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Efficient Synthesis of Novel Triazolo[5,1-*b*]purines by Diacetoxyiodobenzene-Mediated Oxidative Cyclization of Schiff Bases

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Abstract: In this work, we have developed a method for synthesizing new 8-substituted triazolo[5,1-*b*]purines using diacetoxyiodobenzene as an oxidizing agent with good yields (59–67%). The advantages of this approach include mild reaction conditions and removing the need to use transition metals. Based on the results obtained, a plausible reaction pathway was proposed. The developed approach opens new possibilities for the preparation of previously inaccessible condensed purine derivatives, which are of interest for the development of biomolecules with a variety of pharmacological applications. The structures of the compounds were confirmed by the data of ^{1}H, ^{13}C NMR spectroscopy, IR spectroscopy, and an elemental analysis.

Keywords: purines; pyrimidine; oxidation; triazolo[5,1-*b*]purines; cyclization; azolo[1,5-*a*]pyrimidines; Schiff bases

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1. Introduction

Natural purines are among the most known and well-studied representatives of nitrogen heterocycles due to their involvement in the regulation of essential biological processes in many living organisms [1–3]. The presence of these heterocyclic fragments in the structure of nucleic acids has inspired active research aimed at creating modified nucleosides and peptide nucleic acids, which, in turn, has led to the development of new drugs based on purines [4–11] (Figure 1).

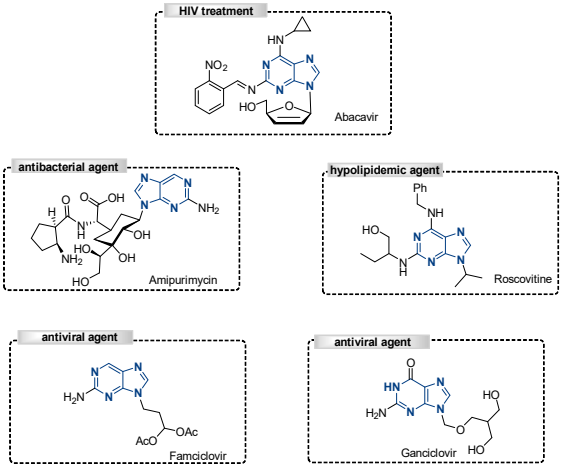
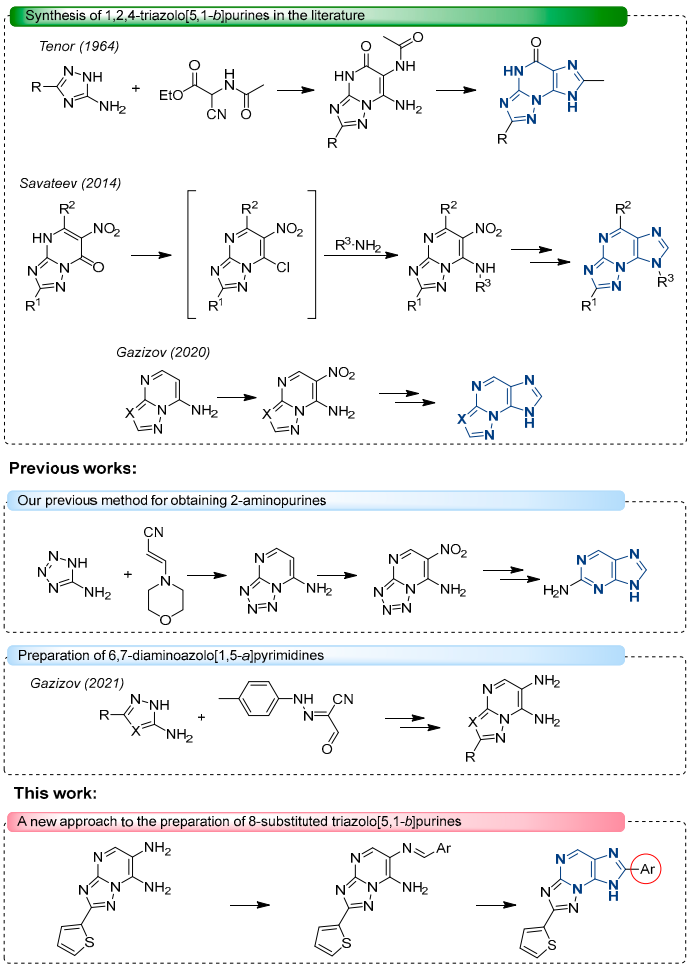


Figure 1. Examples of purine-based drugs.

Indeed, drugs based on natural purines are used to treat different types of cancer [12–15], including leukemia, with medications that have different mechanisms of action [16,17];

they are also included in antiretroviral therapy, one of the few ways to treat HIV [18–20]. Originally, such drugs were guanine- and adenine-based nucleosides [21,22], but subsequently, self-modified aglycones were also used. Some of these modified systems include 2-aminopurine derivatives that are not direct analogs of guanine [23,24]. Not only do 2-aminopurines have a wide range of biological activities [25–28] but they also exhibit fluorescent properties [29,30], which provide possibilities for their use in analyzing the geometry and dynamics of nucleic acids [31,32]. Based on this, it is essential to develop new polycyclic structures based on 2-aminopurine to obtain compounds for the use as potential drugs or organic luminescent materials.

By polycyclic structures, we primarily refer to azoloannelated purines, namely triazolo [5,1-*b*]purines. In the literature, there are few methods for obtaining such heterocyclic systems, and all involve the sequential annelation of the pyrimidine cycle to the 1,2,4-triazole moiety, followed by the formation of the imidazole ring (Scheme 1). For example, Tenor and Kröger use 2-acetamidocyanoacetic ester for this purpose [33], while in more recent work, the construction is based on the corresponding nitro derivatives [34,35]. Previously, we developed a method for the preparation of 2-aminopurine starting from aminotetrazole [36], and a preparation of 6,7-diaminoazolo [1,5-*a*]pyrimidines was proposed in Gazizov's publication [37,38]. Combining the ideas of these works, the present study, proposes a new approach to obtain C-8 modified triazolo[5,1-*b*]purines, starting from 6,7-diamino-2-thienyl-1,2,4-triazolo[1,5-*a*]pyrimidine and involving oxidation of the corresponding Schiff bases.



Scheme 1. State-of-the-art and current work [33–36,38].

