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Stereoselective synthesis of (*E*)-halomethylidene[1,3]thiazolo[3,2-*a*]thieno[3,2-*e*]pyrimidinium and analogous [1,3]oxazolo[3,2-*a*]thieno[3,2-*e*]pyrimidinium halides starting from 3-*N*-substituted 2-propargylthio(oxy)thieno[2,3-*d*]pyrimidin-4-ones

Abstract: A convenient procedure for the stereoselective synthesis of [1,3]thiazolo[3,2-*a*]thieno[3,2-*e*]pyrimidinium halides and analogous [1,3]oxazolo[3,2-*a*]thieno[3,2-*e*]pyrimidinium halides **5** and **6** is reported. 2-Propargylthio-3-*R*-thieno[2,3-*d*]pyrimidin-4-ones and 2-propargyloxy-3-*R*-thieno[2,3-*d*]pyrimidin-4-ones were treated with bromine or iodine in AcOH to afford (*E*)-halomethylidene[1,3]thiazolo[3,2-*a*]thieno[3,2-*e*]pyrimidinium and (*E*)-halomethylidene-[1,3]oxazolo[3,2-*a*]thieno[3,2-*e*]pyrimidinium halides, respectively.

Keywords: electrophilic halocyclization; [1,3]oxazolo[3,2-*a*]thieno[3,2-*e*]pyrimidinium halides; [1,3]thiazolo[3,2-*a*]thieno[3,2-*e*]pyrimidinium halides; stereoselective synthesis.

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Introduction

A literature survey revealed that thieno[2,3-*d*]pyrimidines are valuable starting materials in organic synthesis [1–4] and exhibit a broad range of biological activities [5, 6], including anti-inflammatory, analgesic [6], and neurotropic properties [7]. They are also useful as kinase inhibitors [8, 9], monocarboxylate transporter 1 inhibitors [10], various receptor antagonists [11], immunomodulators [12], and agents for therapy of cerebral ischemia [13], malaria [14], and Alzheimer's disease [15]. Considering these observations, it was envisaged to synthesize a new

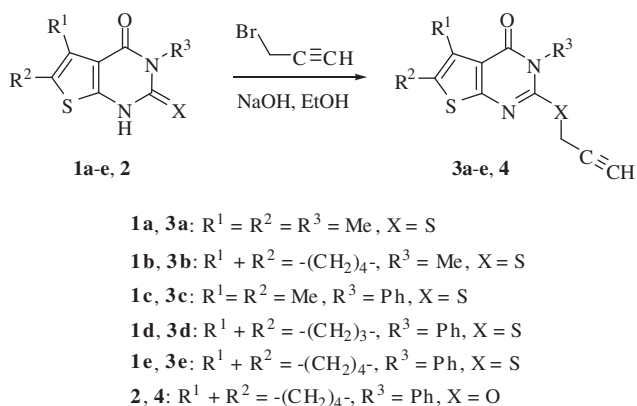
condensed compound by introducing an additional ring to the thieno[2,3-*d*]pyrimidine system. In recent years, heteroannulation processes based on electrophilic halocyclization has proved to be useful in producing various condensed heterocycles such as imidazothiazole [16], thiazoloquinoline [17], thiazolopyrazolopyrimidine [18], thiazolotriazole [19–23], and thiazolo(oxazolo)-thienopyrimidine [24–27]. It has been shown [28] that most halocyclization processes are stereo- and regioselective and are efficient. In this report, we describe the reactivity of 3-substituted 2-propargylthio(oxy)-thieno[2,3-*d*]pyrimidin-4-ones in a series of halocyclization reactions with bromine or iodine.

Results and discussion

We have recently described [25] the regioselective halocyclization of 2-allyloxythieno[2,3-*d*]pyrimidines leading to oxazolothienopyrimidine derivatives. In this context, and considering that the presence of a halomethylidene moiety in the final polycyclic ensemble could be of interest for further functionalization, we wish to report our results on the halocyclization of 2-propargylthio(oxy)-thieno[2,3-*d*]pyrimidin-4-ones **3** and **4** upon treatment with bromine and iodine.

The starting compounds **3** and **4** were conveniently obtained by reaction of the corresponding thieno[2,3-*d*]pyrimidines **1**, **2** with propargyl bromide in EtOH in the presence of sodium hydroxide (Scheme 1).

