Sergiy V. Vlasov*, Sergiy M. Kovalenko, Pavlo E. Shynkarenko, Konstantin Yu. Krolenko and Vitaliy S. Vlasov

Synthesis and antimicrobial evaluation of 3-(4-arylthieno[2,3-*d*]pyrimidin-2-yl)-2*H*-chromen-2-ones

https://doi.org/10.1515/hc-2018-0013
Received January 21, 2018; accepted May 4, 2018; previously published online June 23, 2018

Abstract: Syntheses of 3-(4-arylthieno[2,3-*d*]pyrimidin-2-yl)-2*H*-chromen-2-ones **5** by the reaction of 2-iminocoumarin-3-carboxamides **1** with (2-aminothiophen-3-yl)(aryl) methanones **2** and by the alternative Suzuki coupling of 4-chlorothieno[2,3-*d*]pyrimidin-2-yl-2*H*-chromen-2-one **7** with arylboronic acids were developed. Compound **5d** showed higher antimicrobial activity against *Staphylococcus aureus* than the reference drug streptomycin.

Keywords: arylation; coumarin; coupling; rearrangement; thiophene.

Introduction

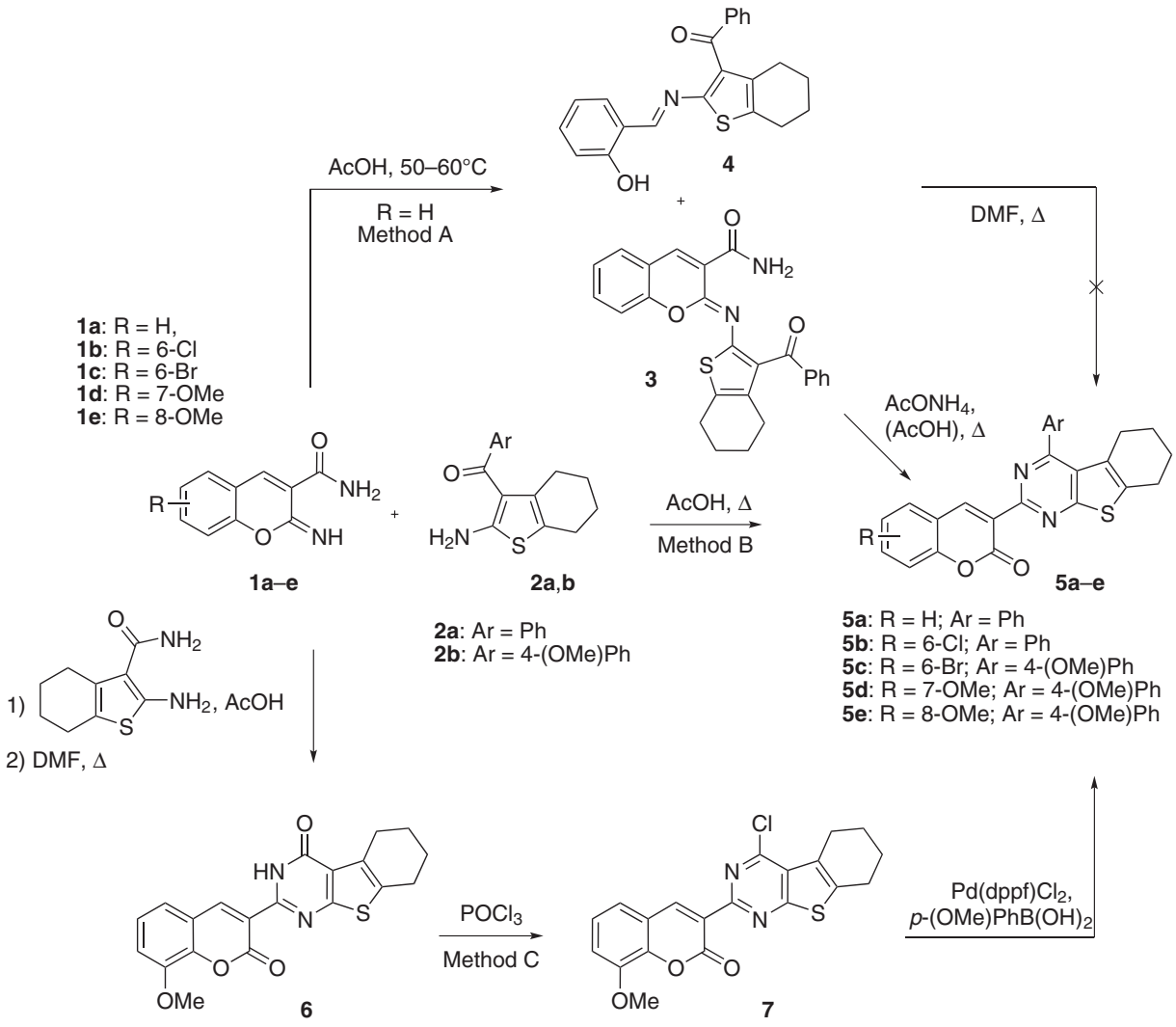
4-Arylthieno[2,3-*d*]pyrimidines have been studied as adenosine receptor modulators [1], agonists of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) receptors [2] and inhibitors of heat shock protein 90 (Hsp90) [3]. Some derivatives inhibit transforming growth factor (TGF)-β receptor kinase [4] and the IκB kinase (IKK)-β and/or tumor necrosis factor (TNF)-α receptor [5]. The effective approaches to the preparation of these compounds are the Thorpe reaction [2, 4], cyclization of 2-amino-3-aroylthiophenes [6, 7], arylation of thieno[2,3-*d*]pyrimidines by Suzuki coupling [8] or aluminum trichloride catalyzed reactions [9]. It is also known that coumarins modified at position 3 with heterocyclic fragments display antimicrobial properties [10–12]. Earlier, the 'recyclization' reactions of 2-aminobenzophenones with 2-iminocoumarin-3-carboxamides were reported as an easy one-step method for the preparation of 3-(4-arylquinazolin-2-yl)-2*H*-chromen-2-ones [13] as well as the preparation of 2-(2-oxo(imino)-2*H*-chromen-3-yl) thieno[2,3-*d*]pyrimidin-4(3*H*)-ones using the methods of 'recyclization' of 2-iminocoumarins [14–17]. The reaction of 2-iminocoumarin-3-carboxamides **1** with (2-aminothiophen-3-yl)(aryl)methanones **2** has never been studied before.