2. Materials and Methods

Commercial reagents were obtained from Sigma-Aldrich (Burlington, MA, USA), Acros Organics (Antwerpen, Belgium), or Alfa Aesar (Ward Hill, MA, USA), and were used without preprocessing. All workup and purification procedures were performed using analytical-grade solvents. The spectra were acquired using a Bruker DRX-400 (Karlsruhe, Germany) spectrometer at 400 MHz (^{1}H) and 101 MHz (^{13}C), respectively, or a Bruker Avance NEO 600 instrument at 151 MHz (^{13}C), using DMSO-*d6* and CF_3COOD as solvents and an external reference, respectively. Chemical shifts are expressed in δ (parts per million, ppm) values and coupling constants are expressed in hertz (Hz). The following abbreviations are used for the multiplicity of NMR signals: s, singlet; d, doublet; t, triplet; dd, doublet of doublet; m, multiplet; and AN, anthracene. IR spectra were recorded on a Bruker α spectrometer equipped with a ZnSe ATR accessory. Elemental analysis was performed on a PerkinElmer PE 2400 elemental analyzer (Waltham, MA, USA). Melting points were determined on a Stuart SMP3 (Staffordshire, UK) and are uncorrected. Monitoring the reaction progress was completed using TLC on Sorbfil plates (Imid Ltd., Krasnodar, Russia) (the eluent is EtOAc, visualizing with UV light).

General procedure (1) for the synthesis of 4-(aryl)-amino)-2-(thiophen-2-yl)-[1,2,4]triazolo[1,5-*a*]pyrimidin-7-amine (**3a**–**g**).

To a suspension of 2.32 g (0.01 mol) 2-(thiophen-2-yl)-[1,2,4]triazolo[1,5-*a*]pyrimidin-6,7-diamine **1** in 20 mL DMF, the 0.01 mol of corresponding aldehyde **3a**–**g** and 10% mol (0.06 mL) of $MeSO_3H$ were added and the mixture was heated at 120 °C on an oil bath for 12 h. The reaction mixture was cooled to room temperature and the precipitate was filtered. The precipitate was then washed with MeOH and Et_2O.

6-((4-(Dimethylamino)benzylidene)amino)-2-(thiophen-2-yl)-[1,2,4]triazolo[1,5-*a*]pyrimidin-7-amine (**3a**). The reaction was performed according to the general procedure (1) employing 1.49 g (0.01 mol, 1 equiv.) of 4-(dimethylamino)benzaldehyde **2a**. Yellow powder. Yield 86% (3.12 g). mp. 283–285 °C. IR ν, cm^{-1}: 3270, 3233, 1276, 1237. ^{1}H NMR (400 MHz, DMSO-d_6) δ, ppm (*J*, Hz): 8.73 (1H, s, -CH=N), 8.55 (1H, s, H-4), 7.91 (4H, m, H-2″, H-3″, H-5″, H-6″), 7.84 (1H, d, *J* = 3.6 Hz, H-3′), 7.74 (1H, d, *J* = 5.0 Hz, H-5′), 7.25 (1H, t, *J* = 3.5 Hz, H-4′), 6.79 (2H, d, *J* = 8.5 Hz, NH_2), 3.03 (6H, s, $(CH_3)_2$). ^{13}C NMR (101 MHz, DMSO-d_6) δ, ppm (*J*, Hz): 160.61, 157.70, 155.01, 152.92, 145.25, 142.55, 134.46 (2C), 131.01 (2C), 129.19, 128.57, 128.11, 124.82, 118.91, 118.87 (2C). Calculated for $C_{18}H_{17}N_7S$: C 59.49, H 4.71, N, 26.98; found: C 59.41, H 4.76, N 27.04.

6-((4-Methoxybenzylidene)amino)-2-(thiophen-2-yl)-[1,2,4]triazolo[1,5-*a*]pyrimidin-7-amine (**3b**). The reaction was performed according to the general procedure (1) employing 1.36 g (0.01 mol, 1 equiv.) of 4-methoxybenzaldehyde **2b**. Yellow powder. Yield 81% (2.83 g). mp. >300 °C. IR ν, cm^{-1}: 3265, 3235, 1218, 1178. ^{1}H NMR (400 MHz, DMSO-d_6) δ, ppm (*J*, Hz): 8.86 (1H, s, -CH=N), 8.62 (1H, s, H-4), 8.21 (2H, s, NH_2), 8.06 (2H, d, *J* = 8.7, H-2″, H-6″), 7.85 (1H, dd, *J* = 3.7, 1.3 Hz, H-3′), 7.76 (1H, dd, *J* = 5.0, 1.3 Hz, H-5′), 7.25 (1H, dd, *J* = 5.0, 3.6 Hz, H-4′), 7.06 (d, *J* = 8.7 Hz, 2H, H-3″, H-5″), 3.85 (3H, s, CH_3). ^{13}C NMR (101 MHz, DMSO-d_6) δ, ppm (*J*, Hz): 161.77, 160.09, 156.38, 154.75, 145.12, 142.30, 133.79, 130.72 (2C), 129.40, 128.91, 128.20, 127.76, 117.52, 114.06 (2C), 55.40. Calculated for $C_{17}H_{14}N_6OS$: C 58.27, H 4.03, N, 23.98; found: C 58.21, H 4.14, N 23.94.

6-((Anthracen-9-ylmethylene)amino)-2-(thiophen-2-yl)-[1,2,4]triazolo[1,5-a]pyrimidin-7-amine (3c). The reaction was performed according to the general procedure (1) employing 2.06 g (0.01 mol, 1 equiv.) of 9-anthracenecarboxaldehyde **2c**. Orange powder. Yield 82% (3.44 g). mp. 270–272 °C. IR ν, cm^{-1}: 3404, 3143, 1278, 1217. ^{1}H NMR (400 MHz, DMSO-d_6) δ, ppm (*J*, Hz): 10.08 (1H, s, -CH=N), 8.62 (1H, s, H-4), (3H, m, 3x H_{AN}), 8.80 (1H, s, H-4), 8.19 (2H, d, *J* = 8.2 Hz, 2x H_{AN}), 8.15 (2H, s, NH_2), 7.89 (1H, dd, *J* = 3.7, 1.2 Hz, H-3′), 7.79 (1H, dd, *J* = 5.0, 1.2 Hz, H-5′), 7.63 (4H, m, 4x H_{AN}), 7.27 (1H, dd, *J* = 5.0, 3.6 Hz, H-4′). ^{13}C NMR (101 MHz, DMSO-d_6) δ, ppm (*J*, Hz): 160.73, 158.08, 155.52, 145.46, 143.85, 134.25, 131.35 (4C), 130.98, 130.70 (4C), 129.50, 129.34, 128.72, 128.36, 127.99, 127.84, 126.09, 125.82, 119.58. Calculated for $C_{24}H_{16}N_6S$: C 68.55, H 3.84, N, 19.99; found: C 68.50, H 3.89, N 19.27.