The (thio)ethers **3**, **4** were allowed to react with bromine and iodine in glacial acetic acid. This procedure provides a convenient access to (*E*)-halomethylidene substituted thiazolothienopyrimidinium halides **5a–e**, **6b–e**



Scheme 1

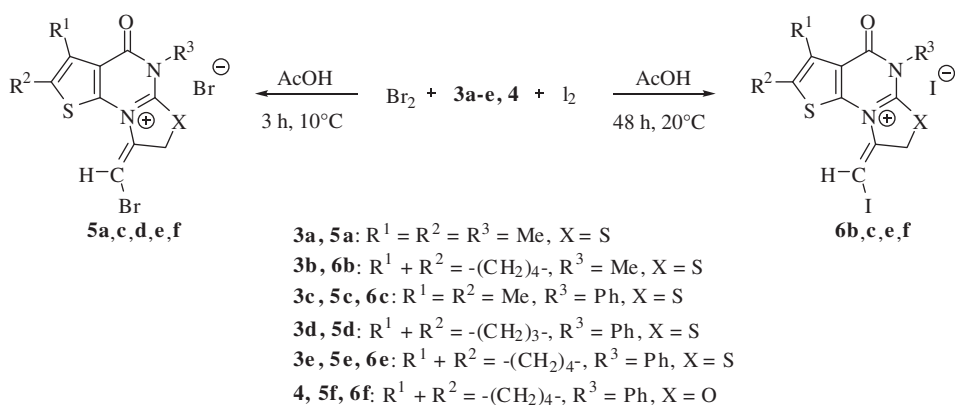
and oxazolothienopyrimidinium halides **5f**, **6f** (Scheme 2). In most cases, the crude products were pure enough for analytical purposes or could be easily purified by crystallization.

The plausible mechanism for the formation of the thiazole (oxazole) ring is shown in Scheme 3. The cyclization reactions are believed to proceed through activation of the carbon-carbon triple bond by coordination to Hal^+ . The resultant complex **A** or **B** undergoes intramolecular

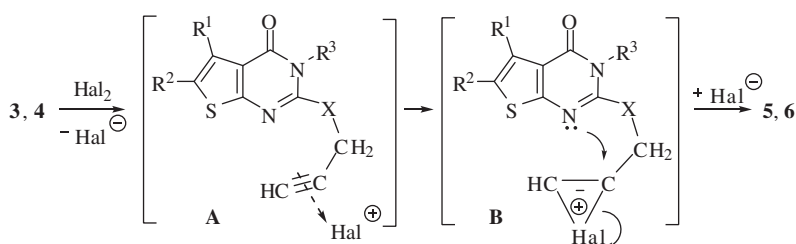
cyclization with the involvement of the pyrimidine nitrogen to give the corresponding salt **5** or **6**.

The structural assignments of the products **3–6** were based on elemental analysis, IR and NMR data. For example, ^1H NMR spectra of bromide salts **5** lack the signals of the propargyl moiety. The signal of $\text{C}(7)\text{H}_2$ protons appears as a broad singlet at 4.34 ppm (for **5a**) and 5.01 ppm (for **5f**), whereas the signal of exocyclic methylidene proton is markedly downshifted and appears as a singlet at 7.28 ppm (for **5a**) and 7.45 ppm (for **5f**).

The downfield shift is most likely the result of a deshielding field effect of the positively charged nitrogen atom which is syn-periplanar to HCHal proton. In the IR spectra of salts **5** and **6**, a bathochromic shift is observed for $\text{C}=\text{O}$ and $\text{C}=\text{N}^+$ bands in comparison to the spectra of the substrates, which confirms the presence of a positively charged nitrogen in the molecule [27]. The ionic nature of products was confirmed by titration of the halide ion using equimolar quantities of AgBF_4 . The halocyclization reaction of compounds **3** and **4** proved to be stereoselective. The suggested (*E*)-configuration of the halomethylidene moiety is consistent with the results of the 2D-NOESY experiment [29] which revealed no cross-peaks between the exocyclic methylidene protons and cyclic methylene protons.