Results and discussion

We studied the reaction of compounds **1** with compounds **2** as the way for synthesis of compounds **5** (Scheme 1). The previous studies showed the effectiveness of such a two-step procedure for the preparation of similar compounds [15–17]. Thus, heating a mixture of compounds **1a** and **2a** at 50–60°C in glacial acetic acid (method A) furnished the intermediate compound **3**, albeit in a low yield and with insufficient purity. Analysis of the liquid chromatography/mass spectrometry (LC/MS) data of the crude mixture suggested that the major product **3** was contaminated with compounds **2a** (Ar = Ph), **4** and **5a**.

Attempts to rearrange compounds **3** to **5** by heating in dimethylformamide (DMF) failed. The use of glacial acetic acid (8 h of boiling) for the attempted rearrangement of **3** gave traces of compound **5a**. However, heating of the crude product **3** in glacial acetic acid in the presence of ammonium acetate for 3 h furnished the desired product **5a** in a yield of 18%. For the synthesis of compounds **5**, heating of equimolar amounts of compounds **1** and **2** in glacial acetic acid (method B) was also tried. Products **5** were isolated in yields of 61–82% after quenching the mixture with cold water followed by crystallization of the resultant precipitate from ethanol. In the third experiment (method C), product **5e** was obtained by a Suzuki coupling of compound **7** with 4-methoxyphenylboronic acid, which

***Corresponding author: Sergiy V. Vlasov,** Organic Chemistry Department, National University of Pharmacy, 53, Pushkinska str., Kharkiv 61002, Ukraine, e-mail: sergiy.vlasov@gmail.com
Sergiy M. Kovalenko: Organic Chemistry Department, V. N. Karazin Kharkiv National University, 4, Svobody Sq., Kharkiv 61022, Ukraine
Pavlo E. Shynkarenko: Enamine Ltd., 78, Chervonotkatska str., Kiev 02094, Ukraine
Konstantin Yu. Krolenko: Medicinal Chemistry Department, National University of Pharmacy, 53, Pushkinska str., Kharkiv 61002, Ukraine
Vitaliy S. Vlasov: Pharmacoinformatics Department, National University of Pharmacy, 53, Pushkinska str., Kharkiv 61002, Ukraine