2-(Thiophen-2-yl)-6-((thiophen-3-ylmethylene)amino)-[1,2,4]triazolo[1,5-*a*]pyrimidin-7-amine (**3d**). The reaction was performed according to the general procedure (1) employing 1.12 g (0.01 mol, 1 equiv.) of thiophene-2-carboxaldehyde **2d**. Yellow powder. Yield 68% (2.22 g). mp. >300 °C. IR ν, cm^{-1}: 3407, 3231, 1258. ^{1}H NMR (400 MHz, DMSO-d_6) δ, ppm (*J*, Hz): 9.04 (1H, s, -CH=N), 8.56 (1H, s, H-4), 7.84 (1H, d, *J* = 3.6 Hz, H_{thpen}), 7.81 (2H, s, NH_2), 7.68 (1H, dd, *J* = 15.9, 4.3 Hz, H_{thpen}), 7.66 (1H, dd, *J* = 13.1, 3.6 Hz, H-5_{thpen}), 7.62 (1H, dd, *J* = 5.1, 1.6 Hz, H_{thpen}), 7.19 (q, *J* = 4.5 Hz, 2H, H_{thpen}). ^{13}C NMR (101 MHz, DMSO-d_6) δ, ppm (*J*, Hz): 160.64, 155.27, 151.62, 145.23, 143.35, 143.19, 134.20, 133.24, 131.80, 129.46, 128.70, 128.60, 128.30, 117.88. Calculated for $C_{14}H_{10}N_6S_2$: C 51.52, H 3.09, N, 25.75; found: C 51.43, H 3.18, N 25.79.

6-((4-Bromobenzylidene)amino)-2-(thiophen-2-yl)-[1,2,4]triazolo[1,5-*a*]pyrimidin-7-amine (**3e**). The reaction was performed according to the general procedure (1) employing 1.85 g (0.01 mol, 1 equiv.) of 4-bromobenzaldehyde **2e**. Light green crystalline powder. Yield 70% (2.79 g). mp. >300 °C. IR ν, cm^{-1}: 3238, 1258. ^{1}H NMR (600 MHz, DMSO-d_6) δ, ppm (*J*, Hz): 8.99 (1H, s, -CH=N), 8.83 (1H, s, H-4), 8.77 (1H, dd, *J* = 4.5, 1.3 Hz, H_{ar}), 8.62 (2H, s, NH_2), 8.57 (1H, dd, *J* = 8.0, 1.1 Hz, H_{ar}), 8.12 (1H, m, H-3′), 7.86 (1H, dd, *J* = 3.6, 1.3 Hz, H_{ar}), 7.78 (1H, dd, *J* = 4.9, 1.2 Hz, H_{ar}), 7.63 (1H, ddd, *J* = 7.4, 5.0, 1.3 Hz, H-5′), 7.25 (1H, m, H-4′). ^{13}C NMR (151 MHz, DMSO-d_6) δ, ppm (*J*, Hz): 160.30, 155.04, 153.16, 152.74, 147.93, 146.19, 142.75, 133.39 (2C), 129.29, 128.33 (2C), 128.15, 125.77, 123.26, 115.58. Calculated for $C_{16}H_{11}BrN_6S$: C 48.13, H 2.78, N, 21.05; found: C 48.18, H 2.75, N 21.03.

6-((Pyridin-2-ylmethylene)amino)-2-(thiophen-2-yl)-[1,2,4]triazolo[1,5-*a*]pyrimidin-7-amine (**3f**). The reaction was performed according to the general procedure (1) employing 1.07 g (0.01 mol, 1 equiv.) of 3-pyridinecarboxaldehyde **2f**. Dark yellow powder. Yield 65% (2.08 g). mp. 183–185 °C. IR ν, cm^{-1}: 3449, 3083, 1186. ^{1}H NMR (400 MHz, DMSO-d_6) δ, ppm (*J*, Hz): 8.93 (1H, s, -CH=N), 8.74 (1H, s, H-4), 8.69 (1H, d, *J* = 4.0 Hz H-3′), 8.60 (1H, d, *J* = 8.0 Hz, H-6″), 8.30 (2H, s, NH_2), 7.93 (1H, td, *J* = 7.7, 1.8 Hz, H-4″), 7.85 (1H, dd, *J* = 3.6, 1.2 Hz, H-5′), 7.65 (1H, dd, *J* = 5.0, 1.2 Hz, H-4′), 7.47 (1H, dd, *J* = 7.4, 4.8 Hz, H-5″), 7.21 (1H, dd, *J* = 5.0, 3.6 Hz, H-3″). ^{13}C NMR (151 MHz, DMSO-d_6) δ, ppm (*J*, Hz): 160.29, 155.07, 153.60, 153.09, 148.17, 146.11, 142.80, 138.72, 133.43, 129.25, 128.31, 128.11, 125.66, 123.01, 115.64. Calculated for $C_{15}H_{11}N_7S$: C 56.06, H 3.45, N, 30.51; found: C 56.11, H 3.44, N 30.57.

6-((4-(Diphenylamino)benzylidene)amino)-2-(thiophen-2-yl)-[1,2,4]triazolo[1,5-*a*]pyrimidin-7-amine (**3g**). The reaction was performed according to the general procedure (1) employing 2.73 g (0.01 mol, 1 equiv.) of 4-(diphenylamino)benzaldehyde **2g**. Yellow powder. Yield 61% (2.97 g). mp. 265–267 °C. IR ν, cm^{-1}: 3444, 3057, 1274. ^{1}H NMR (400 MHz, DMSO-d_6) δ, ppm (*J*, Hz): 8.81 (1H, s, -CH=N), 8.60 (1H, s, H-4), 8.16 (2H, s, NH_2), 7.95 (2H, d, *J* = 8.4 Hz, H_{C6H4}), 7.83 (H, m, H_{Ph}), 7.75 (H, m, H_{Ph}), 7.37 (4H, t, *J* = 7.7 Hz, H_{Ph}), 7.23 (H, dd, *J* = 5.0, 3.6 Hz, H_{Ph}), 7.13 (6H, m, H_{Ph}), 6.96 (2H, d, *J* = 8.3 Hz, H_{C6H4}). ^{13}C NMR (101 MHz, DMSO-d_6) δ, ppm (*J*, Hz): 160.07, 156.06, 154.71, 149.93, 146.38 (2C), 145.05, 142.24, 133.79, 130.22 (2C), 129.74 (4C), 128.88, 128.17, 127.72, 125.19 (4C), 124.25 (2C), 120.57 (2C), 117.65 (2C). Calculated for $C_{28}H_{21}N_7S$: C 68.97, H 4.34, N, 20.11; found: C 69.04, H 4.29, N 20.17.