Scheme 2



Scheme 3

Conclusions

(*E*)-Halomethylidene-[1,3]thiazolo[3,2-*a*]thieno[3,2-*e*]pyrimidinium and (*E*)-halomethylidene-[1,3]oxazolo[3,2-*a*]thieno[3,2-*e*]pyrimidinium halides **5**, **6** were obtained by stereoselective halocyclization of 2-propargylthio-thieno[2,3-*d*]pyrimidin-4-ones and 2-propargyloxy-3-thieno[2,3-*d*]pyrimidin-4-ones **3** and **4**. The method is experimentally simple and efficient.

Experimental

Infrared spectra were recorded on a Pye-Unicam SP3–300 spectrometer using KBr pellets. 2D-NOESY experiments were carried out for compounds **5e**, **6e**, **6f** in CDCl₃ on a Varian Mercury-400 instrument. Elemental analyses were performed at the microanalytical unit of the Institute of Organic Chemistry National Academy of Science (Kiev, Ukraine). Melting points were determined using a Kofler block instrument. All reagents were obtained from commercial suppliers and used without any further purification. Dry solvents were prepared according to standard methods.

General procedure for 3-substituted 2-prop-2-yn-1-ylthio(oxy)-thieno[2,3-*d*]pyrimidin-4-ones **3a–e** and **4**

The starting thieno[2,3-*d*]pyrimidine **1a–e**, **2** [27] (20 mmol) was dissolved in 200 mL of ethanol (96%) containing sodium hydroxide (20 mmol) by heating. Propargyl bromide (25 mmol) was added to the cooled solution and the reaction mixture was heated for 1 h at 80°C. Then the mixture was allowed to cool to room temperature and the resultant solid product was filtered off, and washed with ethanol (20 mL) and warm water (50 mL). The pure product was obtained by crystallization from glacial acetic acid.

3,5,6-Trimethyl-2-(prop-2-yn-1-ylthio)thieno[2,3-*d*]pyrimidin-4(3*H*)-one (3a) Yield 3.60 g (68%); colorless crystals; mp 199°C; IR: ν 1675 (C=O), 1580 (C=N⁺) cm^{−1}; ¹H NMR (300 MHz, (CD₃)₂SO): δ 4.07 (d, 2H, *J* = 2.4 Hz, CH₂), 3.44 (s, 3H, CH₃), 3.22 (bs, 1H, CH), 2.33, 2.37 (2s, 3H each, 2CH₃). Anal. Calcd for C₁₂H₁₂N₂O₂S: C, 54.52; H, 4.58; N, 10.60; S, 24.25. Found: C, 54.48; H, 4.51; N, 10.60; S, 24.12.

3-Methyl-2-(prop-2-yn-1-ylthio)-5,6,7,8-tetrahydro[1]benzo-thieno[2,3-*d*]pyrimidin-4(3*H*)-one (3b) Yield 4.30 g (74%); colorless crystals; mp 179°C; IR: ν 1690 (C=O), 1585 (C=N⁺) cm^{−1}; ¹H NMR (300 MHz, (CD₃)₂SO): δ 4.06 (d, 2H, *J* = 2.4 Hz, CH₂), 3.42 (s, 3H, CH₃), 3.23 (bs, 1H, CH), 2.70, 2.83 (2m, 2H each, 2CH₂), 1.76 (m, 4H, 2CH₂). Anal. Calcd for C₁₄H₁₄N₂O₂S: C, 57.90; H, 4.86; N, 9.65; S, 22.08. Found: C, 58.01; H, 4.81; N, 9.78; S, 22.00.

5,6-Dimethyl-3-phenyl-2-(prop-2-yn-1-ylthio)thieno[2,3-*d*]pyrimidin-4(3*H*)-one (3c) Yield 4.64 g (71%); colorless crystals; mp 242°C; IR: ν 1680 (C=O), 1580 (C=N⁺) cm^{−1}; ¹H NMR (300 MHz, (CD₃)₂SO): δ 7.55

(m, 3H, C₆H₅), 7.37 (m, 2H, C₆H₅), 3.91 (d, 2H, *J* = 2.4 Hz, CH₂), 3.06 (bs, 1H, CH), 2.34, 2.36 (2s, 3H each, 2CH₃). Anal. Calcd for C₁₇H₁₄N₂O₂S: C, 62.55; H, 4.32; N, 8.58; S, 19.64. Found: C, 62.52; H, 4.20; N, 8.57; S, 19.59.