Scheme 1 Synthesis of 3-(4-arylthieno[2,3-*d*]pyrimidin-2-yl)-2*H*-chromen-2-ones **5**.

had been prepared from the available intermediate **6** [15, 16] by treatment with $POCl_3$ (method C). The Suzuki reaction proceeded slowly and required 12 h for completion. The target compound **5e** was isolated in a 45% yield after chromatographic purification. In comparison, method B is the most convenient way of obtaining 3-(4-arylthieno-[2,3-*d*]pyrimidin-2-yl)-2*H*-chromen-2-ones **5**.

The antimicrobial activity of compounds **5** at a concentration of 100 μg/mL in dimethyl sulfoxide (DMSO) solution against the *Staphylococcus aureus* (ATCC 25923) strain was investigated using the agar well diffusion assay [18, 19]. It was found that compounds **5a–c, e** show antimicrobial activity that is comparable to the activity of the reference drug streptomycin under similar conditions. However, compound **5d** displays activity against the strain *S. aureus* that exceeds the activity of streptomycin at a concentration of 100 μg/mL.

Conclusions

New approaches to the synthesis of 3-(4-arylthieno[2,3-*d*] pyrimidin-2-yl)-2*H*-chromen-2-ones **5** were studied. It was found that 'recyclization' of 2-iminocoumarin-3-carboxamides in reaction with (2-amino-4,5,6,7-tetrahydro-1-benzothiophen-3-yl)(aryl)methanones (method B) is the most expedient synthetic route. Products **5** show antimicrobial activity against *S. aureus* (ATCC 25923). Compound **5d** exhibits higher antimicrobial activity than the reference drug streptomycin.

Experimental

2-Iminocoumarin-3-carboxamides **1a–e**, (2-amino-4,5,6,7-tetrahydro-1-benzothiophen-3-yl)(aryl)methanones **2a,b** and

2-(8-methoxy-2-oxo-2*H*-chromen-3-yl)-5,6,7,8-tetrahydro[1]benzothieno[2,3-*d*]pyrimidin-4(3*H*)-one **6** were prepared according to the previously reported methods [15, 20, 21]. The antimicrobial activity of compounds **5** was tested using the agar well diffusion method [18, 19].

3-(4-Chloro-5,6,7,8-tetrahydro[1]benzothieno[2,3-*d*]pyrimidin-2-yl)-8-methoxy-2*H*-chromen-2-one (7)

To 2.0 g (5.2 mmol) of 2-(8-methoxy-2-oxo-2*H*-chromen-3-yl)-5,6,7,8-tetrahydro[1]benzothieno[2,3-*d*]pyrimidin-4(3*H*)-one (**6**) was added 10.0 mL of phosphorus oxychloride, and the mixture was stirred under reflux for 5 h. The excess of $POCl_3$ was distilled off and the residue was treated with ice-cold water. The resultant precipitate was filtered off, washed with ethanol and then with hexanes.

Compound **7** was obtained in a 79% yield as a yellow powder; mp 123–124°C; ^{1}H NMR (400 MHz, $CDCl_3$): 1.91 (m, 4H, CH_2CH_2); 2.88 (m, 2H, CH_2); 3.09 (m, 2H, CH_2); 3.96 (s, 3H, OCH_3); 7.09–7.24 (m, 3H, Ar-H); 8.58 (s, 1H, CH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.2, 22.4, 26.1, 26.2, 56.3, 114.6, 119.5, 120.2, 124.4, 124.6, 127.1, 127.3, 140.7, 144.2, 145.4, 147.0, 153.0, 155.0, 157.7, 169.2; IR (KBr): ν 2938, 2840, 1743, 1678, 1608, 1558, 1560, 1537, 1479, 1438, 1418, 1349, 1301 cm^{-1}; LC-MS: *m*/*z* 399 [M + H]$^+$. Anal. Calcd for $C_{20}H_{15}ClN_2O_3S$: C, 60.23; H, 3.79; N, 7.02. Found: C, 60.35; H, 3.88; N, 7.21.