General procedure (2) for the synthesis of aryl-4-(2-(thiophen-2-yl)-*6H*-[1,2,4]triazolo [5,1-*b*]purin-7-yl)aniline (**4a**–**g**) is as follows:

To a solution of the corresponding Schiff base (0.001 mol), **3a**–**g** in 5 mL CF_3COOH and 0.40 g (0.00125 mol, 1.25 equiv.) of $PhI(OAc)_2$ were added. The reaction mixture was stirred at room temperature for 4 h. Then, 5 mL MeOH was added to the reaction mixture. The resulting solution was stirred for another 15 min and then evaporated. The residue was purified by flash chromatography; eluent—$CHCl_3$/MeOH (9/1).

N,*N*-Dimethyl-4-(2-(thiophen-2-yl)-*6H*-[1,2,4]triazolo[5,1-*b*]purin-7-yl)aniline (**4a**). The reaction was performed according to the general procedure (2) employing 0.45 g (0.00125 mol, 1 equiv.) of ((4-(dimethylamino)benzylidene)amino)-2-(thiophen-2-yl)-[1,2,4]triazolo [1,5-*a*]pyrimidin-7-amine **3a**. Yellow powder. Yield 60% (0.27 g). mp. 275-277 °C. IR ν, cm^{-1}: 3088, 3059, 1133, 1094. ^{1}H NMR (400 MHz, DMSO-d_6) δ, ppm (*J*, Hz): 13.71 (1H, s, NH), 8.94 (1H, s, H-4), 8.10 (2H, d, *J* = 8.8 Hz, H-2″, H-6″), 7.87 (1H, dd, *J* = 3.6, 1.2 Hz,

H-3′), 7.61 (1H, dd, *J* = 5.0, 1.2 Hz, H-5′), 7.21 (1H, dd, *J* = 5.0, 3.6 Hz, H-4′), 6.83 (2H, d, *J* = 8.8 Hz, H-3″, H-5″), 3.10 (6H, s, $(CH3)_2$). ^{13}C NMR (101 MHz, DMSO-d_6) δ, ppm (*J*, Hz): 159.24, 154.93, 153.95, 152.14, 144.88, 139.03, 133.84, 128.45 (2C), 128.31, 127.99, 127.18, 120.37, 114.47, 111.62 (2C), 40.3 (2C). Calculated for $C_{18}H_{15}N_7S$: C 59.82, H 4.18, N, 27.13; found: C 59.78, H 4.23, N 27.04.

7-(4-Methoxyphenyl)-2-(thiophen-2-yl)-*6H*-[1,2,4]triazolo[5,1-*b*]purine (**4b**). The reaction was performed according to the general procedure (2) employing 0.44 g (0.00125 mol, 1 equiv.) of ((4-methoxybenzylidene)amino)-2-(thiophen-2-yl)-[1,2,4]triazolo[1,5-*a*]pyrimidin-7-amine **3b**. White powder. Yield 66% (0.28 g). mp. >300 °C. IR ν, cm^{-1}: 3061, 2839, 1438, 1177. ^{1}H NMR (400 MHz, DMSO-d_6) δ, ppm (*J*, Hz): 13.99 (1H, s, NH), 9.03 (1H, s, H-4), 8.24 (2H, d, *J* = 8.8 Hz, H-2″, H-6″), 7.88 (1H, dd, *J* = 3.6, 1.2 Hz, 1H, H-3′), 7.62 (1H, d, *J* = 5.0 Hz, 1H, H-5′), 7.21 (1H, dd, *J* = 5.0, 3.6 Hz, H-4′), 7.12 (2H, d, *J* = 8.6 Hz, H-3″, H-5″), 4.04 (3H, s, CH_3). ^{13}C NMR (101 MHz, DMSO-d_6) δ, ppm (*J*, Hz): 161.92, 159.46, 154.14, 153.78, 144.57, 140.30, 133.84, 129.05 (2C), 128.69, 128.29, 127.48, 120.65, 120.49, 114.77 (2C), 55.52. Calculated for $C_{17}H_{12}N_7OS$: C 58.61, H 3.47, N, 24.12; found: C 58.52, H 3.55, N 24.08.

7-(Anthracen-9-yl)-2-(thiophen-2-yl)-*6H*-[1,2,4]triazolo[5,1-*b*]purine (**4c**). The reaction was performed according to the general procedure (2) employing 0.52 g (0.00125 mol, 1 equiv.) of (anthracen-9-ylmethylene)amino)-2-(thiophen-2-yl)-[1,2,4]triazolo[1,5-*a*]pyrimidin-7-amine **3c**. Orange powder. Yield 59% (0.31 g). mp. >300 °C °C. IR ν, cm^{-1}: 3378, 3363, 1057. ^{1}H NMR (400 MHz, DMSO-d_6) δ, ppm (*J*, Hz): 14.59 (1H, s, NH), 9.29 (1H, s, H-4), 8.95 (1H, s, H_{AN}), 8.27 (2H, d, *J* = 8.3 Hz, 2H, H_{AN}), 7.93 (1H, dd, *J* = 3.7, 1.2 Hz, H-3′), 7.84 (2H, d, *J* = 8.6 Hz, H_{AN}), 7.78 (1H, d, *J* = 5.0, H-5′), 7.60 (5H, m, H-5′, H_{AN}), 7.22 (1H, dd, *J* = 5.0, 3.6 Hz, H-4′). ^{13}C NMR (101 MHz, DMSO-d_6) δ, ppm (*J*, Hz): 159.56, 154.22, 152.17, 144.46, 133.78 (2C), 130.61 (2C), 130.55 (2C), 130.18, 128.75 (2C), 128.66, 128.33 (2C), 127.55, 127.48, 125.87 (2C), 125.27 (2C), 123.16, 120.64. Calculated for $C_{24}H_{14}N_6S$: C 68.88, H 3.37, N, 20.08; found: C 68.80, H 3.35, N 20.03.

