doublet of doublets at 5.4 ppm, the proton of a hydroxyl group gives 1H doublet at 5.91 ppm. These results unequivocally prove the structure of **3a**. A single-crystal X-ray diffraction was used to determine the crystal structure of compound **3b** (Figure. 1).

*Part 1. See literature¹

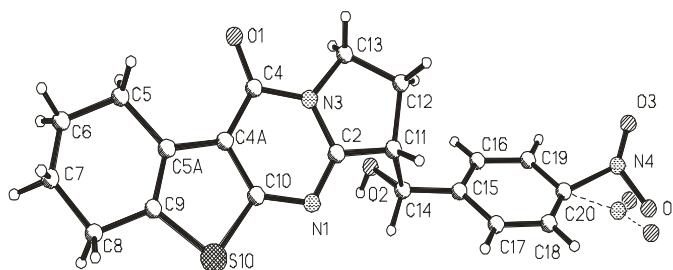
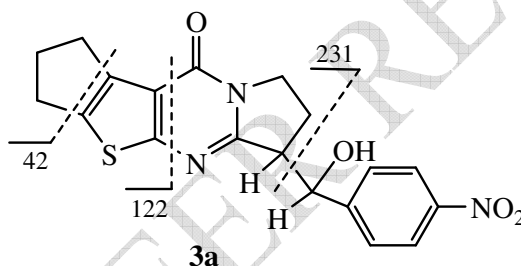


Figure 1. Single crystal structure of 2,3-tetramethylene-8-(4-nitrophenyl-, hydroxymethyl)-7,8-dihydropyrrolo[1,2-*a*]thieno[2,3-*d*]pyrimidine-4-one (**3b**).

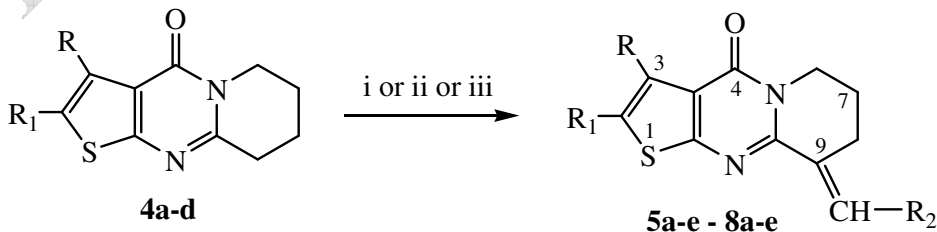
The formation of products **3a, b** can be explained by the presence of electrophilic nitro- group which strongly reduces the electronic density in the aromatic ring, and as a result of this no water withdrawal occurs from compounds **3a, b**.

The mass spectrum of 2,3-trimethylene-8-(4-nitrophenyl-, hydroxymethyl)-7,8-dihydropyrrolo[1,2-*a*]thieno[2,3-*d*]pyrimidine-4-one (**3a**) shows an ion *m/z* 365 which results from the lost of single water molecule from **3a**, cleavage of C $_{\alpha}$ -CH(OH) single bond results in an ion *m/z* 231. There are also fragments of thieno[2,3-*d*]pyrimidine-4-one (*m/z* 150) and thiophene ring (*m/z* 80). It shows, that the fragmentation of tricyclic thieno[2,3-*d*]pyrimidine-4-ones occurs on various directions:



It is expected that the condensation of 2,3-dimethyl-, -tri-, -tetra-, -pentamethylene-6,7,8,9-tetrahydropyrrolo[1,2-*a*]thieno[2,3-*d*]pyrimidine-4-ones **4a-d** with aromatic aldehydes results in the formation of products with arylidene or aryl, hydroxymethyl fragments, depending on the structure of aromatic aldehydes. The condensation reactions under acidic conditions, contrary to tricyclic quinazoline-4-ones⁸, takes place with more difficulty with the formation of a mixture of products.

The reaction of 2,3-dimethyl-, -tri-, -tetra-, -pentamethylene-6,7,8,9-tetrahydropyrrolo[1,2-*a*]thieno[2,3-*d*]pyrimidine-4-ones, **4a-d**, with aldehydes using the method described in¹ has shown that condensation goes more slowly compared to reactions with **1a-d** and the corresponding arylidene derivatives are formed in relatively low yields. Using *n*-propanol (Scheme 2, iii) instead of ethanol and boiling compounds **4a-d** with benzaldehyde, 4-dimethylamino-, 3,4-dimethoxy- and 3,4-methylenedioxybenzaldehydes and furfural in the presence of sodium hydroxide for 7-8 h at 97°C results in corresponding 9-arylidene derivatives (**5a-e - 8a-e**) (Table 1, Scheme 2)



