Development of a Reproducible and Scalable Method for the Synthesis of Biologically Active Pyrazolo[1,5-*a*]pyrimidine Derivatives

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Abstract—A reproducible and scalable method has been developed for the synthesis of a series of 3,6-substituted pyrazolo[1,5-*a*]pyrimidines, which are the basis for the rational design of selective inhibitors of AMP-activated protein kinase. Regarding the formation of new types of the carbon skeleton, the applicability of the Suzuki–Miyaura cross-coupling using the Buchwald ligands to form C–C bond in the sterically hindered position 6 of 5,7-dimethyl-substituted pyrazolo[1,5-*a*]pyrimidine has been shown.

Keywords: pyrazolo[1,5-*a*]pyrimidine, pyridine-1*H*-pyrazol-5-amine, AMPK inhibitor, Compound C, cross-coupling

AMP-activated protein kinase (AMPK) is a key regulatory protein sustainably attracting the research interest. This is due to the fact that AMPK is strongly engaged in the energy homeostasis of individual cells as well as the whole organism [1]. Despite complex structure of the kinase existing as a multi-subunit complex, several approaches to its direct and indirect activation, including through the kinase-kinase processes, have been developed [2]. In view of this, the efforts have been mainly directed at the search and development of novel small molecule AMPK activators [3].

Evidently, the inhibition of such a multifunctional regulatory protein is of interest, in addition to the activation. This has been confirmed in the studies by a well-recognized specialist in the field, prof. Hardie [4]. However, whereas direct activation of AMPK is possible under the action of small molecule compounds affine to one of three activation sites, rather unique structure of which allows the development of selective activators [5, 6], it has been considered that the inhibitors can be only found among the compounds capable of direct interaction with the ATP-binding pocket due to the formation of hydrogen bonds similar to the interaction

of adenine. So far, two small molecule structures possessing a certain degree of selectivity in the inhibition of the AMPK activity have been known: dorsomorphin (Compound C) and SBI-0206965 [7, 8]. In view of extremely conserved nature of the ATP-binding pocket of kinases, the complexity of the development of highly selective inhibitors is obvious.
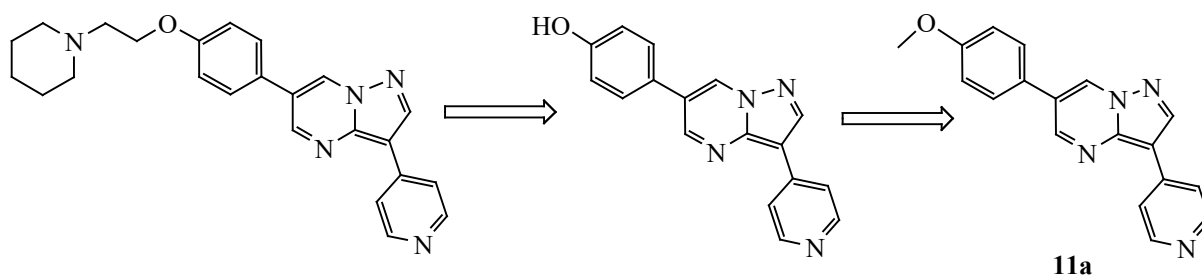
Historically, dorsomorphin (Scheme 1) was the first AMPK inhibitor. It was identified via the high-throughput screening. In further studies, dorsomorphin did not show significant inhibition of a series of kinases structurally
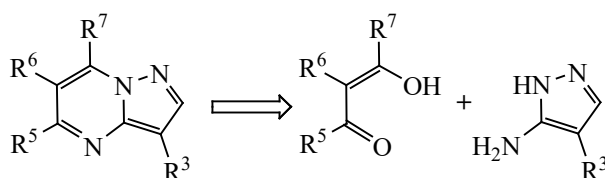
Scheme 1.
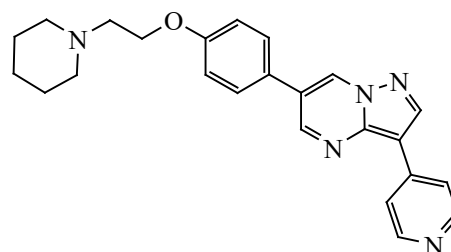
Dorsomorphin (Compound C)

Scheme 2.

Scheme 3.

related to AMPK and has been hence considered the first selective inhibitor of AMPK [9].

Despite strong interest to the modulation of the AMPK activity, neither systematic studies of the structure–activity relationships for dorsomorphin nor rational design of highly selective inhibitors of AMPK based on this molecule have been performed. At the same time, the ability of dorsomorphin to inhibit different kinases has attracted the attention of researchers. The attempts to change the target and investigate the structure–activity relationship of the derivatives of pyrazolo[1,5-*a*]pyrimidine with respect to KDR (Kinase insert Domain Receptor; also known as vascular endothelial growth factor receptor 2) [10] and the kinases regulating the BMP-dependent (Bone Morphogenetic Protein) signaling pathways [11] have been made.

The initial stages of rational design require the creation of a library of several tens of compounds for the primary study of the structure-activity relationship, and the structure variation should be systemic and provide differences in the binding of a small molecule compound to a target protein that can be explained by computer modeling data. The simplest analysis results in the identification of the key structure **11a** for constructing a library (Scheme 2), which will allow us to study the effect of three molecular fragments on the biological activity:

—a change in the position of the methoxy group in the phenyl fragment allows targeted changing of the spatial position of the terminal alkylamine chain in the final dorsomorphin analog;

—the presence of the substituents in the pyrimidine ring affords the rotation of the phenyl ring about the C–C bond with respect to the heterocyclic ring;

—variation of the position of the C–C bond bearing the heterocyclic ring in the pyrimidine fragment allows studying of the features of the interaction of a small molecule compound with the ATP-binding pocket of AMPK.

The heterocyclic scaffold of the considered compounds is a rigid planar pyrazolo[1,5-*a*]pyrimidine molecule, a privileged structure for the design of combinatorial libraries for drug discovery [12, 13]. This is determined by the presence of five positions for the introduction of the binding fragments at the periphery of the scaffold. The most available method for the formation of the pyrazolo[1,5-*a*]pyrimidine core is the cyclocondensation of 5-aminopyrazole with various 1,3-biselectrophilic substrates, for example, β-dicarbonyl compounds (Scheme 3).