3-[4-Aryl-5,6,7,8-tetrahydro[1]benzothieno[2,3-*d*]pyrimidin-2-yl]-2*H*-chromen-2-ones (5)

Method A A mixture of 2-iminocoumarin-3-carboxamide **1a** (0.3 g, 1.6 mmol), 2-amino-4,5,6,7-tetrahydro-1-benzothiophen-3-yl)(phenyl) methanone **2a** (0.41 g, 1.6 mmol) and 7 mL of glacial acetic acid was stirred at 50–60°C for 3 h and then cooled. The resultant precipitate of **3** was filtered off and washed with ethanol. To 0.25 g of the crude product **3**, 0.33 g (4.3 mmol) of ammonium acetate and 10 mL of glacial acetic acid were added, and the mixture was heated under reflux for 3 h. After cooling, the mixture was diluted with water and the resultant precipitate of **5** was filtered off, washed with water and dried.

Method B (general method) A mixture of 2-iminocoumarin-3-carboxamide **1** (1.6 mmol), 2-amino-4,5,6,7-tetrahydro-1-benzothiophen-3-yl)(aryl)methanone **2** (1.6 mmol) and 15 mL of glacial acetic acid was heated under reflux for 3–4 h. The product **5** precipitated after the dilution with cold water (up to 50 mL). The precipitate of compound **5** was filtered off, dried and crystallized from ethanol.

3-(4-Phenyl-5,6,7,8-tetrahydro[1]benzothieno[2,3-*d*]pyrimidin-2-yl)-2*H*-chromen-2-one (5a)

This compound was obtained in a 18% yield (method A) and a 72% yield (method B) as a yellow powder; mp 220–221°C; ^{1}H NMR (200 MHz, DMSO-d_6): δ 1.59 (m, 2H, CH_2); 1.79 (m, 2H, CH_2); 2.10 (m, 2H, CH_2); 2.90 (m, 2H, CH_2); 7.36–7.61 (m, 8H, Ar-H); 7.90 (d, 1H, *J* = 7.6 Hz, Ar-H); 8.72 (m, 1H, CH); ^{13}C NMR (125 MHz, DMSO-d_6): δ 22.3, 22.5, 26.0, 27.0, 116.4, 116.5, 119.2, 125.1, 125.4, 127.1, 127.6, 128.3, 129.6, 129.8, 129.9, 130.7, 133.3, 138.5, 139.5, 145.2, 154.2, 155.1, 158.1, 160.9, 168.8; IR (KBr): ν 3050, 2940, 2860, 2837, 1738, 1606, 1558, 1524, 1508, 1492, 1458, 1443, 1434, 1408, 1360, 1348, 1306 cm^{-1}; LC-MS: *m*/*z* 411 [M + H]$^+$. Anal. Calcd for $C_{25}H_{18}N_2O_2S$: C, 73.15; H, 4.42; N, 6.82. Found: C, 73.26; H, 4.58; N, 6.90.

6-Chloro-3-(4-phenyl-5,6,7,8-tetrahydro[1]benzothieno[2,3-*d*]pyrimidin-2-yl)-2*H*-chromen-2-one (5b)

This compound was obtained in a 68% yield (method B) as a yellow powder; mp 203–204°C; ^{1}H NMR (200 MHz, DMSO-d_6): δ 1.58 (m, 2H, CH_2); 1.80 (m, 2H, CH_2); 2.09 (m, 2H, CH_2); 2.89 (m, 2H, CH_2); 7.44–7.70 (m, 7H, Ar-H); 8.01 (d, 1H, *J* = 2.1 Hz, Ar-H); 8.69 (s, 1H, CH); ^{13}C NMR (125 MHz, DMSO-d_6): δ 22.3, 22.5, 26.0, 27.0, 118.3, 120.5, 126.2, 127.1, 127.5, 128.3, 128.7, 128.8, 129.6, 129.8, 132.7, 138.5, 139.7, 144.0, 152.8, 154.6, 157.5, 160.8, 168.7; IR (KBr): ν 3056, 2931, 2857, 1755, 1606, 1560, 1518, 1489, 1444, 1430, 1399, 1360, 1301 cm^{-1}; LC-MS: *m*/*z* 445 [M + H]$^+$. Anal. Calcd for $C_{25}H_{17}ClN_2O_2S$: C, 67.49; H, 3.85; N, 6.30. Found: C, 67.71; H, 3.89; N, 6.50.