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

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

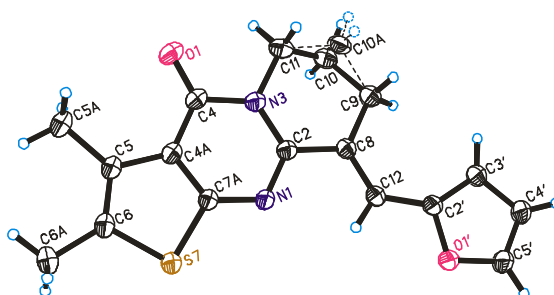
Entry	Starting materials				Product	Yield, %
	Substrate	R	R ₁	R ₂		
1	1b		(CH ₂) ₃	C ₆ H ₄ -NO ₂ -4	3a	45
2	1c		(CH ₂) ₄	C ₆ H ₄ -NO ₂ -4	3b	48
3	4a	CH ₃	CH ₃	C ₆ H ₅	5a	66
4	4a	CH ₃	CH ₃	C ₆ H ₄ -N(CH ₃) ₂ -4	5b	55
5	4a	CH ₃	CH ₃	C ₆ H ₃ -(CH ₃ O) ₂ -3,4	5c	65
6	4a	CH ₃	CH ₃	C ₆ H ₃ -(OCH ₂ O)-3,4	5d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

It is necessary to emphasize that carrying out the 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 monoarylidene derivatives only **5 a-e - 8 a-e** in 55-90 % yields.

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

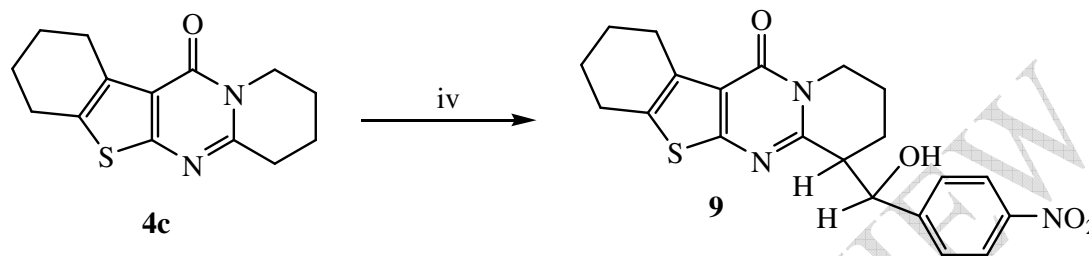
The chemical shift of an α-CH₂ group protons of initial compound **4a** is absent in ¹H NMR spectrum, a four-proton multiplet (β-, γ-CH₂) at 1.83-1.92 ppm turns to a two-proton multiplet (γ-CH₂) with chemical shift 1.91-1.96 ppm. Protons of β-CH₂ group give a doublet of triplets, δ-CH₂-groups give a triplet at 3.95-4.07 ppm. Olefin protons =CHPh, (=CHAr, =CHHet) are displayed as a not split one-proton triplet (^mJ=1.7-2.2 Hz). For compounds **7a, 7b** these protons are observed as a one-proton singlet. The analysis of ¹H NMR spectrum shows, that condensation goes only on the α-methylene group. Other methylene and methyl groups at positions 2 and 3 of compound **4a** do not participate in the reaction.

The reaction through the α-methylene 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** (Figure. 2).⁹



It is necessary to note that 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 condensation reactions 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 in various conditions: at **4a-d: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 (78⁰C), n-propanol (97⁰C), n-butanol (117⁰C) haven't been successful.

Condensation reaction of compound **4c** with 4-nitrobenzaldehyde, similar to compounds **1b**, **c**, results in the formation of 2,3-tetramethylene-9-(4-nitrophenyl-, hydroxymethyl)-6,7,8,9-tetrahydropyrido[1,2-*a*]thieno[2,3-*d*]pyrimidine-4-one (**9**), and we managed to capture an intermediate product of electrophilic additions in 55 % yield (Table. 1, Scheme 3):



Scheme 3. Reagents and conditions: (iv) 4-O₂N-C₆H₄-CHO, NaOH, n-C₃H₇OH, 97⁰C, 1 h

The IR spectrum of compound **9** shows absorption bands for a hydroxyl group (ν_{OH}) at 3324 cm⁻¹, ν_{CH_2} groups between 2855-2932 cm⁻¹, carbonyl groups $\nu_{C=O}$ at 1667 cm⁻¹, $\nu_{C=N}$ at 1591 cm⁻¹, nitrogroup (ν_{NO_2}) at 1519 cm⁻¹, and ν_{C-N} at 1480 cm⁻¹.

Thus, the condensation reaction of 2,3-disubstituted 6,7,8,9-tetrahydropyrido[1,2-*a*]thieno[2,3-*d*]pyrimidine-4-ones with aldehydes under alkaline and acidic conditions goes exclusively through α -CH₂ groups, forming α -arylidene(furfurilidene-2)-(**5 a-e** - **8 a-e**) or α -(aryl-, -hydroxymethyl) derivatives (**3a,b**; **9**).