The key heterocyclic element in this scheme is 4-substituted 1*H*-pyrazole-5-amine. We synthesized this compound via the linear strategy, starting from

Scheme 4.
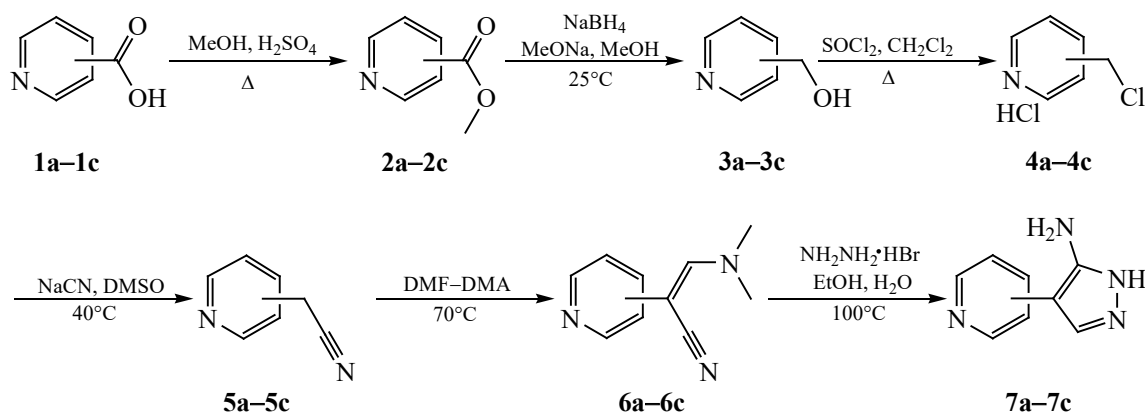
4-pyridyl (**a**), 3-pyridyl (**b**), 2-pyridyl (**c**).

isonicotinic (**1a**), nicotinic (**1b**), and picolinic (**1c**) acids (Scheme 4).

The esterification stage leading to the methyl esters **2a**–**2c** was performed via a procedure adopted from [14]; the synthesis procedure optimization increased the yield to 84–92%. Compounds **2a**–**2c** were reduced into the pyridinemethanols **3a**–**3c** with sodium borohydride following a relatively novel modification with sodium methylate catalysis [15]. Decomposition of a rather stable borate complex of the target product with HCl was an important step of this reaction. The chloromethylpyridines **4a**–**4c** were obtained via the method [16] with additional crystallization of the product from isopropanol, to completely remove the acidic impurities, which was required to successfully accomplish the further stage of the synthesis. An attractive possibility to use the chloromethylpyridines in the form of bases [17] turned out to be unrealistic due to their strong self-condensation.

The 2-pyridylacetonitriles **5a**–**5c** were obtained via nucleophilic substitution with sodium cyanide in an aprotic bipolar solvent (DMSO). The synthesis procedure with the product yield 34% was first suggested in [18]. Its later modifications [16, 19] allowed the increase in the yield due to the use of a rather large excess of sodium cyanide, since one equivalent of the nucleophile was required for neutralization of the starting chloromethylpyridine in the form of hydrochloride. Alternatively, the addition of an equimolar amount of triethylamine to the reaction mixture to obtain the chloromethylpyridine base in situ led to significant decrease in the yield. The use of a minimal excess of sodium cyanide (2.2 eq.), in contrast

to the earlier suggested three-fold excess [19], afforded the 2-pyridylacetonitriles with stable yields exceeding 80%. The product could be isolated via vacuum distillation at the residual pressure of 0.7–2 kPa, avoiding the use of the Kugelrohr apparatus [16]. The obtained 2-pyridylacetonitriles were rather stable as the bases to be stored at 4°C and could be used in the further synthesis without the conversion into the hydrochlorides [11].

The procedure for the synthesis of the 3-dimethylamino-2-pyridylacrylonitriles **6a**–**6c** reported in the literature [11] required the use of 20-fold excess of dimethylformamide dimethyl acetal and resulted in predominant resin formation. Optimization of the process allowed decreasing the dimethylformamide dimethyl acetal excess to 1.3, performing the synthesis under much milder conditions and evaluating the true yellowish color of the crystalline products **6a**–**6c** due to the developed purification procedure.

The stage of ring formation of the 3-dimethylamino-2-pyridylacrylonitriles **6a**–**6c** to the aminopyrazoles **7a**–**7c** was performed using the hydrazine base as well as its different salts. The highest yields were achieved using hydrazinium bromide in the ethanol–water medium, as recommended in [11]. Thus, the six-stage synthesis of 4-pyridyl-1*H*-pyrazol-5-amines **7a**–**7c** was reproducibly performed with the average yield of 41% with respect to the starting acids **1a**–**1c**.

The next stage of the synthesis yielded the target pyrazolo[1,5-*a*]pyrimidine fragment. Depending on the used 1,3-biselectrophilic compound, either functionalized semi-product at R^1 = Br (Scheme 5) or the target product

Scheme 5.
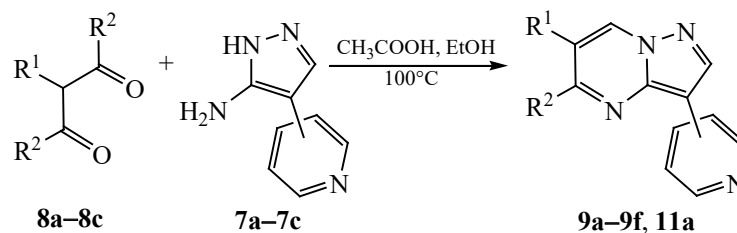
R¹ = Br, R² = H (**8a**), CH₃ (**8b**); R¹ =4-OCH₃-C₆H₄, R² = H (**8c**); R¹ = Br, R² = H, 4-pyridyl (**9a**), 3-pyridyl (**9b**), 2-pyridyl (**9c**); R¹ = Br, R² = CH₃, 4-pyridyl (**9d**), 3-pyridyl (**9e**), 2-pyridyl (**9f**); R¹ =4-OCH₃-C₆H₄, R² = H, 4-pyridyl (**11a**).