6-Bromo-3-[4-(4-methoxyphenyl)-5,6,7,8-tetrahydro[1]benzothieno[2,3-*d*]pyrimidin-2-yl]-2*H*-chromen-2-one (5c)

This compound was obtained in a 61% yield (method B) as a yellow powder; mp 253–254°C; ^{1}H NMR (200 MHz, DMSO-d_6): δ 1.63 (m, 2H, CH_2); 1.84 (m, 2H, CH_2); 2.22 (m, 2H, CH_2); 2.91 (m, 2H, CH_2); 3.86 (s, 3H, OCH_3); 7.08 (d, 2H, *J* = 8.8 Hz, H-3′, H-5′); 7.40 (d, 1H, *J* = 8.8 Hz, H-8); 7.55 (*d*, 2H, *J* = 8.8 Hz, H-2′, H-6′); 7.77 (dd, 1H, J_1 = 8.8 Hz, J_2 = 2.4 Hz, H-7); 8.15 (d, 1H, *J* = 2.4 Hz, H-5); 8.67 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 22.4, 22.5, 26.1, 27.3, 55.7, 113.7, 116.6, 118.6, 121.1, 126.3, 127.1, 127.7, 130.8, 131.4, 131.7, 135.4, 139.3, 143.8, 153.2, 154.7, 157.5, 160.5, 160.7, 168.8; IR (KBr): ν 3072, 2936, 2837, 1743, 1608, 1557, 1494, 1427, 1396, 1360, 1331, 1298 cm^{-1}; LC-MS: *m*/*z* 521 [M + H]$^+$. Anal. Calcd for $C_{26}H_{19}BrN_2O_3S$: C, 60.12; H, 3.69; N, 5.39. Found: C, 60.17; H, 3.88; N, 5.34.

7-Methoxy-3-[4-(4-methoxyphenyl)-5,6,7,8-tetrahydro[1]benzothieno[2,3-*d*]pyrimidin-2-yl]-2*H*-chromen-2-one (5d)

This compound was obtained in a 82% yield (method B) as a yellow powder; mp 199–200°C; ^{1}H NMR (200 MHz, DMSO-d_6): δ 1.62 (m, 2H, CH_2); 1.80 (m, 2H, CH_2); 2.10 (m, 2H, CH_2); 2.90 (m, 2H, CH_2); 3.83 (s, 3H, OCH_3); 3.87 (s, 3H, OCH_3); 6.98 (dd, 1H, J_1 = 8.8 Hz, J_2 = 2.4 Hz, 6-H); 7.04–7.10 (m, 3H, H-3′, H-5′, H-8); 7.56 (d, 2H, *J* = 8.8 Hz, H-2′, H-6′); 7.81 (d, 1H, *J* = 8.8 Hz, H-5); 8.70 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 22.4, 22.5, 26.0, 27.3, 55.7, 56.5, 100.7, 112.8, 113.3, 113.7, 121.7, 126.8, 127.7, 131.0, 131.3, 138.7, 145.4, 155.4, 156.3, 158.3, 160.6, 160.7, 163.8, 168.8; IR (KBr): ν 3066, 2933, 2902, 2860, 2838, 1746, 1607, 1578, 1561, 1508, 1496, 1462, 1439, 1404, 1385, 1352, 1303 cm^{-1}; LC-MS: *m*/*z* 471 [M + H]$^+$. Anal. Calcd for $C_{27}H_{22}N_2O_4S$: C, 68.92; H, 4.71; N, 5.95. Found: C, 68.95; H, 4.89; N, 5.97.