Mass spectra were acquired on a high-res DFS spectrometer, ¹H (400 MHz) spectra were recorded on Unityplus 400 in CDCl₃ and DMSO-*d*₆ at room temperature. Chemical shifts of ¹H were measured relative to HMDS as internal standard. Solvents were purified by standard procedures. Mps were measured on a Boetius and MEL-TEMP, and are not uncorrected. Reactions were monitored by TLC on Sorbfil and Whatman UV-254 precoated aluminum plates (eluent: benzene-methanol, 3:1 and 5:1), which were visualized under UV radiation.

2,3-Dimethyl- (1a), -tri- (1b), -tetra- (1c) and 2,3-pentamethylene-7,8-dihydropyrrolo[1,2-*a*]thieno[2,3-*d*]pyrimidine-4-one (1d); 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-one (4d) were synthesized using a method as described in ¹.

2,3-Trimethylene-8-(4-nitrophenyl-, hydroxymethyl)-7,8-dihydropyrrolo[1,2-*a*]thieno[2,3-*d*]pyrimidine-4-one (3a)

In 10 mL ethanol was dissolved 0.024 g (0.6 mmol) of NaOH, after dissolution of alkali were added 0.464 g (2 mmol) of **1b** and 0.3 g (2 mmol) of 4-nitrobenzaldehyde and boiled in water bath for 0.5-4 h. The solvent was distilled off, and the residue was recrystallized from benzene to obtain compound **3a**.

Brown powder; yield: 0.34 g (45%); Mp 221-223⁰C (benzene), R_f=0.79 (benzene-methanol, 5:1).

IR (KBr): 3378, 650, 1540, 1519, 1475 cm⁻¹

¹H NMR (400MHz, DMSO-*d*₆): δ = 1.77-1.86 (1H, m, 7-Ha), 2.06-2.14 (1H, m, 7-Hb), 2.30-2.37 (2H, m, 2-CH₂-CH₂), 2.87 (4H, t, *J*=7.0, 2-CH₂, 3-CH₂), 3.63 (1H, td, *J*=7.0, *J*=2.6, 8-H), 3.78-3.85 (1H, m, 6-Ha), 3.93-4.0 (1H, m, 6-Ha), 5.4 (1H, dd, *J*=4.8, *J*=2.6, CH(OH)), 5.91 (1H, d, *J*=4.8, OH), 7.68 (2H, d, *J*=8.4, H_{Ar}-2,6), 8.18 (2H, d, *J*=8.8, H_{Ar}-3,5)

MS (EI): m/z (%)= 384 ([M+1]⁺, 2.1), 383 ([M]⁺, 11.2), 365 ([M-H₂O]⁺, 3.5), 336 (4.1), 335 (11.9), 233 (29.3), 232 (88.9), 231 ([M-CH(OH)-C₆H₄-NO₂]⁺, 100), 230 ([M-CH₂(OH)-C₆H₄-NO₂]⁺, 20), 204 (4.2), 150 (14), 122 (5), 121 (6), 92 (13.2), 80 (4.8), 43 (52), 42 (7.5)

2,3-Tetramethylene-8-(4-nitrophenyl-, hydroxymethyl)-7,8-dihydropyrrolo[1,2-*a*]thieno[2,3-*d*]pyrimidine-4-one (3b)

Compound **3b** was prepared by the same method as that described above for **3a**.

Brown powder; yield: 0.38 g (48%); Mp 210-212⁰C (benzene), *R*_f=0.52 (benzene-methanol, 5:1).

IR (KBr): 3320, 1671, 1557, 1517, 1481 cm⁻¹

¹H NMR (400MHz, DMSO): δ= 1.70-1.77 (4H, m, 3-CH₂-(CH)₂), 1.78-1.85 (1H, m, 7-Ha), 2.05-2.11 (1H, m, 7-Hb), 2.69 (2H, t, *J*=5.9, 2-H), 2.83 (2H, t, *J*=6.1, 3-H), 3.62 (1H, td, *J*=6.9, *J*=2.3, 8-H), 3.77-3.83 (1H, m, 6-Ha), 3.91-3.98 (1H, m, 6-Hb), 5.37 (1H, dd, *J*=4.6, *J*=2.3, CH(OH)), 5.90 (1H, d, *J*=4.6, OH), 7.68 (2H, d, *J*=8.6, H_{Ar}-2,6), 8.18 (2H, d, *J*=8.9, H_{Ar}-3,5)

MS (EI): m/z (%)= 397 ([M]⁺, 42), 380 (3.1), 247 (62.2), 246 ([M-C(OH)-C₆H₄-NO₂]⁺, 82.5), 245 ([M-CH(OH)-C₆H₄-NO₂]⁺, 100), 232 (4.9), 218 (40), 205 (4.9), 151 (35), 92 (6.3), 82 (7.7)

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

In 10 mL n-propanol was dissolved 0.024 g (0.6 mmol) NaOH. After the complete dissolution were added 0.492 g (2 mmol) compounds of **4a** and 0.212 g (0.2 mL) (2 mmol) (d =1.0498 g/mL) of benzaldehyde and boiled for 7-8 h. The dropped out precipitate have filtered, washed out with cyclohexane and dried. After recrystallization from benzene was obtained the substance **5a**.