Scheme 6.
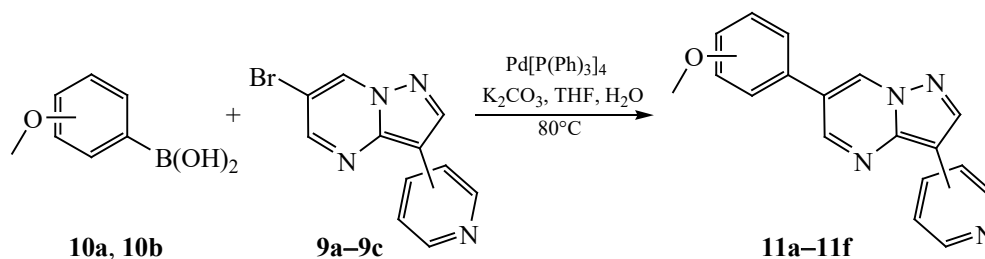
4-OCH₃, 4-pyridyl (**11a**), 3-pyridyl (**11b**), 2-pyridyl (**11c**); 3-OCH₃, 4-pyridyl (**11d**), 3-pyridyl (**11e**), 2-pyridyl (**11f**).

at R^1 = 4-OMe-C₆H₄ could be obtained. In view of the chemical synthesis strategy, the second approach somewhat advantageous due to the use of the parallel synthesis of the substituted 1,3-biselectrophile, but considering the combinatorial strategy, the building of the functionalized pyrazolo[1,5-*a*]pyrimidine structure seemed favorable. In this study, we explored both approaches.

Bromomalonic aldehyde **8a** was synthesized according to the procedure [20, 21], which turned out to be well reproducible in terms of the product yield and purity. Acetylacetone was brominated to 3-bromoacetylacetone **8b** following the general principles of the preparation of α-halocarbonyl compounds. 4-Methoxyphenylmalonic aldehyde **8c** was synthesized as described in [22], from 4-methyoxyphenylacetic acid. The cyclocondensation reactions with the formation of compounds **9a**–**9f** and **11a** were performed in the ethanol–acetic acid mixture. The products commonly did not require specific purification, but isolation of compounds **9d**–**9f** was more time-consuming.

The formation of the C–C bond between 6-bromo-3-pyridylpyrazolo[1,5-*a*]pyrimidines and 3- or 4-methoxy-substituted phenyl was performed via the Suzuki–Miyaura reaction (Scheme 6). For this purpose, 3-methoxyphenyl- and 4-methoxyphenylboronic acids were synthesized as described in [23]. The reaction proceeded with satisfactory yield (82–87%) and afforded high-purity products **11a**–**11f**.

At the same time, the use of the standard Pd[P(Ph)₃]₄ catalyst for the formation of the C–C bond did not afford the detectable amounts of the target products in the case of 6-bromo-5,7-dimethyl-substituted 3-pyridylpyrazolo[1,5-*a*]pyrimidines **9d**–**9f**. However, the use of the Pd₂dba₃/S-Phos catalytic system proposed by Buchwald for sterically hindered cross-coupling cases [24] gave the satisfactory results and afforded compounds **12a**–**12f** in 67–78% yield (Scheme 7).

In summary, we propose the reproducible and scalable laboratory method for the synthesis of the pyrazolo[1,5-*a*]pyrimidine derivatives for creating a library of potentially active inhibitors of the AMPK

Scheme 7.
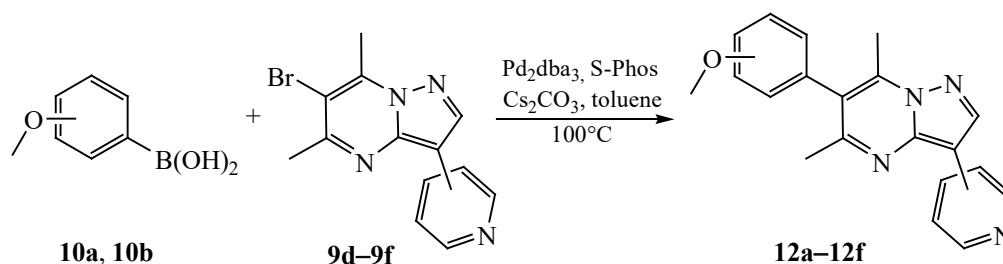
4-OCH₃, 4-pyridyl (**12a**), 3-pyridyl (**12b**), 2-pyridyl (**12c**); 3-OCH₃, 4-pyridyl (**12d**), 3-pyridyl (**12e**), 2-pyridyl (**12f**).

kinase activity. In this study we characterized the earlier unknown compounds and synthesized novel derivatives of pyrazolo[1,5-*a*]pyrimidine. The high efficiency of the Suzuki–Miyaura cross-coupling for the formation of the carbon skeleton of the AMPK-targeted pyrazolo[1,5-*a*]pyrimidines was demonstrated.

EXPERIMENTAL

The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance III HD 400 spectrometer operating at 400 and 100 MHz, respectively, in DMSO-d_6 and CDCl₃. The mass spectra were recorded on an LCMS-2020 monoquadrupole chromato–mass spectrometer (Shimadzu) with electrospray ionization (ESI) in the positive mode. For the identification, the products were purified on an Isolera Four flash chromatograph (Biotage) with SNAP KP-Sil 100 g cartridges (Biotage).

General procedure for the preparation of methyl esters of pyridinecarboxylic acids 2a–2c. 50 g of pyridinecarboxylic acid **1a**–**1c** (0.41 mol) was suspended in 300 mL of anhydrous methanol. 26 mL of sulfuric acid (0.49 mol) was added under stirring over 30 min; the reaction mixture was homogenized. The obtained solution was refluxed for 12 h. When the reaction was complete, methanol was distilled off under reduced pressure; the residue was poured at 300 g of ice and pH was adjusted to 8–9 with dry Na₂CO₃. The product was extracted with ethyl acetate (3×150 mL). The combined organic layers were washed with water (2×100 mL), dried over Na₂SO₄, and the solvent was distilled off under reduced pressure. Methyl ester of pyridinecarboxylic acid was purified via vacuum distillation at residual pressure of 2.7 kPa. Yield 47–

51 g (84–92%). The obtained compounds are described in Supplementary Information.

General procedure for the preparation of pyridine-methanols 3a–3c. 0.2 g of metallic sodium was added to 20 mL of anhydrous methanol. When sodium was completely dissolved, 20 g of methyl ester of pyridinecarboxylic acid **2a**–**2c** (0.15 mol) was added at cooling and then 11.4 g of freshly pounded NaBH₄ (0.3 mol) was added at vigorous stirring. The reduction reaction had an induction period and could proceed very vigorously; if temperature was sharply increased, the flask was put into an ice bath. The mixture was stirred for 3 h at room temperature, and then 150 mL of methanol was added to remove excess of NaBH₄. Methanol was distilled off to dryness, then 100 mL of 20% solution of HCl was added, the mixture was heated under stirring for 1 h, cooled, and neutralized with dry K₂CO₃ to pH 8–9. The obtained mixture of the salts, water, and separated pyridinemethanol was extracted with ethyl acetate (3×100 mL). The organic layer was dried over Na₂SO₄ and the solvent was distilled off under reduced pressure. The pyridinemethanol was purified via vacuum distillation at reduced pressure of 0.13 kPa. Yield 12.4–13.0 g (78–82%). The obtained compounds are described in Supplementary Information.