8-Methoxy-3-[4-(4-methoxyphenyl)-5,6,7,8-tetrahydro[1]benzothieno[2,3-*d*]pyrimidin-2-yl]-2*H*-chromen-2-one (5e)

Method C A mixture of compound **7** (1.0 g, 2.51 mmol), 4-methoxyphenylboronic acid (0.42 g, 2.76 mmol), potassium carbonate

(1.56 g, 11.28 mmol) and Pd(dppf)Cl_2 (0.041 g, 0.05 mmol) in a mixed solvent of 1,4-dioxane/H_2O (40 mL, 6:1) was stirred at 90°C for 12 h. The reaction progress was monitored by thin-layer chromatography (TLC) eluting with ethyl acetate/hexanes, 1:1, and using ultraviolet (UV) detection at 365 nm. The mixture was quenched with water and extracted with chloroform (3×50 mL). The combined extracts were dried over Na_2SO_4 and concentrated under reduced pressure, and the residue was subjected to silica gel chromatography eluting with $CHCl_3$/MeOH (95:5–90:10). Compound **5e** was obtained in a 74% yield (method B) and a 45% yield (method C) as a yellow powder; mp 236–237°C (method B); mp 237–238°C (method C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.64 (m, 2H, CH_2); 1.87 (m, 2H, CH_2); 2.21 (m, 2H, CH_2); 2.88 (m, 2H, CH_2); 3.86 (s, 3H, OCH_3); 3.94 (s, 3H, OCH_3); 6.99 (d, 2H, *J* = 8.1 Hz, H-3′, H-5′); 7.05–7.19 (m, 3H, Ar-H); 7.52 (d, 2H, *J* = 8.8 Hz, H-2′, H-6′); 8.50 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.5, 22.6, 26.2, 27.3, 55.4, 56.3, 113.4, 114.2, 119.8, 120.1, 124.2, 126.4, 127.4, 130.8, 131.1, 139.3, 144.0, 144.5, 146.9, 154.8, 158.4, 160.4, 160.6, 169.4; IR (KBr): ν 3078, 2942, 2906, 2838, 1742, 1608, 1576, 1557, 1514, 1497, 1479, 1436, 1404, 1387, 1341, 1303 cm^{-1}; LC-MS: *m*/*z* 471 $[M+H]^+$. Anal. Calcd for $C_{27}H_{22}N_2O_4S$: C, 68.92; H, 4.71; N, 5.95. Found: C, 68.99; H, 4.86; N, 6.07.

Acknowledgments: The authors gratefully acknowledge the Head of Microorganism Biochemistry and Biotechnology Laboratory of the NAMS Institute of Microbiology and Immunology of Ukraine and Dr. Tatyana P. Osolodchenko for conducting the microbiological experiment.

References

[1] Baraldi, P. G. Preparation of thienylmethanones as allosteric adenosine receptor modulators. U.S. Patent 6323214, November 27, 2001.

[2] Bonger, K. M.; Hoogendoorn, S.; van Koppen, C. J.; Timmers, C. M.; van der Marel, G. A.; Overkleeft, H. S. Development of selective LH receptor agonists by heterodimerization with a FSH receptor antagonist. *Med. Chem. Lett.* **2011**, *2*, 85–89.

[3] Kung, P.-P.; Meng, J. J. Preparation of 2-aminopyrimidine derivatives as HSP-90 inhibitors. Int. Pat. 2008059368, May 22, 2008.

[4] Hoelzemann, G.; Dorsch, D.; Greiner, H.; Amendt, C.; Zenke, F. Preparation of alkoxythienopyrimidine derivatives for use as TGF-beta receptor kinase modulators. Int. Pat. 2010149257, December 29, 2010.

[5] Wada, M.; Sueda, N.; Komine, T.; Katsuyama, K.; Tsuchida, H.; Kojima, R.; Kawamura, O. Preparation of thieno[2,3-*d*]pyrimidine compounds as IKK-β and or TNF-α inhibitors. Int. Pat. 2008020622, February 21, 2008.

[6] Abdelrazek, F. M.; Mohamed, A. M.; Elsayed, A. N. Synthesis of some new thieno[2,3-*d*]pyrimidine derivatives. *Afinidad* **2008**, *65*, 322–326.

[7] Ishikawa, F.; Yamaguchi, H. Cyclic guanidines. XIII. Synthesis of 2-amino-4-phenyl-3,4-dihydrothieno[2,3-*d*]pyrimidine derivatives. *Chem. Pharm. Bull.* **1980**, *28*, 3172–3177.

[8] Bugge, S.; Kaspersen, S. J.; Sundby, E.; Hoff, B. H. Route selection in the synthesis of C-4 and C-6 substituted thienopyrimidines. *Tetrahedron* **2012**, *68*, 9226–9233.