2,7-Di(thiophen-2-yl)-*6H*-[1,2,4]triazolo[5,1-*b*]purine (**4d**). The reaction was performed according to the general procedure (2) employing 0.41 g (0.00125 mol, 1 equiv.) of 2-(thiophen-2-yl)-6-((thiophen-2-ylmethylene)amino)-[1,2,4]triazolo[1,5-*a*]pyrimidin-7-amine **3d**. Gray powder. Yield 62% (0.25 g). mp. 254–256 °C. IR ν, cm^{-1}: 3082, 1281, 1189. ^{1}H NMR (400 MHz, DMSO-d_6) δ, ppm (*J*, Hz): 14.46 (1H, s, NH), 9.10 (1H, s, H-4), 8.06 (1H, d, *J* = 3.8 Hz, H-3″), 7.95 (1H, d, *J* = 5.0 Hz, H-5″), 7.90 (1H, dd, *J* = 3.6, 1.2 Hz, H-3′), 7.77 (1H, d, *J* = 5.0 Hz, H-5′), 7.33 (1H, dd, *J* = 5.0, 3.7 Hz, H-4″), 7.25 (1H, dd, *J* = 5.1, 3.6 Hz, H-4′). ^{13}C NMR (101 MHz, DMSO-d_6) δ, ppm (*J*, Hz): 159.56, 154.18, 149.12, 133.73 (2C), 131.73 (2C), 131.32 (2C), 129.38, 128.97, 128.78, 128.31, 127.54. Calculated for $C_{14}H_8N_6S_2$: C 51.84, H 2.49, N, 25.91; found: C 51.79, H 2.45, N 25.90.

7-(4-Bromophenyl)-2-(thiophen-2-yl)-*6H*-[1,2,4]triazolo[5,1-*b*]purine (**4e**). The reaction was performed according to the general procedure (2) employing 0.49 g (0.00125 mol, 1 equiv.) of ((4-bromobenzylidene)amino)-2-(thiophen-2-yl)-[1,2,4]triazolo[1,5-*a*]pyrimidin-7-amine **3e**. Yellow powder. Yield 66% (0.33 g). mp. >300 °C. IR ν, cm^{-1}: 3081, 1087, 1044. ^{1}H NMR (600 MHz, DMSO-d_6) δ, ppm (*J*, Hz): 14.52 (1H, s, NH), 9.16 (1H, s, H-4), 8.24 (2H, m, H-2″, H-6″), 7.90 (1H, dd, *J* = 3.5, 1.2 Hz, H-3′), 7.86 (2H, m, H-3″, H-5″), 7.77 (1H, dd, *J* = 5.0, 1.2 Hz, H-5′), 7.25 (1H, dd, *J* = 5.0, 3.6 Hz, H-4′). ^{13}C NMR (151 MHz, DMSO-d_6 + CF_3COOD) δ, ppm (*J*, Hz): 159.56, 154.22, 152.41 (2C), 144.23, 141.17, 133.71, 132.43 (2C), 129.13 (2C), 128.82, 128.35, 127.58, 127.46, 125.23. Calculated for $C_{16}H_9BrN_6S$: C 48.38, H 2.28, N, 21.16; found: C 48.43, H 2.26, N 21.21.

7-(Pyridin-2-yl)-2-(thiophen-2-yl)-*6H*-[1,2,4]triazolo[5,1-*b*]purine (**4f**). The reaction was performed according to the general procedure (2) employing 0.40 g (0.00125 mol, 1 equiv.) of ((pyridin-2-ylmethylene)amino)-2-(thiophen-2-yl)-[1,2,4]triazolo[1,5-*a*]pyrimidin-7-amine **3f**. Beige powder. Yield 64% (0.25 g). mp. >300 °C. IR ν, cm^{-1}: 3084, 3029, 1140. ^{1}H NMR (600 MHz, DMSO-d_6+CF_3COOD) δ, ppm (*J*, Hz): 9.03 (1H, s, H-4), 8.75 (1H, d, *J* = 4.8 Hz, H-2″), 8.41 (1H, d, *J* = 7.8 Hz, H-5″), 8.04 (1H, td, *J* = 7.7, 1.7 Hz, H-4″), 7.88 (1H, dd, *J* = 3.5, 1.2 Hz, H-3′), 7.68 (1H, d, *J* = 5.0 Hz, H-5′), 7.57 (1H, dd, *J* = 7.6, 4.8 Hz, H-3″), 7.19 (1H, dd, *J* = 5.0, 3.5 Hz, H-4′). ^{13}C NMR (151 MHz, DMSO-d_6+CF_3COOD) δ, ppm (*J*, Hz): 159.36,

154.12, 152.82, 150.08, 146.73, 144.97, 142.44, 138.96, 133.56, 129.50, 128.82, 128.60, 126.72, 123.52, 121.66. Calculated for $C_{15}H_9N_7S$: C 56.42, H 2.84, N, 30.70; found: C 56.51, H 2.91, N 30.65.

N,*N*-Diphenyl-4-(2-(thiophen-2-yl)-*6H*-[1,2,4]triazolo[5,1-*b*]purin-7-yl)aniline (**4g**). The reaction was performed according to the general procedure (2) employing 0.61 g (0.00125 mol, 1 equiv.) of ((4-(diphenylamino)benzylidene)amino)-2-(thiophen-2-yl)-[1,2,4]triazolo[1,5-*a*]pyrimidin-7-amine **3g**. Yellow powder. Yield 67% (0.41 g). mp. >300 °C. IR ν, cm^{-1}: 1453, 1315, 1272. ^{1}H NMR (400 MHz, DMSO-d_6) δ, ppm (*J*, Hz): 14.13 (1H, s, NH), 9.06 (1H, s, H-4), 8.16 (2H, d, *J* = 8.5 Hz, H_{C6H4}), 7.91 (1H, d, *J* = 4.0 Hz, H-3′), 7.76 (1H, d, *J* = 5.0 Hz, H-5′), 7.42 (4H, t, *J* = 7.7 Hz, H_{Ph}), 7.26 (1H, t, *J* = 4.3 Hz, H-4′), 7.20 (6H, m, H_{Ph}), 7.06 (2H, d, *J* = 8.5 Hz, H_{C6H4}).^{13}C NMR (101 MHz, DMSO-d_6) δ, ppm (*J*, Hz): 160.07, 154.75, 154.28, 150.87, 146.66 (4C), 134.44 (2C), 130.36 (4C), 129.12 (2C), 128.69, 127.91, 126.18 (4C), 125.20 (3C), 120.77 (3C). Calculated for $C_{28}H_{19}N_7S$: C 69.26, H 3.94, N, 20.19; found: C 69.34, H 3.88, N 20.22.