General procedure for the preparation of chloro-methylpyridine hydrochlorides 4a–4c. 20 mL of thionyl chloride (32.8 g, 0.28 mol) was added dropwise at stirring to a solution of 15 g of pyridinemethanol **3a**–**3c** (0.14 mol) in 200 mL of dichloromethane, avoiding the mixture heating above 30°C. When the substrate addition was complete, the reaction mixture was stirred for 3 h and then the solvent was distilled off under reduced pressure. 200 mL of isopropanol was added to the residue; the

suspension was stirred for 30 min and then the solvent was distilled off to dryness under reduced pressure. The chloromethylpyridine hydrochloride was recrystallized from isopropanol with activated charcoal. The obtained products were stable and did not contain any acidic impurities. Yield 17.8–19.8 g (79–88%). The obtained compounds are described in Supplementary Information.

General procedure for the preparation of 2-pyridyl-acetonitriles 5a–5c. 22 g of NaCN (0.45 mol) was poured with 200 mL of dry DMSO in a porcelain mortar; the obtained solvate was triturated into the homogeneous suspension and put into a flask. 30.8 g of dry chloromethylpyridine hydrochloride **4a–4c** (0.19 mol) was added in portions under stirring so that the temperature did not exceed 40°C. Upon the addition, the mixture was stirred for 2 h at 40°C and then poured into a solution of 100 g of K_2CO_3 and 14 g of KOH in 500 mL of water. The obtained mixture was extracted with ethyl acetate (4×200 mL), while the formation of three layers was observed. The combined organic layers were washed with 100 mL of a brine and dried over Na_2SO_4; the solvent was distilled off under reduced pressure. 2-Pyridylacetonitrile was isolated via double distillation under reduced pressure. The first distillation was performed at residual pressure of 0.5–0.6 kPa without separation into fractions. The second distillation was started at 2.7 kPa to distill off the extracted DMSO, then the pressure was reduced to 1.3 kPa to distill the 2-pyridylacetonitrile. Yield 18.2–19.3 g (81–86%). The obtained 2-pyridylacetonitriles were rather stable in the form of the base and could be stored at 4°C; their conversion into the hydrochloride was not required for further synthesis [11]. The obtained compounds are described in Supplementary Information.

General procedure for the preparation of 3-di-methylamino-2-pyridylacrylonitriles 6a–6c. A mixture of 20 g of 2-pyridylacetonitrile **5a–5c** (0.17 mol), 26 g of dimethylformamide dimethyl acetal (0.22 mol), and 150 mL of DMF was stirred at 70°C for 4 h. When the reaction was complete, the mixture was distilled off under reduced pressure and then dried as much as possible under reduced pressure of 70 Pa. The obtained mass was recrystallized from a minimum amount of ethyl acetate. The formed precipitate was dissolved in 800 mL of ethyl acetate, filtered off on a paper filter, and passed through 10 cm layer of silica gel. The solvent was distilled off to obtain pale yellow crystalline mass of 3-dimethylamino-2-pyridylacrylonitrile. Yield 23.8–25.0 g (80–85%). The

obtained compounds are described in Supplementary Information.

General procedure for the preparation of 4-pyridyl-1*H*-pyrazol-5-amines 7a–7c. A mixture of 20 g of 3-dimethylamino-2-pyridylacrylonitrile **6a–6c** (0.12 mol), 26 g of hydrazine hydrobromide (0.23 mol), 200 mL of ethanol, and 30 mL of water was refluxed under stirring for 6 h. When the reaction was completed, ethanol was distilled off under reduced pressure, and 300 mL of water was added. The mixture pH was adjusted to 8–9 with dry K_2CO_3 and the mixture was vigorously stirred for 30 min. 200 mL of water was distilled off under reduced pressure; the residue was filtered off and dried in air. Crude 4-pyridyl-1*H*-pyrazol-5-amine was recrystallized from ethanol. Yield 16.3–17 g (88–92%). The obtained compounds are described in Supplementary Information.

Bromomalonic aldehyde (8a). 25 g of 1,1,3,3-tetra-methoxypropane (0.152 mol), 25 mL of water, and 1.1 mL of concentrated HCl was stirred to obtain the homogeneous solution. The mixture was cooled on an ice bath, and 7.8 mL of bromine (24.3 g, 0.152 mol) was added dropwise with stirring at such a rate that the reaction mixture had time to become colourless and its temperature did not exceed 15°C. Upon the addition, the mixture was evaporated at 2.7 kPa and the bath temperature of 40°C. The obtained sticky crystalline mass was washed with 50 mL of ice water and 20 mL of cold CH_2Cl_2. The product was finally dried under reduced pressure. Yield 17–20 g (73–86%).

3-Bromoacetylacetone (8b). 7.7 mL of bromine (24 g, 0.15 mol) was added dropwise at cooling and stirring to a mixture of 15 g of acetylacetone (0.15 mol), 5 mL of concentrated HCl, and 100 mL of water at such a rate that the reaction mixture had time to become colourless and its temperature did not exceed 15°C. When the reaction was completed, 200 mL of ethyl acetate was added and the mixture was stirred for 5 min; the organic layer was separated and washed with 10% solution of $NaHCO_3$ to neutral reaction. The solvent was distilled off under reduced pressure, and the obtained 3-bromoacetylacetone was used in further synthesis without additional purification.

General procedure for the preparation of 6-substituted 3-pyridylpyrazolo[1,5-*a*]pyrimidines 9a–9f, 11a. 16 g of 4-pyridyl-1*H*-pyrazol-5-amine **7a–7c** (0.1 mol) and 0.1 mol of dicarbonyl compound **8a–8c** were dissolved in a mixture of 150 mL of glacial acetic acid and 150 mL ethanol. The obtained solution

was refluxed under stirring for 6 h. The reaction mixture was distilled off to dryness, then 400 mL of water and 20 g of K_2CO_3 were added, and the obtained suspension was stirred for 10 min. The precipitate was filtered off and washed with small amount of ethanol. If necessary, the product was recrystallized from toluene. Yield 23.7–25.3 g (86–92%) for compounds **9a**–**9c**, 24.2–25.3 g (75–82%) for compounds **9d**–**9f**, and 24.2 g (80%) for compound **11a**.