[9] Kumar, K. S.; Chamakuri, S.; Vishweshwar, P.; Iqbal, J.; Pal, M. $AlCl_3$-induced (hetero)arylation of thienopyrimidines: a new synthesis of 4-substituted thieno[2,3-*d*]pyrimidines. *Tetrahedron Lett.* **2010**, *51*, 3269–3273.

[10] Mohamed, H. M.; El-Wahab, A. H. F. A.; Ahmed, K. A.; El-Agrody, A. M.; Bedair, A. H.; Eid, F. A.; Khafagy, M. M. Synthesis, reactions and antimicrobial activities of 8-ethoxycoumarin derivatives. *Molecules* **2012**, *17*, 971–988.

[11] Arshad, A.; Osman, H.; Bagley, M. C.; Lam, C. K.; Mohamad, S.; Zahariluddin, A. S. M. Synthesis and antimicrobial properties of some new thiazolyl coumarin derivatives. *Eur. J. Med. Chem.* **2011**, *46*, 3788–3794.

[12] Patel, R. V.; Kumari, P.; Rajani, D. P.; Chikhalia, K. H. Synthesis of coumarin-based 1,3,4-oxadiazol-2-ylthio-*N*-phenyl/benzothiazolyl acetamides as antimicrobial and antitubercular agents. *Med. Chem. Res.* **2013**, *22*, 195–210.

[13] Rusanova, S. V.; Zhuravel, I. A.; Kovalenko, S. N.; Chernykh, V. P.; Baumer, V. N. Recyclization of 2-iminocoumarins using nucleophilic reagents. 6. Reaction of 2-iminocoumarin-3-carboxamides with 2-aminobenzophenones. *Chem. Heterocycl. Compd.* **2004**, *40*, 1323–1331.

[14] Vasylyev, M. V.; Bilokin, Y. V.; Branytska, O. V.; Kovalenko, S. M.; Chernykh, V. P. A facile method for synthesis of heterocycles containing tetrahydrobenzo[4,5]thieno[2,3-*d*]pyrimidine and coumarin moieties. *Heterocycl. Commun.* **1999**, *5*, 241–242.

[15] Kovalenko, S. M.; Vlasov, S. V.; Chernykh, V. P. Recyclization of 2-imino-2*H*-1-benzopyrans under the action of nucleophillic reagents – reaction of 2-iminocoumarin-3-carboxamides with 2-aminothiophene-3-carboxamides. *Synthesis* **2006**, *5*, 847–852.

[16] Kovalenko, S. M.; Vlasov, S. V.; Chernykh, V. P. Synthesis of 5-methyl-4-oxo-2-(coumarin-3-yl)-*N*-aryl-3,4-dihydrothieno[2,3-*d*]pyrimidine-6-carboxamides. *Heteroatom Chem.* **2007**, *18*, 341–346.

[17] Shynkarenko, P. E.; Vlasov, S. V.; Kovalenko, S. M.; Shishkina, S. V.; Shishkin, O. V.; Chernykh, V. P. Convenient synthesis of substituted 2-(2-iminocoumarin-3-yl)thieno[2,3-*d*]pyrimidin-4-ones. *J. Heterocycl. Chem.* **2010**, *47*, 800–806.

[18] Coyle, M. B. Manual of Antimicrobial Susceptibility Testing; Ed. American Society for Microbiology: Washington, 2005; pp 29, 39.

[19] Performance Standards for Antimicrobial Susceptibility Testing; Twenty-Second Informational Supplement. Document M100-S22; CLSI: Wayne, 2012; Vol. 32, p 169.

[20] Czerney, P.; Hartmann, H. Synthesis of 3-cyanocoumarins. *J. Prakt. Chem.* **1981**, *323*, 691–693.

[21] Tranberg, C. E.; Zickgraf, A.; Giunta, B. N.; Luetjens, H.; Figler, H.; Murphree, L. J.; Falke, R.; Fleischer, H.; Linden, J.; Scammells, P. J.; et al. 2-Amino-3-aroyl-4,5-alkylthiophenes: agonist allosteric enhancers at human A_1 adenosine receptors. *J. Med. Chem.* **2002**, *45*, 382–389.