Aim. Basing on our earlier finding of inhibitory activity of 5-(4-quinazolylamino)-3-arylindazoles against human protein kinase CK2, the synthesis of new nitrogen containing heterocyclic derivatives was performed in order to find novel inhibitors of this kinase. Methods. Organic synthesis, NMR spectroscopy. Results. A series of 4-chloroquinazolines, 4-chloroquinolines, 4-chloropyrazolo[3,4-d]pyrimidines and 4-chlorothieno[2,3-d]pyrimidine was synthesized. Reaction of these intermediates with 5-amino-3-(3,4-dichlorophenyl)-indazole gave us a series of 14 novel heterocyclic derivatives of 5-amino-3-arylindazole. Conclusions. Besides new quinazoline derivatives – the quinoline and thieno[2,3-d]pyrimidine derivatives of similar structure but different polarity were obtained. Also a series of 1-methylpyrazolo[3,4-d]pyrimidine derivatives with decreased lipophilicity was synthesized.

Keywords: synthesis, indazole, quinazoline, thieno[2,3-d]pyrimidine, pyrazolo[3,4-d]pyrimidine, protein kinase CK2 inhibitor

Introduction

Serine/threonine protein kinase CK2 is one of the first discovered kinases [1]. Despite the long history of CK2 investigations, a number of its functions are not completely determined. This is due to CK2 unique properties, such as constitutive activity, high pleiotropicity (CK2 phosphorylates more than 500 proteins) [2], dual-substrate specificity [3,4], and localization in different cell compartments [5]. Experimental results clearly showed that CK2 is involved in
regulating transcription, translation, cell proliferation, survival, and apoptosis [6]. Overexpression and overactivity of CK2 are associated with the development of neurodegenerative, inflammatory, cardio-vascular diseases, virus infections, and all the cancers that have been examined [7,8]. Therefore, small-molecular inhibitors of CK2 would be important compounds for the development of clinical agents.

The search for CK2 inhibitors has been carried out for over 20 years [9, 10]. Most of the identified CK2 inhibitors belong to coumarins [11], halogenated benzimidazoles (TBB) [12], anthraquinones (emodin) [13], indoloquinazolines (IQA) [14], thieno[2,3-d]pyrimidines [15, 16], 4,5,6,7-tetrahalogeno-1H-isooindole-1,3(2H)-diones [17], flavones derivatives (luteolin, FLC26, FNH79) [18-20], 1,3-thiazole-5-carboxylic acid derivatives [21], quinolones [22], aurones [23, 24] and naphthyridines (CX-4945, CX-5011) [25, 26].

Indazole, also called benzopyrazole, is a heterocyclic molecule in which the pyrazole ring is fused with the benzene ring. Indazole derivatives have been reported as inhibitors of FGFR1 kinase, Aurora kinase, Pim kinase, Bcr-Abl tyrosine kinase [27]. Also, previously it has been described that 5-amino-3-arylindazole core (Fig. 1) could be a good starting point for the protein kinase inhibitors design [28].

Taking into account this fact, the main aim of this work was to find novel inhibitors of human protein kinase CK2 among the 5-hetarylamino-1H-indazole derivatives.

**Materials and Methods**

Starting materials and solvents were purchased from commercial suppliers and used without further purification. $^1$H NMR spectra were recorded on a Varian Mercury 300 instrument at 302 MHz or Varian VXR 400 instrument at 400 MHz. $^{13}$C NMR spectra were recorded on a Varian Mercury 300 instrument at 76 MHz or Varian VXR 400 instrument at 101 MHz. Chemical shifts were described as parts per million (δ) downfield from an internal standard of tetramethylsilane. All tested compounds had ≥ 95 % purity as determined by this method.