General procedure for the preparation of 6-aryl-substituted 3-pyridylpyrazolo[1,5-*a*]pyrimidines 11a–11f. 2 g of 6-halogenated 3-pyridylpyrazolo[1,5-*a*]pyrimidine **9a**–**9c** (7.3 mmol), 0.05 g of Pd[P(Ph)$_3$]$_4$ (0.043 mmol, 0.5 mol %), and 1.66 g of methoxyphenylboronic acid **10a**, **10b** (11 mmol) were dissolved under stirring in 80 mL of THF. The obtained mixture was stirred for 30 min under a weak argon stream, and then a solution of 5 g of K_2CO_3 (36 mmol) in 50 mL of water was added. The reaction was performed at refluxing and vigorous stirring under a weak argon stream for 4 h. When the reaction was completed, the solvent was distilled off to dryness under reduced pressure. The residue was stirred in 200 mL of boiling toluene and then filtered keeping hot. The filtrate was treated with 1 g of silica gel under boiling and stirring, filtered again, and the solution volume was adjusted to 15 mL. A day later, the formed precipitate was filtered off and dried. Yield 1.80–1.92 g (82–87%).

6-(4-Methoxyphenyl)-3-(pyridin-4-yl)pyrazolo-[1,5-*a*]pyrimidine (11a). Yield 1.92 g (87%), yellowish crystals, mp 215°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 3.83 s (3H, OCH$_3$), 7.10 d (2H, CH$_{Ar}$, $^3J_{HH}$ 8.8 Hz), 7.84 d (2H, CH$_{Ar}$, $^3J_{HH}$ 8.8 Hz), 8.15 d (2H, CH$_{Ar}$, $^3J_{HH}$ 6.2 Hz), 8.59 d (2H, CH$_{Ar}$, $^3J_{HH}$ 6.2 Hz), 8.96 s (1H, CH$_{Ar}$), 9.12 d (1H, CH$_{Ar}$, $^4J_{HH}$ 2.3 Hz), 9.52 d (1H, CH$_{Ar}$, $^4J_{HH}$ 2.3 Hz). ^{13}C NMR spectrum (DMSO-d_6), δ$_C$, ppm: 55.33 (OCH$_3$), 106.08 (C$_{Ar}$), 114.72 (CH$_{Ar}$), 119.62 (CH$_{Ar}$), 122.16 (C$_{Ar}$), 125.34 (C$_{Ar}$), 128.28 (CH$_{Ar}$), 132.61 (CH$_{Ar}$), 139.28 (C$_{Ar}$), 143.80 (CH$_{Ar}$), 143.84 (C$_{Ar}$), 149.98 (CH$_{Ar}$), 150.79 (CH$_{Ar}$), 159.70 (C$_{Ar}$OCH$_3$). Mass spectrum, *m*/*z* (I_{rel}, %): 303.1 (100) [*M* + H]$^+$.

6-(4-Methoxyphenyl)-3-(pyridin-3-yl)pyrazolo-[1,5-*a*]pyrimidine (11b). Yield 1.85 g (84%), yellowish crystals, mp 165–166°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 3.83 s (3H, OCH$_3$), 7.10 d (2H, CH$_{Ar}$, $^3J_{HH}$ 8.9 Hz), 7.48 d. d. d (1H, CH$_{Ar}$, $^3J_{HH}$ 8.0, 4.8, $^5J_{HH}$ 0.9 Hz), 7.83 d (2H, CH$_{Ar}$, $^3J_{HH}$ 8.9 Hz), 8.45 d. d (1H, CH$_{Ar}$, $^3J_{HH}$ 4.7, $^4J_{HH}$ 1.6 Hz), 8.52 d. d. d (1H, CH$_{Ar}$,

$^3J_{HH}$ 8.0, $^4J_{HH}$ 2.3, 1.7 Hz), 8.88 s (1H, CH$_{Ar}$), 9.07 d (1H, CH$_{Ar}$, $^4J_{HH}$ 2.3 Hz), 9.36 d. d (1H, CH$_{Ar}$, $^4J_{HH}$ 2.3, $^5J_{HH}$ 0.8 Hz), 9.48 d (1H, CH$_{Ar}$, $^4J_{HH}$ 2.3 Hz). ^{13}C NMR spectrum (DMSO-d_6), δ$_C$, ppm: 55.32 (OCH$_3$), 105.80 (C$_{Ar}$), 114.70 (CH$_{Ar}$), 121.81 (C$_{Ar}$), 123.78 (CH$_{Ar}$), 125.48 (C$_{Ar}$), 128.03 (C$_{Ar}$), 128.21 (CH$_{Ar}$), 132.30 (CH$_{Ar}$), 132.39 (CH$_{Ar}$), 142.95 (CH$_{Ar}$), 143.29 (C$_{Ar}$), 146.68 (CH$_{Ar}$), 146.89 (CH$_{Ar}$), 150.23 (CH$_{Ar}$), 159.63 (C$_{Ar}$OCH$_3$). Mass spectrum, *m*/*z* (I_{rel}, %): 303.1 (100) [*M* + H]$^+$.

6-(4-Methoxyphenyl)-3-(pyridin-2-yl)pyrazolo-[1,5-*a*]pyrimidine (11c). Yield 1.81 g (82%), yellow crystals, mp 184–185°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 3.82 s (3H, OCH$_3$), 7.10 d (2H, CH$_{Ar}$, $^3J_{HH}$ 8.8 Hz), 7.23 d. d. d (1H, CH$_{Ar}$, $^3J_{HH}$ 7.5, 4.8, $^5J_{HH}$ 1.2 Hz), 7.83 d (2H, CH$_{Ar}$, $^3J_{HH}$ 8.8 Hz), 7.87 t. d (1H, CH$_{Ar}$, $^3J_{HH}$ 7.8, $^4J_{HH}$ 1.9 Hz), 8.46 d. t (1H, CH$_{Ar}$, $^3J_{HH}$ 7.9, $^5J_{HH}$ 1.1 Hz), 8.60 d. d. d (1H, CH$_{Ar}$, $^3J_{HH}$ 4.9, $^4J_{HH}$ 1.9, $^5J_{HH}$ 1.0 Hz), 8.81 s (1H, CH$_{Ar}$), 9.09 d (1H, CH$_{Ar}$, $^4J_{HH}$ 2.3 Hz), 9.49 d (1H, CH$_{Ar}$, $^4J_{HH}$ 2.3 Hz). ^{13}C NMR spectrum (DMSO-d_6), δ$_C$, ppm: 55.31 (OCH$_3$), 109.66 (C$_{Ar}$), 114.69 (CH$_{Ar}$), 120.30 (CH$_{Ar}$), 121.11 (CH$_{Ar}$), 121.79 (C$_{Ar}$), 125.47 (C$_{Ar}$), 128.23 (CH$_{Ar}$), 132.54 (CH$_{Ar}$), 136.74 (CH$_{Ar}$), 143.57 (C$_{Ar}$), 144.07 (CH$_{Ar}$), 149.39 (CH$_{Ar}$), 150.44 (CH$_{Ar}$), 150.93 (C$_{Ar}$), 159.63 (C$_{Ar}$OCH$_3$). Mass spectrum, *m*/*z* (I_{rel}, %): 303.1 (100) [*M* + H]$^+$.