3-Phenyl-2-(prop-2-yn-1-ylsulfanyl)-3,5,6,7-tetrahydro-4*H*-cyclopenta[4,5]thieno[2,3-*d*]pyrimidin-4-one (3d) Yield 4.20 g (62%); colorless crystals; mp 249°C; IR: ν 1660 (C=O), 1580 (C=N⁺) cm^{−1}; ¹H NMR (300 MHz, (CD₃)₂SO): δ 7.43–7.57 (m, 5H, C₆H₅), 3.92 (d, 2H, *J* = 2.4 Hz, CH₂), 3.18 (bs, 1H, CH), 2.90 (m, 4H, 2CH₂), 2.39 (m, 2H, CH₂). Anal. Calcd for C₁₈H₁₄N₂O₂S: C, 63.88; H, 4.17; N, 8.28; S, 18.95. Found: C, 63.71; H, 4.21; N, 8.20; S, 18.88.

3-Phenyl-2-(prop-2-yn-1-ylthio)-5,6,7,8-tetrahydro[1]benzo-thieno[2,3-*d*]pyrimidin-4(3*H*)-one (3e) Yield 4.65 g (66%); colorless crystals; mp 208°C; IR: ν 1680 (C=O), 1585 (C=N⁺) cm^{−1}; ¹H NMR (300 MHz, (CD₃)₂SO): δ 7.56 (m, 3H, C₆H₅), 7.41 (m, 2H, C₆H₅), 3.96 (d, 2H, *J* = 2.4 Hz, CH₂), 3.17 (bs, 1H, CH), 2.77 (m, 4H, 2CH₂), 1.77 (m, 4H, 2CH₂). Anal. Calcd for C₁₉H₁₆N₂O₂S: C, 64.75; H, 4.58; N, 7.95; S, 18.19. Found: C, 64.67; H, 4.51; N, 7.93; S, 18.02.

3-Phenyl-2-(prop-2-yn-1-yloxy)-5,6,7,8-tetrahydro[1]benzo-thieno[2,3-*d*]pyrimidin-4(3*H*)-one (4) Yield 5.85 g (87%); colorless crystals; mp 189°C; IR: ν 1700 (C=O), 1590 (C=N⁺) cm^{−1}; ¹H NMR (300 MHz, (CD₃)₂SO): δ 7.27–7.55 (m, 5H, C₆H₅), 4.77 (d, 2H, *J* = 2.4 Hz, CH₂), 3.49 (t, 1H, *J* = 2.4 Hz, CH), 2.75 (m, 4H, 2CH₂), 1.79 (m, 4H, 2CH₂). Anal. Calcd for C₁₉H₁₆N₂O₂S: C, 67.84; H, 4.79; N, 8.33; S, 9.53. Found: C, 67.87; H, 4.73; N, 8.12; S, 9.55.

General procedure for (*E*)-bromomethylidene-[1,3]thiazolo(oxazolo)-[3,2-*a*]thieno[3,2-*e*]pyrimidinium bromides **5a** and **5c–f**

A solution of bromine (1.76 g, 11 mmol) in glacial acetic acid (10 mL) was added dropwise within 30 min to a cooled (15°C) and vigorously stirred solution of compound **3** or **4** (5 mmol) in glacial acetic acid (150 mL). The temperature of the mixture was kept below 15°C while stirring was continued for 3 h. The resultant precipitate was collected by filtration and suspended in acetone (50 mL). The mixture was stirred for 30 min, filtered, and the solid material was washed with warm acetic acid (50 mL) to give pure compounds **5a–e**. Compound **5f** was additionally crystallized from dimethylformamide (DMF).

(8*E*)-8-(Bromomethylidene)-2,3,5-trimethyl-4-oxo-4,5,7,8-tetrahydro[1,3]thiazolo[3,2-*a*]thieno[3,2-*e*]pyrimidin-9-ium bromide (5a) Yield 1.24 g (67%); colorless crystals; mp 217–218°C; IR: ν 1730 (C=O), 1605 (C=N⁺) cm^{−1}; ¹H NMR (300 MHz, (CD₃)₂SO): δ 7.29 (s, 1H, =CHBr), 4.34 (s, 2H, CH₂), 3.21 (s, 3H, CH₃), 2.33 (s, 6H, 2CH₃). Anal. Calcd for C₁₂H₁₂Br₂N₂O₂S: C, 33.98; H, 2.85; N, 6.60; Br, 37.88. Found: C, 34.66; H, 2.77; N, 6.52; Br, 37.65.