The procedure for the synthesis of 7-(thiophen-2-yl)-*3H*-[1,2,3]triazolo[4,5-*e*][1,2,4]triazolo[1,5-*a*]pyrimidine (**5**) is as follows:

To a mixture of 5.0 mL acetic acid and 0.350 mL of isoamyl nitrite (0.0026 mol), 0.3 g (0.0013 mol) of 2-(thiophen-2-yl)-[1,2,4]triazolo[1,5-*a*]pyrimidine-6,7-diamine was added, **1** and the mixture was heated at 60 °C on an oil bath for 5 h. The resulting suspension was cooled to room temperature and the precipitate was filtered out to give the pure product.

7-(Thiophen-2-yl)-3H-[1,2,3]triazolo[4,5-*e*][1,2,4]triazolo[1,5-*a*]pyrimidine (**5**). Yellow powder. Yield 58% (0.18 g). mp. >300 °C. IR ν, cm^{-1}: 3082, 1513. ^{1}H NMR (400 MHz, DMSO-d_6) δ, ppm (*J*, Hz): 9.66 (1H, s, H-4), 7.90 (1H, dd, *J* = 3.6, 1.3 Hz, H-3′), 7.79 (1H, dd, *J* = 5.0, 1.3 Hz, H-5′), 7.26 (1H, dd, *J* = 5.0, 3.6 Hz, H-4′). ^{13}C NMR (101 MHz, DMSO-d_6) δ, ppm (*J*, Hz): 159.86, 154.79, 149.00, 143.15, 132.90, 129.42, 129.16, 128.42, 127.94. Calculated for $C_9H_5N_7S$: C 44.44, H 2.07, N, 40.31; found: C 44.37, H 2.12, N 40.33.

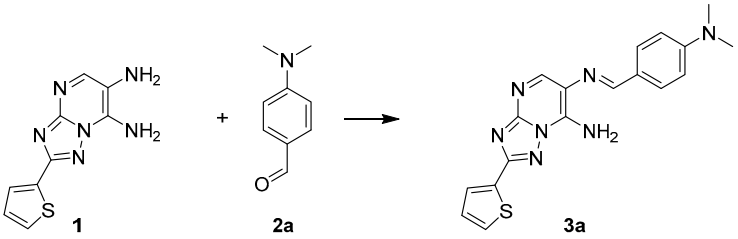
The procedure for the synthesis of 7-methyl-2-(thiophen-2-yl)-*6H*-[1,2,4]triazolo[5,1-*b*]purine (**6**) is as follows:

To a mixture of 3.0 mL (0.018 mol) of triethylorthoacetate and 1.0 mL (0.01 mol) of acetic anhydride, 0.3 g (0.0013 mol) of 2-(thiophen-2-yl)-[1,2,4]triazolo[1,5-*a*]pyrimidine-6,7-diamine was added **1** and the mixture was heated at 145 °C on an oil bath for 4 h. The resulting solution was evaporated and 5.0 mL acetone was added. The precipitate was filtered out to provide the pure product.

7-Methyl-2-(thiophen-2-yl)-*6H*-[1,2,4]triazolo[5,1-*b*]purine (**6**). Brown powder. Yield 62% (0.21 g). mp. >300 °C. IR ν, cm^{-1}: 3334, 1284. ^{1}H NMR (400 MHz, DMSO-d_6) δ, ppm (*J*, Hz): 13.69 (1H, s, NH), 9.03 (1H, s, H-4), 7.85 (1H, dd, *J* = 3.7, 1.2 Hz, H-3′), 7.74 (1H, dd, *J* = 5.0, 1.2 Hz, H-5′), 7.24 (1H, dd, *J* = 5.0, 3.6 Hz, H-4′), 2.65 (3H, s, CH_3). ^{13}C NMR (101 MHz, DMSO-d_6) δ, ppm (*J*, Hz): 159.37, 155.36, 153.90, 144.15, 140.33, 133.84, 128.63, 128.25, 127.39, 119.61, 14.97. Calculated for $C_{11}H_8N_6S$: C 51.55, H 3.15, N, 32.79; found: C 51.50, H 3.19, N 32.70.

3. Results and Discussion

To obtain 8-substituted triazolo[5,1-*b*]purines, we selected 2-(thiophen-2-yl)-6,7-diamino-1,2,4-triazolo[1,5-*a*]pyrimidine **1** as an initial substrate since it is fairly easy to synthesize according to the method [14] and it has an additional conjugated heterocyclic ring, allowing us to obtain a polycyclic purine structure. First, we optimized the reaction of diamine **1** with 4-(*N*,*N*-dimethylamino)benzaldehyde **2a** (Scheme 2) under various conditions as shown in Table 1.



Scheme 2. Preparation of the Schiff base **3a**.

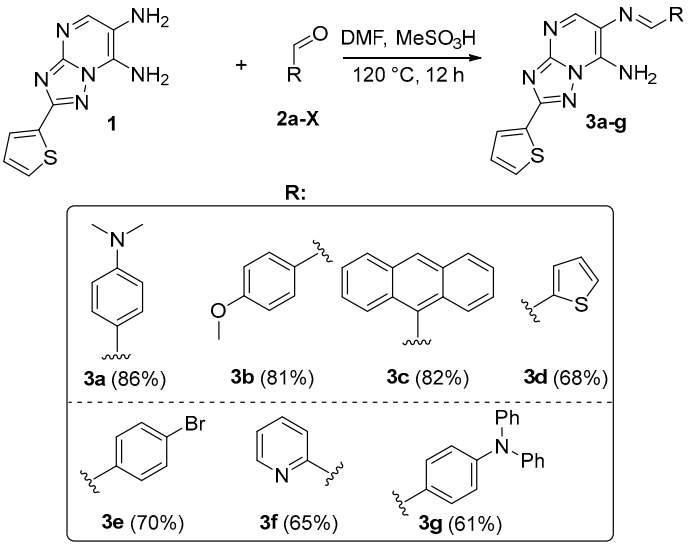
Table 1. Optimization of condensation reaction [1].