6-(3-Methoxyphenyl)-3-(pyridin-4-yl)pyrazolo-[1,5-*a*]pyrimidine (11d). Yield 1.9 g (86%), yellowish crystals, mp 169–170°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 3.86 s (3H, OCH$_3$), 7.01–7.05 m (1H, CH$_{Ar}$), 7.44–7.47 m (3H, CH$_{Ar}$), 8.16 d (2H, CH$_{Ar}$, $^3J_{HH}$ 6.2 Hz), 8.59 d (2H, CH$_{Ar}$, $^3J_{HH}$ 6.2 Hz), 8.99 s (1H, CH$_{Ar}$), 9.16 d (1H, CH$_{Ar}$, $^4J_{HH}$ 2.3 Hz), 9.62 d (1H, CH$_{Ar}$, $^4J_{HH}$ 2.3 Hz). ^{13}C NMR spectrum (DMSO-d_6), δ$_C$, ppm: 55.33 (OCH$_3$), 106.19 (C$_{Ar}$), 112.35 (CH$_{Ar}$), 114.34 (C$_{Ar}$), 119.17 (CH$_{Ar}$), 119.66 (CH$_{Ar}$), 122.15 (C$_{Ar}$), 130.34 (CH$_{Ar}$), 133.66 (CH$_{Ar}$), 134.54 (C$_{Ar}$), 139.20 (C$_{Ar}$), 144.13 (CH$_{Ar}$), 149.99 (CH$_{Ar}$), 150.93 (CH$_{Ar}$), 159.95 (C$_{Ar}$OCH$_3$). Mass spectrum, *m*/*z* (I_{rel}, %): 303.1 (100) [*M* + H]$^+$.

6-(3-Methoxyphenyl)-3-(pyridin-3-yl)pyrazolo-[1,5-*a*]pyrimidine (11e). Yield 1.91 g (87%), yellowish crystals, mp 173–174°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 3.86 s (3H, OCH$_3$), 7.00–7.05 m (1H, CH$_{Ar}$), 7.43–7.47 m (3H, CH$_{Ar}$), 7.48 d. d. d (1H, CH$_{Ar}$, $^3J_{HH}$ 8.0, 4.8, $^5J_{HH}$ 0.9 Hz), 8.46 d. d (1H, CH$_{Ar}$, $^3J_{HH}$ 4.7, $^4J_{HH}$ 1.6 Hz), 8.52 d. d. d (1H, CH$_{Ar}$, $^3J_{HH}$ 8.0, $^4J_{HH}$ 2.3, 1.7 Hz), 8.91 s (1H, CH$_{Ar}$), 9.11 d (1H, CH$_{Ar}$, $^4J_{HH}$

2.3 Hz), 9.37 d. d (1H, CH_{Ar}, $^4J_{HH}$ 2.3, $^5J_{HH}$ 0.9 Hz), 9.59 d (1H, CH_{Ar}, $^4J_{HH}$ 2.3 Hz). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 55.32 (OCH_3), 105.92 (C_{Ar}), 112.27 (CH_{Ar}), 114.27 (CH_{Ar}), 119.11 (CH_{Ar}), 121.80 (C_{Ar}), 123.79 (CH_{Ar}), 127.95 (C_{Ar}), 130.33 (CH_{Ar}), 132.44 (CH_{Ar}), 133.36 (CH_{Ar}), 134.67 (C_{Ar}), 143.31 (CH_{Ar}), 143.58 (C_{Ar}), 146.72 (CH_{Ar}), 146.96 (CH_{Ar}), 150.36 (CH_{Ar}), 159.95 ($\underline{C}_{Ar}OCH_3$). Mass spectrum, m/z (I_{rel}, %): 303.1 (100) $[M + H]^+$.

6-(3-Methoxyphenyl)-3-(pyridin-2-yl)pyrazolo-[1,5-a]pyrimidine (11f). Yield 1.83 g (82%), yellow crystals, mp 171°C. ^1H NMR spectrum (DMSO-d_6), δ, ppm: 3.86 s (3H, OCH_3), 7.00–7.05 m (1H, CH_{Ar}), 7.24 d. d. d (1H, CH_{Ar}, $^3J_{HH}$ 7.5, 4.8, $^5J_{HH}$ 1.2 Hz), 7.43–7.46 m (3H, CH_{Ar}), 7.87 t. d (1H, CH_{Ar}, $^3J_{HH}$ 7.7, $^4J_{HH}$ 1.9 Hz), 8.47 d. t (1H, CH_{Ar}, $^3J_{HH}$ 7.9, $^5J_{HH}$ 1.1 Hz), 8.60 d. d. d (1H, CH_{Ar}, $^3J_{HH}$ 4.8, $^4J_{HH}$ 1.9, $^5J_{HH}$ 0.9 Hz), 8.84 s (1H, CH_{Ar}), 9.12 d (1H, CH_{Ar}, $^4J_{HH}$ 2.3 Hz), 9.59 d (1H, CH_{Ar}, $^4J_{HH}$ 2.3 Hz). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 55.32 (OCH_3), 109.76 (C_{Ar}), 112.33 (CH_{Ar}), 114.24 (CH_{Ar}), 119.13 (CH_{Ar}), 120.35 (CH_{Ar}), 121.17 (CH_{Ar}), 121.78 (C_{Ar}), 130.31 (CH_{Ar}), 133.59 (CH_{Ar}), 134.66 (C_{Ar}), 136.75 (CH_{Ar}), 143.85 (C_{Ar}), 144.41 (CH_{Ar}), 149.40 (CH_{Ar}), 150.57 (CH_{Ar}), 150.86 (C_{Ar}), 159.94 ($\underline{C}_{Ar}OCH_3$). Mass spectrum, m/z (I_{rel}, %): 303.1 (100) $[M + H]^+$.