**(2-Chloro-5-nitropheryl)-3,4-dichlorobenzophenone, 5.** To a stirred suspension of 25 g (0.124 mol) of 2-chloro-5-nitrobenzoic acid 4 in 50 ml of 1,2-dichloroethane, 2-3 drops of DMF and 15 ml (0.205 mol) of thionyl chloride were added. The mixture was being refluxed until the complete dissolution of acid and cessation of release of gaseous SO₂ and hydrogen chloride in a bubble counter over the condenser. Then volatile components were evaporated under reduced pressure, 25 ml of 1,2-dichloroethane were added to the residue and evaporation of volatile components was repeated. To the crude 2-chloro-5-nitrobenzoic chloride, 70 ml (0.62 mol) of 1,2-dichlorobenzene and 17 g (0.127 mol) of aluminium chloride were added. The mixture was being heated at 100 °C under stirring for 4-6 hours until cessation of release of gaseous hydrogen chloride. After cooling to room temperature, the viscous reaction mixture was diluted with
250 ml of cold water and 10 ml of conc. hydrochloric acid. Crude reaction product was extracted with 100 ml of CH$_2$Cl$_2$. The organic layer was evaporated at 100 °C under 20 mm Hg. The residue was recrystallized from isopropanol giving 35 g (85 %) of 5 as yellow crystals. $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 8.4 (dd, $J = 8.8$ Hz, 2.7 Hz, 1H), 8.38 (d, $J = 2.7$ Hz, 1H), 7.92 (d, $J = 2.0$ Hz, 1H), 7.89 (d, J = 8.8 Hz, 1H), 7.75 (d, 8.5 Hz, 1H), 7.7 (dd, J = 8.5 Hz, 2.0 Hz, 1H).

3-(3,4-Dichlorophenyl)-1H-indazol-5-amine, 6. To a solution of 35 g (0.106 mol) of ketone 5 in 50 ml of dimethylformamide, 7 ml of hydrazine hydrate were added. The reaction mixture was being refluxed for 1 hour. After cooling to room temperature 5-nitro-3-(3,4-dichlorophenyl)-1H-indazole hydrochloride appeared as a bright yellow precipitate. It was separated by filtration and further recrystallized from dimethylformamide to remove the impurity of (2,3-dichlorophenyl)-1H-indazole isomer. After recrystallization, 8.5 g (23 %) of pure 5-nitro-3-(3,4-dichlorophenyl)-1H-indazole hydrochloride were obtained as a yellow powder. $^1$H NMR (302 MHz, DMSO-$d_6$) $\delta$ 13.92 (br s, 1H), 8.91 (d, $J = 2.1$ Hz, 2H), 8.24 (dd, $J = 9.2$, 2.0 Hz, 2H), 8.15 (d, $J = 2.0$ Hz, 2H), 7.99 (dd, $J = 8.4$, 2.0 Hz, 2H), 7.76 (d, $J = 9.2$ Hz, 2H), 7.74 (d, $J = 8.4$ Hz, 2H); $^{13}$C NMR (76 MHz, DMSO-$d_6$) $\delta$ 144.3, 138.8, 136.6, 135.8, 131.9, 129.5, 127.6, 121.5, 118.7, 111.6, 100.2.

General procedure of synthesis of heterocyclic chloro derivatives. To a suspension of 20 mmol of heterocyclic compound 8-21 in 20 ml of phosphorous oxychloride[], 4.2 g (20 mmol) of phosphorous pentachloride were added. The mixture was being refluxed under stirring until complete dissolution of starting material. After cooling to room temperature the volatile material was evaporated under reduced pressure. Residue was dissolved in 50 ml of chloroform and carefully basified with NaHCO$_3$ solution under good stirring (caution! effervescence takes place). Organic layer was separated, dried with Na$_2$SO$_4$ and evaporated, leaving chloro-derivative 22-35, that was immediately used in the next step without purification.

