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

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Abstract: Syntheses of 3-(4-arylthieno[2,3-d]pyrimidin-2-yl)-2H-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-2H-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 IxB 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-aryltiophenones [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)-2H-chromen-2-ones [13] as well as the preparation of 2-(2-oxo(imino)-2H-chromen-3-yl)thieno[2,3-d]pyrimidin-4(3H)-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
had been prepared from the available intermediate 6 [15, 16] by treatment with POCl₃ (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)-2H-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 anti-microbial 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.

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

Conclusions

New approaches to the synthesis of 3-(4-arylthieno[2,3-d]pyrimidin-2-yl)-2H-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-2H-chromen-3-yl)-5,6,7,8-tetrahydro[1]benzothieno[2,3-d]pyrimidin-4(3H)-one (1) 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-2H-chromen-2-one (7)

To 2.0 g (5.2 mmol) of 2-(8-methoxy-2-oxo-2H-chromen-3-yl)-5,6,7,8-tetrahydro[1]benzothieno[2,3-d]pyrimidin-4(3H)-one (6) was added 10.0 mL of phosphorus oxychloride, and the mixture was stirred under reflux for 5 h. The excess of POCl₃ 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; ¹H NMR (400 MHz, CDCl₃): 1.91 (m, 4H, CH₂CH₂); 2.88 (m, 2H, CH₂); 3.09 (m, 2H, CH₂); 3.96 (s, 3H, OCH₃); 7.09–7.24 (m, 3H, Ar-H); 8.58 (s, 1H, CH); 13C NMR (100 MHz, CDCl₃): 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, 165.4, 167.0, 153.0, 155.0, 157.7, 169.2; IR (KBr): v 2938, 2840, 1743, 1678, 1608, 1558, 1560, 1479, 1638, 1418, 1349, 1301 cm⁻¹; LC-MS: m/z 399 [M + H]⁺. Anal. Calcd for C₂₆H₂₁ClN₂O₃: C, 67.16; H, 3.79; N, 7.02. Found: C, 60.35; H, 3.88; N, 7.21.

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

This compound was obtained in a 68% yield (method B) as a yellow powder; mp 203–204 °C; ¹H NMR (200 MHz, DMSO-d₆): δ 1.58 (m, 2H, CH₂); 1.80 (m, 2H, CH₂); 2.09 (m, 2H, CH₂); 2.89 (m, 2H, CH₂); 7.44–7.70 (m, 7H, Ar-H); 8.01 (d, 1H, J = 2.1 Hz, Ar-H); 8.69 (s, 1H, CH); 13C NMR (125 MHz, DMSO-d₆): δ 22.3, 22.5, 26.0, 270.118, 132.0, 125.6, 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): v 3056, 2931, 2875, 1755, 1606, 1560, 1518, 1489, 1444, 1430, 1399, 1360, 1301 cm⁻¹; LC-MS: m/z 445 [M + H]⁺. Anal. Calcd for C₂₆H₂₁ClN₂O₃: C, 67.49; H, 3.85; N, 6.30. Found: C, 67.71; H, 3.89; N, 6.50.

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

This compound was obtained in a 61% yield (method B) as a yellow powder; mp 253–254 °C; ¹H NMR (200 MHz, DMSO-d₆): δ 1.63 (m, 2H, CH₂); 1.84 (m, 2H, CH₂); 2.22 (m, 2H, CH₂); 2.91 (m, 2H, CH₂); 3.86 (s, 3H, OCH₃); 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 = 8.8 Hz, J = 2.4 Hz, H-7); 8.15 (d, 1H, J = 2.4 Hz, H-5); 8.67 (s, 1H); 13C NMR (125 MHz, DMSO-d₆): δ 22.6, 22.6, 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, 143.8, 153.2, 154.7, 1575, 160.5, 160.7, 168.8; IR (KBr): v 3072, 2936, 2837, 1743, 1608, 1575, 1494, 1427, 1396, 1360, 1331, 1298 cm⁻¹; LC-MS: m/z 521 [M + H]⁺. Anal. Calcd for C₂₆H₁₇BrN₂O₃: 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]-2H-chromen-2-one (5d)

This compound was obtained in a 82% yield (method B) as a yellow powder; mp 199–200 °C; ¹H NMR (200 MHz, DMSO-d₆): δ 1.62 (m, 2H, CH₂); 1.80 (m, 2H, CH₂); 2.10 (m, 2H, CH₂); 2.90 (m, 2H, CH₂); 3.83 (s, 3H, OCH₃); 3.87 (s, 3H, OCH₃); 6.98 (dd, 1H, J = 2.4 Hz, H-6); 7.06–7.10 (m, 3H, H-3', H-5', H-8); 7.56 (d, 2H, J = 8.8 Hz, H-2, H-6); 7.78 (d, 1H, J = 8.8 Hz, H-5); 8.70 (s, 1H); 13C NMR (75 MHz, DMSO-d₆): δ 22.4, 22.5, 26.0, 27.3, 55.7, 56.5, 100.2, 112.8, 113.3, 113.7, 126.8, 127.7, 131.0, 131.3, 138.7, 154.5, 155.4, 156.3, 158.3, 160.6, 160.7, 163.8, 168.8; IR (KBr): v 3066, 2933, 2902, 2806, 2838, 1746, 1607, 1578, 1561, 1508, 1496, 1462, 1439, 1460, 1385, 1352, 1303 cm⁻¹; LC-MS: m/z 471 [M + H]⁺. Anal. Calcd for C₂₆H₂₃N₂O₃: C, 68.82; 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]-2H-chromen-2-one (5e)

Method C A mixture of compound 7 (1.0 g, 2.51 mmol), 4-methoxyphenol (0.42 g, 2.76 mmol), potassium carbonate
(1.56 g, 11.28 mmol) and Pd(dppf)Cl₂ (0.041 g, 0.05 mmol) in a mixed solvent of 1,4-dioxane/H₂O (40 mL, 61) 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 Na₂SO₄, and concentrated under reduced pressure, and the residue was subjected to silica gel chromatography eluting with CHCl₃/MeOH (95:5–90:10). Compound 5e was obtained in a 76% 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); 1H NMR (400 MHz, CDCl₃): δ 1.64 (m, 2H, CH₂); 2.17 (m, 2H, CH₂); 2.88 (m, 2H, CH₂); 3.86 (s, 3H, OCH₃); 3.94 (s, 3H, OCH₃); 6.99 (d, 1H, J = 8.1 Hz, 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); 13C NMR (100 MHz, CDCl₃): 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 2222, 2227, 2252, 2264, 2723, 2928, 2956, 2838, 2852, 1606, 1576, 1557, 1514, 1479, 1476, 1366, 1604, 1304, 1304 cm⁻¹; LC-MS: m/z 471 [M+H]⁺. Anal. Calcd for C₂₇H₂₁N₂O₄S: C, 68.92; H, 4.71; N, 5.95. Found: C, 68.99; H, 4.86; N, 6.07.

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References