General procedure for the preparation of 6-aryl-5,7-dimethyl-substituted 3-pyridylpyrazolo-[1,5-a]pyrimidines 12a–12f. 0.04 g of $Pd_2(dba)_3$ (0.044 mmol, 0.66 mol %) and 0.08 g of 2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl (Sphos, 0.195 mmol) were dissolved in 120 mL of toluene under stirring and the obtained solution was stirred for 30 min under a weak argon stream. 2 g of 6-halo-5,7-dimethyl-substituted 3-pyridylpyrazolo[1,5-a]pyrimidine **9d**–**9f** (6.6 mmol), 1.66 g of methoxyphenylboronic acid **10a**, **10b** (11 mmol), and 6 g of Cs_2CO_3 (18.4 mmol) were added to the reaction mixture. The reaction was performed at 100°C with vigorous stirring under a weak argon stream for 16 h. When the reaction was completed, the toluene volume was adjusted to 200 mL, heated to boiling, and filtered keeping hot. The filtrate was treated with 1 g of silica gel under boiling and stirring, filtered again, and the solution volume was adjusted to 15 mL. After a day, the formed precipitate was filtered off and dried. Yield 1.46–1.7 g (67–78%).

6-(4-Methoxyphenyl)-5,7-dimethyl-3-(pyridin-4-yl)-pyrazolo[1,5-a]pyrimidine (12a). Yield 1.7 g (78%),

colorless crystals, mp 175–177°C. ^1H NMR spectrum (DMSO-d_6), δ, ppm: 2.35 s (3H, CH_3), 2.48 s (3H, CH_3), 3.84 s (3H, OCH_3), 7.10 d (2H, CH_{Ar}, $^3J_{HH}$ 8.7 Hz), 7.33 d (2H, CH_{Ar}, $^3J_{HH}$ 8.7 Hz), 8.18 d (2H, CH_{Ar}, $^3J_{HH}$ 6.2 Hz), 8.56 d (2H, CH_{Ar}, $^3J_{HH}$ 6.2 Hz), 8.90 s (1H, CH_{Ar}). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 14.89 (CH_3), 24.87 (CH_3), 55.17 (OCH_3), 105.26 (C_{Ar}), 114.26 (CH_{Ar}), 119.40 (CH_{Ar}), 122.21 (C_{Ar}), 126.91 (C_{Ar}), 131.24 (CH_{Ar}), 139.78 (C_{Ar}), 142.81 (CH_{Ar}), 143.84 (C_{Ar}), 144.14 (C_{Ar}), 149.86 (CH_{Ar}), 159.04 (C_{Ar}), 159.51 ($\underline{C}_{Ar}OCH_3$). Mass spectrum, m/z (I_{rel}, %): 331.2 (100) $[M + H]^+$.

6-(4-Methoxyphenyl)-5,7-dimethyl-3-(pyridin-3-yl)-pyrazolo[1,5-a]pyrimidine (12b). Yield 1.52 g (70%), colorless crystals, mp 156–158°C. ^1H NMR spectrum (DMSO-d_6), δ, ppm: 2.35 s (3H, CH_3), 2.48 s (3H, CH_3), 3.84 s (3H, OCH_3), 7.10 d (2H, CH_{Ar}, $^3J_{HH}$ 8.8 Hz), 7.33 d (2H, CH_{Ar}, $^3J_{HH}$ 8.8 Hz), 7.51 d. d. d (1H, CH_{Ar}, $^3J_{HH}$ 8.0, 4.8, $^5J_{HH}$ 0.9 Hz), 8.47 d. d (1H, CH_{Ar}, $^3J_{HH}$ 4.7, $^4J_{HH}$ 1.6 Hz), 8.50 d. d. d (1H, CH_{Ar}, $^3J_{HH}$ 8.0, $^4J_{HH}$ 2.3, 1.7 Hz), 8.78 s (1H, CH_{Ar}), 9.33 d. d (1H, CH_{Ar}, $^4J_{HH}$ 2.3, $^5J_{HH}$ 0.8 Hz). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 14.88 (CH_3), 24.86 (CH_3), 55.16 (OCH_3), 104.70 (C_{Ar}), 114.30 (CH_{Ar}), 121.69 (C_{Ar}), 123.68 (CH_{Ar}), 125.33 (C_{Ar}), 127.95 (C_{Ar}), 131.30 (CH_{Ar}), 136.25 (CH_{Ar}), 139.40 (C_{Ar}), 141.55 (C_{Ar}), 143.99 (C_{Ar}), 146.47 (CH_{Ar}), 150.23 (CH_{Ar}), 158.97 (C_{Ar}), 159.40 ($\underline{C}_{Ar}OCH_3$). Mass spectrum, m/z (I_{rel}, %): 331.2 (100) $[M + H]^+$.

6-(4-Methoxyphenyl)-5,7-dimethyl-3-(pyridin-2-yl)-pyrazolo[1,5-a]pyrimidine (12c). Yield 1.58 g (72%), colorless crystals, mp 170–172°C. ^1H NMR spectrum (DMSO-d_6), δ, ppm: 2.35 s (3H, CH_3), 2.48 s (3H, CH_3), 3.84 s (3H, OCH_3), 7.10 d (2H, CH_{Ar}, $^3J_{HH}$ 8.8 Hz), 7.26 d. d. d (1H, CH_{Ar}, $^3J_{HH}$ 7.5, 4.8, $^5J_{HH}$ 1.2 Hz), 7.53 d (2H, CH_{Ar}, $^3J_{HH}$ 8.8 Hz), 7.90 t. d (1H, CH_{Ar}, $^3J_{HH}$ 7.8, $^4J_{HH}$ 1.9 Hz), 8.43 d. t (1H, CH_{Ar}, $^3J_{HH}$ 7.9, $^5J_{HH}$ 1.1 Hz), 8.57 d. d. d (1H, CH_{Ar}, $^3J_{HH}$ 4.9, $^4J_{HH}$ 1.9, $^5J_{HH}$ 1.0 Hz), 8.76 s (1H, CH_{Ar}). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 14.89 (CH_3), 24.87 (CH_3), 55.17 (OCH_3), 108.92 (C_{Ar}), 114.26 (CH_{Ar}), 120.55 (CH_{Ar}), 121.63 (CH_{Ar}), 122.02 (C_{Ar}), 126.75 (C_{Ar}), 131.43 (CH_{Ar}), 136.53 (CH_{Ar}), 139.07 (CH_{Ar}), 143.28 (C_{Ar}), 144.79 (CH_{Ar}), 149.44 (CH_{Ar}), 150.48 (CH_{Ar}), 159.01 (C_{Ar}), 159.50 ($\underline{C}_{Ar}OCH_3$). Mass spectrum, m/z (I_{rel}, %): 331.2 (100) $[M + H]^+$.