White powder; yield: 0.425 g (66%); Mp 180-182⁰C (benzene), *R*_f=0.88 (benzene-methanol, 5:1).

IR (KBr): 1671, 1551, 1490 cm⁻¹

¹H NMR (400MHz, CDCl₃): δ= 1.92-1.94 (2H, m, 7-H), 2.30 (3H, s, 2-CH₃), 2.43 (3H, s, 3-CH₃), 2.89 (2H, t, *J*=6.7, 8-H), 3.95 (2H, t, *J*=6.0, 6-H), 7.20-7.40 (5H, m, H_{Ph}-2,3,4,5,6), 8.08 (1H, s, CHPh)

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

Compound **5b** was prepared by the same method as that described above for **5a**.

Orange powder; yield: 0.4 g (55%); Mp 201-203⁰C (benzene), *R*_f=0.87 (benzene-methanol, 5:1).

IR (KBr): 1652, 1591, 1497 cm⁻¹

¹H NMR (400MHz, CDCl₃): δ= 1.91-1.96 (2H, m, 7-H), 2.32 (3H, s, 2-CH₃), 2.42 (3H, s, 3-CH₃), 2.88 (2H, t, *J*=5.0, 8-H), 2.96 (6H, s, N(CH₃)₂), 4.04 (2H, t, *J*=5.7, 6-H), 6.65 (2H, d, *J*=8.8, H_{Ar}-3',5'), 7.36 (2H, d, *J*=8.8, H_{Ar}-2',6'), 7.97 (1H, s, CHAr)

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

Compound **5c** was prepared by the same method as that described above for **5a**.

Yellow powder; yield: 0.5 g (65%); Mp 205-207⁰C (methanol), *R*_f=0.83 (benzene-methanol, 5:1).

IR (KBr): 1672, 1573, 1490 cm⁻¹

¹H NMR (400MHz, CDCl₃): δ= 1.92-1.97 (2H, m, 7-H), 2.33 (3H, s, 2-CH₃), 2.43 (3H, s, 3-CH₃), 2.88 (2H, td, *J*=6.5, *J*=2.0, 8-H), 3.85 (3H, s, 3'-OCH₃), 3.87 (3H, s, 4'-OCH₃), 4.06 (2H, t, *J*=5.8, 6-H), 6.84 (1H, d, *J*=8.4, H_{Ar}-5'), 6.93 (1H, d, *J*=2.0, H_{Ar}-2'), 7.02 (1H, dd, *J*=8.5, *J*=2.0, H_{Ar}-6'), 8.00 (1H, t, *J*=2.0, CHAr)

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

Compound **5d** was prepared by the same method as that described above for **5a**.

Yellow powder; yield: 0.44 g (60%); Mp 167-169⁰C (methanol), *R*_f=0.90 (benzene-methanol, 5:1).

IR (KBr): 1668, 1558, 1490 cm⁻¹

¹H NMR (400MHz, CDCl₃): δ= 1.92-1.96 (2H, m, 7-H), 2.33 (3H, s, 2-CH₃), 2.43 (3H, s, 3-CH₃), 2.84 (2H, td, *J*=6.7, *J*=2.2, 8-H), 4.05 (2H, t, *J*=6.0, 6-H), 5.95 (2H, s, O-CH₂), 6.79 (1H, d, *J*=6.7, H_{Ar}-5'), 6.92 (2H, dd, *J*=6.7, *J*=1.8, H_{Ar}-2',6'), 7.95 (1H, t, *J*=2.2, CHAr)

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

Compound **5e** was prepared by the same method as that described above for **5a**.

Yellow powder; yield: 0.52 g (84%); Mp 176-178⁰C (benzene), *R*_f=0.82 (benzene-methanol, 3:1).

IR (KBr): 1669, 1557, 1488 cm⁻¹

¹H NMR (400MHz, CDCl₃): δ= 1.94-1.99 (2H, m, 7-H), 2.32 (3H, s, 2-CH₃), 2.42 (3H, s, 3-CH₃), 2.97 (2H, td, *J*=6.7, *J*=2.2, 8-H), 4.07 (2H, t, *J*=6.0, 6-H), 6.45 (1H, tt, *J*=3.5, *J*=2.0, H_{Het}-4'), 6.56 (1H, d, *J*=3.5, H_{Het}-3'), 7.48 (1H, d, *J*=2.0, H_{Het}-5'), 7.83 (1H, t, *J*=2.2, CHHet)

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

Compound **6a** was prepared by the same method as that described above for **5a**.

White powder; yield: 0.43 g (65%); Mp 196-198⁰C (methanol), *R*_f=0.80 (benzene-methanol, 3:1).