(8*E*)-8-(Bromomethylidene)-2,3-dimethyl-4-oxo-5-phenyl-4,5,7,8-tetrahydro[1,3]-thiazolo[3,2-*a*]thieno[3,2-*e*]pyrimidin-9-ium bromide (5c) Yield 1.51 g (62%); colorless crystals; mp 224–225°C; IR: ν 1730 (C=O), 1610 (C=N⁺) cm^{−1}; ¹H NMR (300 MHz, (CD₃)₂SO): δ 7.20–7.60 (m, 1H, =CHBr, 5H, C₆H₅), 4.36 (s, 2H, CH₂), 2.25, 2.27 (s, 3H each, 2CH₃). Anal. Calcd for C₁₇H₁₄Br₂N₂O₂S: C, 41.99; H, 2.90; N, 5.76; Br, 32.87. Found: C, 41.85; H, 2.86; N, 5.68; Br, 32.88.

(1E)-1-(Bromomethylidene)-5-oxo-4-phenyl-1,2,4,6,7,8-hexahydro-5H-cyclopenta-[4,5]thieno[3,2-e][1,3]thiazolo[3,2-a]pyrimidin-10-ium bromide (5d) Yield 1.69 g (68%); colorless crystals; mp 219–220°C; IR: ν 1730 (C=O), 1615 (C=N⁺) cm⁻¹; ¹H NMR (300 MHz, (CD₃)₂SO): δ 7.37–7.51 (m, 1H, =CHBr, 5H, C₆H₅), 4.95 (s, 2H, CH₂), 2.99 (m, 4H, 2CH₂), 2.31 (m, 2H, CH₂). Anal. Calcd for C₁₈H₁₄Br₂N₂OS₂: C, 43.39; H, 2.83; N, 5.62; Br, 32.07. Found: C, 43.15; H, 2.69; N, 5.58; Br, 32.23.

(1E)-1-(Bromomethylidene)-5-oxo-4-phenyl-1,2,4,5,6,7,8,9-octahydrobenzo[4,5]-thieno[3,2-e][1,3]thiazolo[3,2-a]pyrimidin-11-ium bromide (5e) Yield 1.64 g (64%); colorless crystals; mp 246–247°C; IR: ν 1730 (C=O), 1615 (C=N⁺) cm⁻¹; ¹H NMR (300 MHz, (CD₃)₂SO): δ 7.19–7.52 (m, 1H, =CHBr, 5H, C₆H₅), 4.84 (s, 2H, CH₂), 2.69 (m, 4H, 2CH₂), 1.75 (m, 4H, 2CH₂). Anal. Calcd for C₁₉H₁₆Br₂N₂OS₂: C, 44.55; H, 3.15; N, 5.47; Br, 31.20. Found: C, 44.28; H, 3.11; N, 5.41; Br, 31.33.

(1E)-1-(Bromomethylidene)-5-oxo-4-phenyl-1,2,4,5,6,7,8,9-octahydrobenzo[4,5]-thieno[3,2-e][1,3]oxazolo[3,2-a]pyrimidin-11-ium bromide (5f) Yield 1.79 g (72%); colorless crystals; mp 284–285°C; IR: ν 1740 (C=O), 1625 (C=N⁺) cm⁻¹; ¹H NMR (300 MHz, (CD₃)₂SO): δ 7.52 (m, 3H, C₆H₅), 7.45 (s, 1H, =CHBr), 7.30 (m, 2H, C₆H₅), 5.01 (s, 2H, CH₂), 2.82 (m, 4H, 2CH₂), 1.84 (m, 4H, 2CH₂). Anal. Calcd for C₁₉H₁₆Br₂N₂O₂S: C, 45.99; H, 3.25; N, 5.65; Br, 32.21. Found: C, 45.90; H, 3.21; N, 5.59; Br, 32.45.