Entry	Solvent [2]	Catalyst	Temp (°C)	Yield (%) [3]
entry 1	MeOH	-	reflux	45
entry 2	EtOH	-	reflux	39
entry 3	MeCN	-	reflux	33
entry 4	DMF	-	120	48
entry 5	MeOH	$MeSO_3H$ (10% mol)	reflux	62
entry 6	EtOH	$MeSO_3H$ (10% mol)	reflux	47
entry 7	DMF	$MeSO_3H$ (10% mol)	120	86
entry 8	DMF	$MeSO_3H$ (15% mol)	120	86

[1] Reaction conditions: **1** (0.10 mol), [2] amount of solvent—20 mL, reflux, 12 h, conventional heating with an oil bath, and [3] isolated yields.

It was found that boiling the starting reagents in MeOH, EtOH, MeCN, and DMF without a catalyst for 12 h allowed us to obtain the desired product **3a** with low yields (Table 1, entry 1-4). At the same time, boiling compounds **1** and **2a** in DMF in the presence of methanesulfonic acid led to a significant increase in the conversion of the reaction and easier purification of the product.

With the optimized condition in hand, we carried out the reaction of triazolo[1,5-*a*]pyrimidine-6,7-diamine **1** with various aromatic aldehydes (Scheme 3). Moreover, products **3a**–**g** have been isolated as pure solids by simple filtration of the reaction mixture, which is a significant advantage of the synthetic procedure.



Scheme 3. Preparation of the Schiff bases **3a**–**g**.

All synthesized compounds were fully characterized using ^{1}H-NMR, ^{13}C-NMR, IR-spectroscopy, and elemental analysis. In addition, based on the ^{1}H-^{13}C HMBC correlation data of compound **3b**, it was established that the condensation reaction involves exclusively the amino group in position **6** of the azolopyrimidine system (Figure 2), since the -CH=N

group proton (8.85 ppm) has cross-peaks with C-5 (142.77 ppm) C-2′, C-6′ (131.15 ppm) and C-1′ (129.39 ppm) carbon atoms.

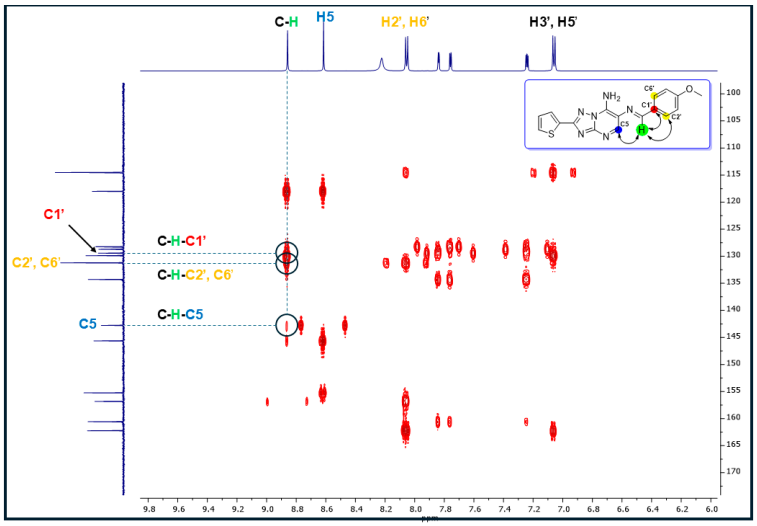
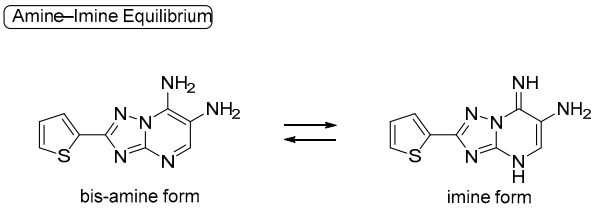


Figure 2. Key interactions of the proton of the methylene fragment in compound **3b**.

The experimental data obtained correlate with the results from the literature [39–41]. It can be assumed that the increased nucleophilicity of the amino group at position 6 of 6,7-diamino-1,2,4-triazolo[1,5-*a*]pyrimidine **1** is caused by the rapid establishment of equilibrium between amine and imine forms [42], as shown in Scheme 4.



Scheme 4. Amine–Imine equilibrium.

The next step was the oxidation of the obtained imines **3a**–**g** into the corresponding azolopurines. As in the previous step, we conducted an optimization of oxidation reaction conditions using different oxidizing agents. The results are summarized in Table 2.

Table 2. Optimization of oxidation reaction [1].

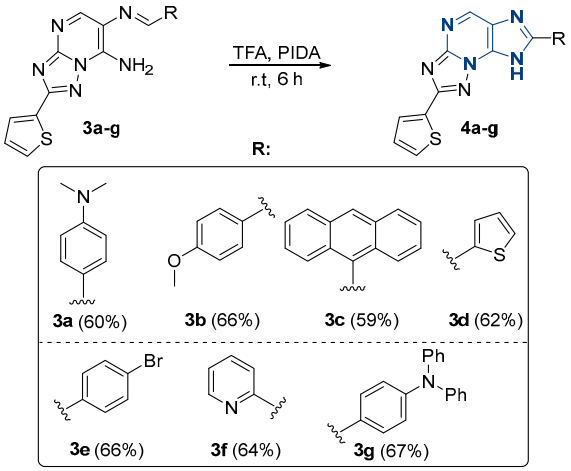
Entry	Oxidant	Solvent [2]	Temp (°C)	t (h)	Yield (%) [3]
entry 1	Pb_3O_4	MeOH	-	3	-
entry 2	DDQ	EtOH	-	12	-
entry 3	$CuCl_2$	MeCN	-	4	-
entry 4	$Cu(CH_3COO)_2$	DMF	-	4	-
entry 5	H_2O_2	-	90	5	-
entry 6	MnO_2	DMF	100	3	-
entry 7	PCC	AcOH	100	6	-
entry 8	PCC	DMF	100	4	27
entry 9	$PhI(OAc)_2$	HCOOH	100	6	23
entry 10	$PhI(OAc)_2$	TFA	r.t	6	60

[1] Reaction conditions: **3a** (0.10 mol), [2] amount of solvent—3 mL, conventional heating with an oil bath, and [3] isolated yields.