IR (KBr): 1678, 1591, 1492 cm⁻¹

¹H NMR (400MHz, CDCl₃): δ= 1.92-1.97 (2H, m, 3-CH₂-CH₂), 2.38-2.43 (2H, m, 7-H), 2.87 (2H, t, *J*=6.7, 2-CH₂), 2.90 (2H, t, *J*=7.3, 3-CH₂), 3.03 (2H, td, *J*=7.0, *J*=2.0, 8-H), 4.08 (2H, t, *J*=6.0, 6-H), 7.27-7.40 (5H, m, H_{Ph}-2',3',4',5',6'), 8.08 (1H, t, *J*=2.0, CHPh)

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

Compound **6b** was prepared by the same method as that described above for **5a**.

Brown powder; yield: 0.44 g (58%); Mp 216-218⁰C (benzene), *R*_f=0.85 (benzene-methanol, 5:1).

IR (KBr): 1658, 1591, 1469 cm⁻¹

¹H NMR (400MHz, CDCl₃): δ= 1.91-1.96 (2H, m, 3-CH₂-CH₂), 2.36-2.42 (2H, m, 7-H), 2.87 (2H, t, *J*=7.3, 2-CH₂), 2.90 (2H, t, *J*=6.3, 3-CH₂), 2.96 (6H, s, N(CH₃)₂), 3.01 (2H, td, *J*=7.3, *J*=2.0, 8-H), 4.07 (2H, t, *J*=6.0, 6-H), 6.66 (2H, d, *J*=9.0, H_{Ar}-3',5'), 7.37 (2H, d, *J*=9.0, H_{Ar}-2',6'), 7.98 (1H, t, *J*=2.0, CHAr)

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

Compound **6c** was prepared by the same method as that described above for **5a**.

Yellow powder; yield: 0.5 g (63%); Mp 204-206⁰C (methanol), *R*_f=0.82 (benzene-methanol, 5:1).

IR (KBr): 1666, 1576, 1469 cm⁻¹

¹H NMR (400MHz, CDCl₃): δ= 1.93-1.98 (2H, m, 3-CH₂-CH₂), 2.38-2.43 (2H, m, 7-H), 2.88 (2H, t, J=6.7, 2-CH₂), 2.91 (2H, t, J=6.0, 3-CH₂), 3.02 (2H, td, J=7.3, J=2.0, 8-H), 3.85, 3.87 (3H, s; 3H, s, OCH₃), 4.08 (2H, t, J=6.0, 6-H), 6.85 (1H, d, J=8.3, H_{Ar}-5'), 6.94 (1H, d, J=2.0, H_{Ar}-2'), 7.03 (1H, dd, J=8.3, J=2.0, H_{Ar}-6'), 8.02 (1H, t, J=2.0, CHAr)

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

Compound **6d** was prepared by the same method as that described above for **5a**.

Brown powder; yield: 0.45 g (60%); Mp 203-205⁰C (methanol), R_f=0.81 (benzene-methanol, 5:1).

IR (KBr): 1669, 1558, 1487 cm⁻¹

¹H NMR (400MHz, CDCl₃): δ= 1.92-1.97 (2H, m, 3-CH₂-CH₂), 2.37-2.43 (2H, m, 7-H), 2.85 (2H, t, J=7.0, 2-CH₂), 2.90 (2H, t, J=5.6, 3-CH₂), 3.02 (2H, td, J=7.0, J=1.7, 8-H), 4.07 (2H, t, J=5.7, 6-H), 5.95 (2H, s, O-CH₂), 6.80 (2H, dd, J=7.0, J=1.7, H_{Ar}-2',6'), 6.92 (1H, d, J=7.0, H_{Ar}-5'), 7.97 (1H, t, J=1.7, CHAr)

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

Compound **6e** was prepared by the same method as that described above for **5a**.

Brown powder; yield: 0.52 g (81%); Mp 190-191⁰C (benzene), R_f=0.88 (benzene-methanol, 5:1).

IR (KBr): 1663, 1542, 1470 cm⁻¹

¹H NMR (400MHz, CDCl₃): δ= 1.95-2.00 (2H, m, 3-CH₂-CH₂), 2.38-2.43 (2H, m, 7-H), 2.86 (2H, t, J=6.9, 2-CH₂), 2.96 (2H, t, J=6.7, 3-CH₂), 3.01 (2H, td, J=7.1, J=2.2, 8-H), 4.09 (2H, t, J=5.9, 6-H), 6.46 (1H, dd, J=3.5, J=1.7, H_{Het}-4'), 6.57 (1H, d, J=3.5, H_{Het}-3'), 7.45 (1H, d, J=1.7, H_{Het}-5') 7.84 (1H, t, J=2.2, CHHet)

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

Compound **7a** was prepared by the same method as that described above for **5a**.