General procedure for (E)-iodomethylidene-[1,3]thiazolo(oxazolo)[3,2-a]thieno[3,2-e]pyrimidinium iodides (6b–f)

A solution of iodine (2.79 g, 11 mmol) in glacial acetic acid (150 mL) was added dropwise within 30 min to the cooled (room temperature) and vigorously stirred solution of compound **3** or **4** (5 mmol) in glacial acetic acid (150 mL). Stirring was then continued for 72 h. The precipitate was collected by filtration and washed with warm acetic acid (50 mL) to give pure compound **6b,c,e**. Compound **6f** was additionally purified by crystallization from DMF.

(1E)-1-(Iodomethylidene)-4-methyl-5-oxo-1,2,4,5,6,7,8,9-octahydrobenzo[4,5]thieno[3,2-e][1,3]thiazolo[3,2-a]pyrimidin-11-ium iodide (6b) Yield 1.77 g (65%); light-brown crystals; mp 195–196°C; IR: ν 1725 (C=O), 1615 (C=N⁺) cm⁻¹; ¹H NMR (300 MHz, (CD₃)₂SO): δ 7.64 (s, 1H, =CHI), 4.71 (s, 2H, CH₂), 3.63 (s, 3H, 2CH₃), 2.88, 2.92 (m, 2H each, 2CH₂), 1.85 (m, 4H, 2CH₂). Anal. Calcd for C₁₄H₁₄I₂N₂OS₂: C, 30.90; H, 2.59; N, 5.15; I, 46.64. Found: C, 30.69; H, 2.55; N, 5.02; I, 46.89.

(8E)-8-(Iodomethylidene)-2,3-dimethyl-4-oxo-5-phenyl-4,5,7,8-tetrahydro[1,3]thiazolo-[3,2-a]thieno[3,2-e]pyrimidin-9-ium iodide (6c) Yield 2.03 g (70%); light-brown crystals; mp 251–252°C; IR: ν 1730 (C=O), 1615 (C=N⁺) cm⁻¹; ¹H NMR (300 MHz, (CD₃)₂SO): δ 7.62–7.75 (m, 1H, =CHI, 5H, C₆H₅), 4.56 (s, 2H, CH₂), 2.51, 2.53 (s, 3H each, 2CH₃). Anal. Calcd for C₁₇H₁₄I₂N₂OS₂: C, 35.19; H, 2.43; N, 4.83; I, 43.74. Found: C, 35.04; H, 2.40; N, 4.77; I, 43.91.

(1E)-1-(Iodomethylidene)-5-oxo-4-phenyl-1,2,4,5,6,7,8,9-octahydrobenzo[4,5]thieno[3,2-e][1,3]thiazolo[3,2-a]pyrimidin-11-ium iodide (6e) Yield 2.15 g (71%); light-brown crystals; mp 230°C; IR: ν 1730 (C=O), 1615 (C=N⁺) cm⁻¹; ¹H NMR (300 MHz, (CD₃)₂SO): δ 7.62–7.79 (m, 1H, =CHI, 5H, C₆H₅), 4.57 (s, 2H, CH₂), 2.87 (m, 4H, 2CH₂), 1.82 (m, 4H, 2CH₂). Anal. Calcd for C₁₉H₁₆I₂N₂OS₂: C, 37.64; H, 2.66; N, 4.62; I, 41.86. Found: C, 37.53; H, 2.61; N, 4.51; I, 42.02.

(1E)-1-(Iodomethylidene)-5-oxo-4-phenyl-1,2,4,5,6,7,8,9-octahydrobenzo[4,5]thieno[3,2-e][1,3]oxazolo[3,2-a]pyrimidin-11-ium iodide (6f) Yield 2.21 g (75%); yellow crystals; mp 274–275°C; IR: ν 1740 (C=O), 1625 (C=N⁺) cm⁻¹; ¹H NMR (300 MHz, (CD₃)₂SO): δ 7.67 (s, 1H, =CHI), 7.48 (m, 3H, C₆H₅), 7.22 (m, 2H, C₆H₅), 4.72 (s, 2H, CH₂), 2.74 (m, 4H, 2CH₂), 1.77 (m, 4H, 2CH₂). Anal. Calcd for C₁₉H₁₆I₂N₂O₂S: C, 38.67; H, 2.73; N, 4.75; I, 43.00. Found: C, 38.55; H, 2.70; N, 4.68; I, 43.88.

Acknowledgments: This work was supported by the Department of Education and Science (DES) of Ukraine (Project GR-0109U000899).

Received March 8, 2013; accepted April 24, 2013; previously published online May 25, 2013

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