Interestingly, the oxidation of Schiff base **3a** turned out to be a non-trivial process. We determined that literature methods for similar processes were not applicable to this

compound. For example, the reaction did not proceed with red lead (Table 2, entry 1) and DDQ (Table 2, entry 2), which are often used in the formation of heterocyclic C-N bonds [43]. Copper (II) salts (Table 2, entry 3, 4) [44] as well as such inorganic oxidizing agents, such as hydrogen peroxide (Table 2, entry 5) and manganese (IV) oxide (Table 2, entry 6), did not show any effect [35]. Interestingly, oxidation occurred with a low yield when using PCC in dimethylformamide upon heating (Table 2, entry 8), while it did not occur when heated in acetic acid (Table 2, entry 7). Finally, using the derivative of hypervalent iodine, namely (diacetoxyiodo)benzene, was successful. It was found that oxidation proceeded by heating in formic acid, but the conversion was low (Table 2, entry 8), however, carrying out the reaction in trifluoroacetic acid at room temperature resulted in product **4a** with 60% yield (Table 2, entry 9).

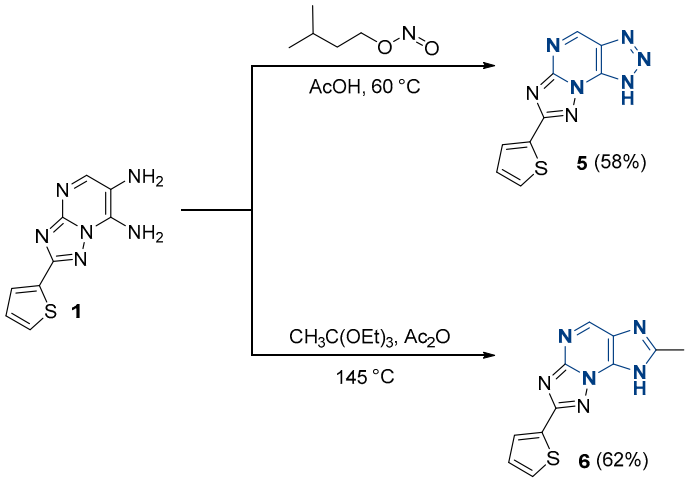
Thus, using the optimized reaction conditions we performed the oxidation of the obtained Schiff bases **3a**–**g** into the corresponding azolopurines **4a**–**g** with yields from 59 to 67%. It should be noted that all derivatives **4a**–**g** were obtained with comparable yields, which indicates an insignificant influence of the nature of the substituents on the oxidation process (Scheme 5). All the synthesized compounds were fully characterized using ^{1}H-NMR, ^{13}C-NMR, IR-spectroscopy, and elemental analysis (Supplementary Materials).



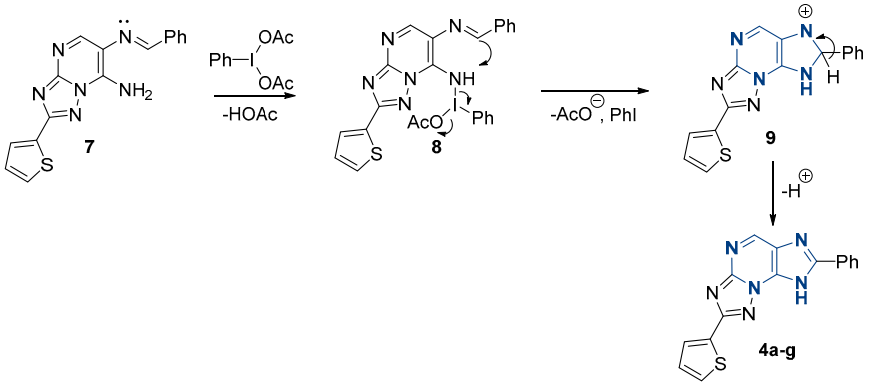
Scheme 5. Preparation of Schiff **4a**–**g** bases.

In addition, we studied the possibility of obtaining purines based on 2-(thiophen-2-yl)-6,7-diamino-1,2,4-triazolo[1,5-*a*]pyrimidine **1** by other methods. Thus, with the action of isoamyl nitrite on diamine **1** in acetic acid upon heating, 7-(thiophen-2-yl)-*1H*-[1,2,3]triazolo[4,5-*e*][1,2,4]triazolo[1,5-*a*]pyrimidine **6** was obtained with a 58% yield, and boiling **1** with triethylorthoacetate in acetic anhydride created 7-methyl-2-(thiophen-2-yl)-*8H*-[1,2,4]triazolo[5,1-*b*]purine in 62% yield (Scheme 6).

Based on the experimental data obtained and previously published studies on the use of (diacetoxyiodo)benzene as an oxidizing agent for the synthesis of condensed systems [45,46], a plausible reaction pathway was proposed (Scheme 7). The first step involves nucleophilic substitution of the acetoxy group of (diacetoxyiodo)benzene to form an intermediate **8**. In the next step, the amino cation is formed by eliminating iodobenzene. Subsequent intramolecular cyclization and aromatization lead to the formation of triazolo[5,1-*b*]purine.



Scheme 6. Preparation of azolopurines **5**,**6**.



Scheme 7. Plausible pathway of oxidation by PIDA.

4. Conclusions

Therefore, we have developed a method for the synthesis of novel 8-substituted triazolo[5,1-*b*]purines using (diacetoxyiodo)benzene as an oxidizing agent by intramolecular C-N bond formation with good yields (59–67%). The advantages of this approach include mild cyclization conditions and good yields of the reaction products. In addition, alternative methods for cyclization of the selected diamine have been proposed to obtain other azolopurine derivatives. The developed approach opens the possibility of obtaining previously inaccessible condensed purine derivatives, which are of interest for creating molecules with varied useful biological and photophysical properties.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/reactions5040058/s1, Figures S1–S33: ^{1}H-, ^{13}C-NMR and IR spectra of compounds **3a**–**g**, **4a**–**g**, **5**, **6**.

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Data Availability Statement: The original contributions presented in this study are included in the article/Supplementary Materials. Further inquiries can be directed to the corresponding authors.

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Conflicts of Interest: The authors declare no conflicts of interest.

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