White powder; yield: 0.5 g (72%); Mp 189-190⁰C (methanol), R_f=0.90 (benzene-methanol, 5:1).

IR (KBr): 1662, 1556, 1492 cm⁻¹

¹H NMR (400MHz, CDCl₃): δ= 1.78-1.83 (4H, m, 3-CH₂-(CH₂)₂), 1.91-1.96 (2H, m, 7-H), 2.72 (2H, t, J=6.0, 2-CH₂), 2.87 (2H, td, J=6.6, J=2.0, 8-H), 2.97 (2H, t, J=6.0, 3-CH₂), 4.05 (2H, t, J=5.9, 6-H), 7.27-7.40 (5H, m, H_{Ph}-2',3',4',5',6'), 8.06 (1H, t, J=2.0, CHPh)

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

Compound **7b** was prepared by the same method as that described above for **5a**.

Orange powder; yield: 0.48 g (62%); Mp 198-200⁰C (benzene), R_f=0.86 (benzene-methanol, 5:1).

IR (KBr): 1662, 1557, 1487 cm⁻¹

¹H NMR (400MHz, CDCl₃): δ= 1.79-1.84 (4H, m, 3-CH₂-(CH₂)₂), 1.90-1.95 (2H, m, 7-H), 2.70 (2H, t, J=5.9, 2-CH₂), 2.88 (2H, td, J=6.6, J=2.0, 8-H), 2.96 (6H, s, N(CH₃)₂), 2.97 (2H, t, J=6.0, 3-CH₂), 4.04 (2H, t, J=5.8, 6-H), 6.65 (2H, d, J=9.0, H_{Ar}-3',5'), 7.37 (2H, d, J=9.0, H_{Ar}-2',6'), 7.97 (1H, t, J=2.0, CHAr)

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

Compound **7c** was prepared by the same method as that described above for **5a**.

Yellow powder; yield: 0.55 g (68%); Mp 194-196⁰C (methanol), *R*_f=0.84 (benzene-methanol, 5:1).

IR (KBr): 1663, 1557, 1488 cm⁻¹

¹H NMR (400MHz, CDCl₃): δ=1.77-1.84 (4H, m, 3-CH₂-(CH₂)₂), 1.93-1.95 (2H, m, 7-H), 2.72 (2H, t, *J*=5.9, 2-CH₂), 2.88 (2H, td, *J*=6.4, *J*=2.0, 8-H), 2.96 (2H, t, *J*=5.9, 3-CH₂), 3.85, 3.87 (3H, s; 3H, s, OCH₃), 4.05 (2H, t, *J*=5.8, 6-H), 6.85 (1H, d, *J*=8.5, H_{Ar}-5'), 6.94 (1H, d, *J*=2.0, H_{Ar}-2'), 7.03 (1H, dd, *J*=8.5, *J*=2.0, H_{Ar}-6'), 8.01 (1H, t, *J*=2.0, CHAr)

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

Compound **7d** was prepared by the same method as that described above for **5a**.

Yellow powder; yield: 0.55 g (70%); Mp 190-192⁰C (methanol), *R*_f=0.87 (benzene-methanol, 5:1).

IR (KBr): 1666, 1541, 1488 cm⁻¹

¹H NMR (400MHz, CDCl₃): δ= 1.78-1.83 (4H, m, 3-CH₂-(CH₂)₂), 1.91-1.95 (2H, m, 7-H), 2.72 (2H, t, *J*=6.0, 2-CH₂), 2.84 (2H, td, *J*=6.4, *J*=2.0, 8-H), 2.96 (2H, t, *J*=6.0, 3-CH₂), 4.04 (2H, t, *J*=5.7, 6-H), 5.95 (2H, s, O-CH₂), 6.8 (1H, d, *J*=8.6, H_{Ar}-5'), 6.92 (2H, dd, *J*=8.6, *J*=1.7, H_{Ar}-2', 6'), 7.96 (1H, t, *J*=2.0, CHAr)

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

Compound **7e** was prepared by the same method as that described above for **5a**.

Yellow powder; yield: 0.58 g (86%); Mp 210-212⁰C (benzene), *R*_f=0.87 (benzene-methanol, 5:1).

IR (KBr): 1651, 1557, 1472 cm⁻¹

¹H NMR (400MHz, CDCl₃): δ= 1.77-1.83 (4H, m, 3-CH₂-(CH₂)₂), 1.94-1.99 (2H, m, 7-H), 2.71 (2H, t, *J*=6.0, 2-CH₂), 2.90 (2H, td, *J*=5.9, *J*=2.0, 8-H), 2.97 (2H, t, *J*=6.3, 3-CH₂), 4.07 (2H, t, *J*=5.8, 6-CH₂), 6.45 (1H, dd, *J*=3.5, *J*=1.8, H_{Het}-4'), 6.56 (1H, d, *J*=3.5, H_{Het}-3'), 7.48 (1H, d, *J*=1.8, H_{Het}-5') 7.83 (1H, t, *J*=2.0, CHHet)

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

Compound **8a** was prepared by the same method as that described above for **5a**.