6-(3-Methoxyphenyl)-5,7-dimethyl-3-(pyridin-4-yl)-pyrazolo[1,5-a]pyrimidine (12d). Yield 1.64 g (75%), colorless crystals, mp 169–170°C. ^1H NMR spectrum

(DMSO-d_6), δ, ppm: 2.35 s (3H, CH$_3$), 2.48 s (3H, CH$_3$), 3.87 s (3H, OCH$_3$), 7.00–7.05 m (1H, CH$_{Ar}$), 7.24–7.26 m (2H, CH$_{Ar}$), 7.43–7.45 m (1H, CH$_{Ar}$), 8.18 d (2H, CH$_{Ar}$, $^3J_{HH}$ 6.2 Hz), 8.56 d (2H, CH$_{Ar}$, $^3J_{HH}$ 6.2 Hz), 8.93 s (1H, CH$_{Ar}$). ^{13}C NMR spectrum (DMSO-d_6), δ$_C$, ppm: 14.89 (CH$_3$), 24.87 (CH$_3$), 55.17 (OCH$_3$), 105.77 (C$_{Ar}$), 112.12 (CH$_{Ar}$), 114.22 (C$_{Ar}$), 118.98 (CH$_{Ar}$), 119.25 (CH$_{Ar}$), 122.10 (C$_{Ar}$), 128.42 (CH$_{Ar}$), 129.98 (CH$_{Ar}$), 134.86 (C$_{Ar}$), 139.49 (C$_{Ar}$), 144.15 (C$_{Ar}$), 149.86 (CH$_{Ar}$), 159.03 (C$_{Ar}$), 159.69 (C$_{Ar}$OCH$_3$). Mass spectrum, m/z (I_{rel}, %): 331.2 (100) $[M + H]^+$.

6-(3-Methoxyphenyl)-5,7-dimethyl-3-(pyridin-3-yl)-pyrazolo[1,5-a]pyrimidine (12e). Yield 1.46 g (67%), colorless crystals, mp 165–167°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.35 s (3H, CH$_3$), 2.48 s (3H, CH$_3$), 3.87 s (3H, OCH$_3$), 7.00–7.05 m (1H, CH$_{Ar}$), 7.24–7.27 m (2H, CH$_{Ar}$), 7.44–7.46 m (1H, CH$_{Ar}$), 7.50 d. d. d (1H, CH$_{Ar}$, $^3J_{HH}$ $^3J_{HH}$ 8.0, 4.8, $^5J_{HH}$ 0.9 Hz), 8.48 d. d (1H, CH$_{Ar}$, $^3J_{HH}$ 4.7, $^4J_{HH}$ 1.6 Hz), 8.51 d. d. d (1H, CH$_{Ar}$, $^3J_{HH}$ 8.0, $^4J_{HH}$ 2.3, 1.7 Hz), 8.85 s (1H, CH$_{Ar}$), 9.35 d. d (1H, CH$_{Ar}$, $^4J_{HH}$ 2.3, $^5J_{HH}$ 0.9 Hz). ^{13}C NMR spectrum (DMSO-d_6), δ$_C$, ppm: 14.89 (CH$_3$), 24.87 (CH$_3$), 55.17 (OCH$_3$), 105.69 (C$_{Ar}$), 112.03 (CH$_{Ar}$), 114.01 (CH$_{Ar}$), 118.94 (CH$_{Ar}$), 121.40 (C$_{Ar}$), 123.54 (CH$_{Ar}$), 127.33 (C$_{Ar}$), 127.93 (CH$_{Ar}$), 130.36 (CH$_{Ar}$), 134.37 (C$_{Ar}$), 138.24 (CH$_{Ar}$), 143.01 (CH$_{Ar}$), 143.79 (C$_{Ar}$), 146.93 (C$_{Ar}$), 150.54 (CH$_{Ar}$), 159.04 (C$_{Ar}$), 159.65 (C$_{Ar}$OCH$_3$). Mass spectrum, m/z (I_{rel}, %): 331.2 (100) $[M + H]^+$.

6-(3-Methoxyphenyl)-5,7-dimethyl-3-(pyridin-2-yl)-pyrazolo[1,5-a]pyrimidine (12f). Yield 1.54 g (71%), colorless crystals, mp 160–162°C. ^{1}H NMR spectrum (DMSo-d_6), δ, ppm: 2.35 s (3H, CH$_3$), 2.48 s (3H, CH$_3$), 3.87 s (3H, OCH$_3$), 7.00–7.05 m (1H, CH$_{Ar}$), 7.24–7.27 m (3H, CH$_{Ar}$), 7.43–7.45 m (1H, CH$_{Ar}$), 7.90 t. d (1H, CH$_{Ar}$, $^3J_{HH}$ 7.7, $^4J_{HH}$ 1.9 Hz), 8.44 d. t (1H, CH$_{Ar}$, $^3J_{HH}$ 7.9, $^5J_{HH}$ 1.1 Hz), 8.57 d. d. d (1H, CH$_{Ar}$, $^3J_{HH}$ 4.8, $^4J_{HH}$ 1.9, $^5J_{HH}$ 0.9 Hz), 8.78 s (1H, CH$_{Ar}$). ^{13}C NMR spectrum (DMSO-d_6), δ$_C$, ppm: 14.89 (CH$_3$), 24.87 (CH$_3$), 55.17 (OCH$_3$), 109.53 (C$_{Ar}$), 112.04 (CH$_{Ar}$), 114.13 (CH$_{Ar}$), 118.96 (CH$_{Ar}$), 120.15 (CH$_{Ar}$), 121.07 (CH$_{Ar}$), 121.77 (C$_{Ar}$), 127.44 (CH$_{Ar}$), 130.88 (CH$_{Ar}$), 136.39 (C$_{Ar}$), 137.93 (C$_{Ar}$), 142.55 (C$_{Ar}$), 144.62 (CH$_{Ar}$), 149.20 (CH$_{Ar}$), 150.24 (C$_{Ar}$), 159.06 (C$_{Ar}$), 159.64 (C$_{Ar}$OCH$_3$). Mass spectrum, m/z (I_{rel}, %): 331.2 (100) $[M + H]^+$.

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Authors declare that they have no conflicts of interest.

SUPPLEMENTARY INFORMATION

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