Yellow powder; yield: 0.556 g (77%); Mp 188-190⁰C (methanol), *R*_f=0.83 (benzene-methanol, 5:1).

IR (KBr): 1667, 1546, 1484 cm⁻¹

¹H NMR (400MHz, CDCl₃): δ= 1.60-1.68 (4H, m, 2-CH₂-(CH₂)₂), 1.82-1.86 (2H, m, γ-CH₂), 1.91-1.95 (2H, m, 3-CH₂-CH₂), 2.79 (2H, t, *J*=5.4, 2-CH₂), 2.86 (2H, td, *J*=6.6, *J*=1.9, 8-H), 3.30 (2H, t, *J*=5.7, 3-CH₂), 4.05 (2H, t, *J*=5.9, 6-H), 7.26-7.40 (5H, m, H_{Ph}-2', 3', 4', 5', 6'), 8.04 (1H, t, *J*=1.9, CHPh)

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

Compound **8b** was prepared by the same method as that described above for **5a**.

Yellow powder; yield: 0.575 g (71%); Mp 186-188⁰C (benzene), *R*_f=0.87 (benzene-methanol, 5:1).

IR (KBr): 1674, 1548, 1479 cm⁻¹

¹H NMR (400MHz, CDCl₃): δ =1.59-1.67 (4H, m, 2-CH₂-(CH₂)₂), 1.81-1.84 (2H, m, 7-H), 1.90-1.95 (2H, m, 3-CH₂-CH₂), 2.77 (2H, t, *J*=5.4, 2-CH₂), 2.88 (2H, td, *J*=5.4, *J*=2.0, 8-H), 2.96 (6H, s, N(CH₃)₂), 3.29 (2H, t, *J*=5.7, 3-CH₂), 4.04 (2H, t, *J*=5.7, 6-H), 6.65 (2H, d, *J*=8.9, H_{Ar}-3',5'), 7.36 (2H, d, *J*=8.9, H_{Ar}-2',6'), 7.94 (1H, t, *J*=2.0, CHAr)

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

Compound **8c** was prepared by the same method as that described above for **5a**.

Yellow powder; yield: 0.641 g (76%); Mp 167-168⁰C (methanol), *R*_f=0.85 (benzene-methanol, 5:1).

IR (KBr): 1660, 1545, 1485 cm⁻¹

¹H NMR (400MHz, CDCl₃): δ = 1.61-1.68 (4H, m, 2-CH₂-(CH₂)₂), 1.83-1.85 (2H, m, 7-H), 1.93-1.95 (2H, m, 3-CH₂-CH₂), 2.78 (2H, t, *J*=5.7, 2-CH₂), 2.87 (2H, td, *J*=6.4, *J*=2.0, 8-H), 3.30 (2H, t, *J*=5.7, 3-CH₂), 3.85, 3.86 (3H, s; 3H, s, OCH₃), 4.06 (2H, t, *J*=5.9, 6-H), 6.85 (1H, d, *J*=8.4, H_{Ar}-5'), 6.94 (1H, d, *J*=2.0, H_{Ar}-2'), 7.02 (1H, dd, *J*=8.4, *J*=2.0, H_{Ar}-6'), 7.98 (1H, t, *J*=2.0, CHAr)

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

Compound **8d** was prepared by the same method as that described above for **5a**.

Yellow powder; yield: 0.53 g (65%); Mp 178-180⁰C (methanol), *R*_f=0.84 (benzene-methanol, 5:1).

IR (KBr): 1663, 1548, 1491 cm⁻¹

¹H NMR (400MHz, CDCl₃): δ = 1.61-1.66 (4H, m, 2-CH₂-(CH₂)₂), 1.82-1.84 (2H, m, 7-H), 1.91-1.94 (2H, m, 3-CH₂-CH₂), 2.78 (2H, t, *J*=5.4, 2-CH₂), 2.83 (2H, td, *J*=6.9, *J*=2.0, 8-H), 3.29 (2H, t, *J*=5.7, 3-CH₂), 4.04 (2H, t, *J*=5.7, 6-H), 5.95 (2H, s, O-CH₂), 6.79 (1H, d, *J*=8.5, H_{Ar}-5'), 6.90 (2H, dd, *J*=8.5, *J*=1.9, H_{Ar}-2',6'), 7.93 (1H, t, *J*=2.0, CHAr)

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

Compound **8e** was prepared by the same method as that described above for **5a**.

Yellow powder; yield: 0.633 g (90%); Mp 170-171⁰C (benzene), *R*_f=0.88 (benzene-methanol, 5:1).

IR (KBr): 1651, 1542, 1478 cm⁻¹

¹H NMR (400MHz, CDCl₃): δ = 1.61-1.67 (4H, m, 2-CH₂-(CH₂)₂), 1.81-1.84 (2H, m, 7-H), 1.95-1.97 (2H, m, 3-CH₂-CH₂), 2.78 (2H, t, *J*=5.7, 2-CH₂), 2.96 (2H, td, *J*=6.7, *J*=2.2, 8-H), 3.29 (2H, t, *J*=5.4, 3-CH₂), 4.07 (2H, t, *J*=5.7, 6-H), 6.45 (1H, dd, *J*=3.5, *J*=1.7, H_{Het}-4'), 6.56 (1H, d, *J*=3.5, H_{Het}-3'), 7.48 (1H, d, *J*=1.7, H_{Het}-5'), 7.82 (1H, t, *J*=2.2, CHHet)

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

Compound **9** was prepared by the same method as that described above for **5a**.

Violet powder; yield: 0.452 g (55%); Mp 160-162⁰C (benzene), *R*_f=0.68 (benzene-methanol, 5:1).

IR (KBr): 3324, 1667, 1591, 1519, 1480 cm⁻¹

MS (EI): m/z (%)= 411 ($[M]^+$, 0.5), 393 ($[M-H_2O]^+$, 100), 365 ($[M-NO_2]^+$, 19.7), 260 ($[M-(HO)CC_6H_4NO_2]^+$, 98.4), 259 ($[M-(HO)CHC_6H_4NO_2]^+$, 38), 232 (69), 150 (15.5), 120 (23).

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References

- (1) Elmuradov, B.Zh.; Bozorov, Kh.A.; Shakhidoyatov, Kh.M. *Chem. Heterocycl. Compd.* **2011**, *46*, 1393.
- (2) (a) Alagarsamy, V.; Meena, S.; Ramseshu, K.V.; Solomon, V.R.; Thirumurugan, K.; Dhanabal, K.; Murugan, M. *Eur. J. Med. Chem.* **2006**, *41*, 1293. (b) Salahuddin, S.K.; Shantakumar, S.M. *Eur. J. Chem.* **2009**, *6*, 801. (c) Al-Taisan, Kh.M.; Al-Hazimi H.M.A.; Al-Shihry, Sh.S. *Molecules* **2010**, *15*, 3932.
- (3) (a) Shetty, N.S.; Ravi, S.; Ahmed, L.I.; Khazi, M. *J. Chem Sci.* **2009**, *121*, 301. (b) Chambharea, R.V.; Khadseb, B.G.; Bobdeb, A.S.; Bahekar R.H. *Eur. J. Med. Chem.* **2003**, *38*, 89. (c) Rashad, A.E.; Shamroukh, A.H.; Abdel-Megeid R.E.; El-Sayed W.A. *Syn. Com.* **2010**, *40*, 1149.
- (4) Magd-El-Din A.A.; Atta, S.M. Sh.; Abd-El-All, A.S.; Galal, Sh.A.; Abdalah M.M. *World J.Chem.* **2009**, *4*, 112.
- (5) (a) Ouf, N.H.; Abd El-Galil, E.A. *Monatsh. Chem.* **2008**, *139*, 579. (b) El-Gazzar, A.-R. B. A.; Hussein, H.A. A.R.; Hafez H.N. *Acta Pharm.* **2007**, *57*, 395. (c) Alagarsamy, V.; Shankar, D.; Solomon, V.R. *Arkivoc*, **2006**, 149.
- (6) (a) Jennings, L.D.; Kincaid, S.L.; Wang Y.D.; Krishnamurthy, G.; Beyer, C.F.; McGinnis, J.P.; Miranda, M.; Discafani, C.M.; Rabindran, S.K. *Bioorg. & Med. Chem. Let.*, **2005**, *15*, 4731. (b) Gorja, D.R.; Kumar, K.Sh.; Mukkanti, K.; Beilstein, M.P. *J. Org. Chem.*, **2011**, *7*, 338. (c) Lilienkampf, A. *Academ. Dissert.* **2007**, 52.
- (7) Gaber H.M.; Bagley, M.Ch. *Eur. J. Chem.* **2011**, *2*, 214.
- (8) (a) Abdurazakov A.Sh.; Elmuradov B.Zh.; Turdibayev, Zh.E.; Shakhidoyatov, Kh.M. *Chem. Nat. Comp.*, **2009**, *45*, 402; (b) Elmuradov, B.Zh.; Abdurazakov, A.Sh.; Shakhidoyatov, Kh.M. *Chem. Nat. Comp.* **2010**, *46*, 262; (c) Elmuradov, B.Zh.; Okmanov, R.Ya.; Abdurazakov, A.Sh.; Tashkhodjaev, B.; Shakhidoyatov, Kh. M. *Acta Crys.* **2010**, *E66*, o1592.
- (9) Bozorov, Kh.A.; Elmuradov, B.Zh.; Okmanov, R.Ya.; Tashkhodjaev, B.; Shakhidoyatov, Kh.M. *Acta Cryst.* **2010**, *E66*, o552.