General procedure of arylation of 5-amine-3-(3,4-dichlorophenyl)-1H-indazol 6. A solution of 2.78 g (10 mmol) of 6 in 5 ml of dimethylformamide was added to the 10 mmol hydrazine hydrate were being added slowly dropwise. The reduction process took at least 8 hours and an additional amount of hydrazine hydrate was added if disappearance of deep yellow-orange coloration of reaction mixture did not take place. Hot reaction mixture was filtered from nickel and solvents were evaporated under reduced pressure. Solid residue was washed with water and dried giving 5.35 g (78 %) of 6 as red-brown solid. $^1$H NMR (302 MHz, DMSO-$d_6$) $\delta$ 13.04 (br s, 1H), 8.05 (d, $J = 1.5$ Hz, 1H), 7.86 (dd, $J_1 = 9.0$ Hz, $J_2 = 1.5$ Hz, 1H), 7.71 (d, $J = 8.4$ Hz, 1H), 7.32 (d, $J = 8.8$ Hz, 1H), 7.09 (s, 1H), 6.86 (dd, $J_1 = 8.8$ Hz, $J_2 = 1.6$ Hz, 1H), 5.01 (s, 2H); $^{13}$C NMR (76 MHz, DMSO-$d_6$) $\delta$ 144.3, 138.8, 136.6, 135.8, 131.9, 129.5, 127.6, 121.5, 118.7, 111.6, 100.2.
of corresponding chloro-derivative 22-35. The mixture was refluxed for 3-5 min to complete dissolution of all components and cooled to room temperature. Solid hydrochloride salts of products 36-49 were filtered off, washed with dimethylformamide and acetone. Soluble in DMF products were converted to the bases by adding 0.25 ml of triethylamine and 25 ml of water to the reaction mixture before filtration. Several products were additionally purified with column chromatography on silica gel, using the eluent system CH$_2$Cl$_2$:MeOH 95:5 ÷ 9:1.

$N$-[3-(3,4-Dichlorophenyl)-1H-indazol-5-yl]-quinazoline-4-amine hydrochloride 36. Yield 53 %. $^1$H NMR (400 MHz, DMSO-$_d$$_6$) $\delta$ 13.45 (br s, 1H), 11.20 (br s, 1H), 8.86 (d, J = 7.6 Hz), 8.73 (s, 1H), 8.43 (s, 1H), 8.14 (s, 1H), 7.75 (m, 2H), 7.67 (m, 2H). $^{13}$C NMR (101 MHz, DMSO-$_d$$_6$) $\delta$ 158.4, 156.3, 150.5, 147.3, 137.7, 137.2, 135.9, 134.0, 132.6, 132.9, 131.4, 130.4, 129.5, 129.5, 129.1, 128.4, 127.5, 119.0, 117.9, 116.6, 99.5.

$N$-[3-(3,4-Dichlorophenyl)-1H-indazol-5-yl]-2-isopropylquinazolin-4-amine hydrochloride 37. Yield 22 %. $^1$H NMR (400 MHz, DMSO-$_d$$_6$) $\delta$ 13.45 (br s, 1H), 9.92 (br s, 1H), 8.92 (s, 1H), 8.58 (d, J = 5.5 Hz, 1H), 8.14 (s, 1H), 7.99 (d, J = 8.2 Hz, 1H), 7.89 (d, J = 8.5 Hz, 1H), 7.79 (d, J = 8.1 Hz, 1H), 7.74 (d, J = 5.3 Hz, 2H), 7.64 (d, J = 8.2 Hz, 1H), 7.57 (t, J = 5.7 Hz, 1H), 3.04 (p, J = 5.8 Hz, 1H), 1.28 (d, J = 5.9 Hz, 6H). $^{13}$C NMR (101 MHz, DMSO-$_d$$_6$) $\delta$ 169.8, 157.8, 140.5, 138.6, 134.5, 133.7, 132.9, 131.7, 131.0, 129.9, 128.8, 128.1, 127.7, 126.5, 125.4, 122.9, 122.8, 119.7, 113.6, 111.7, 110.6, 37.1, 21.6.

$N$-[3-(3,4-Dichlorophenyl)-1H-indazol-5-yl]-2-phenylquinazolin-4-amine hydrochloride 38. Yield 54 %. $^1$H NMR (302 MHz, DMSO-$_d$$_6$) $\delta$ 13.54 (br s, 1H), 10.06 (br s, 1H), 8.76 (s, 1H), 8.60 (d, J = 1.4 Hz, 1H), 8.40 (s, 2H), 8.17 (s, 1H), 7.98 (s, 2H), 7.84 (s, 2H), 7.63 (d, J = 28.8 Hz, 3H), 7.38 (d, J = 25.5 Hz, 3H); $^{13}$C NMR (76 MHz, DMSO-$_d$$_6$) $\delta$ 159.5, 158.5, 150.7, 141.2, 139.3, 138.7, 135.0, 133.9, 133.6, 132.2, 131.5, 130.6, 130.4, 128.7, 128.4, 128.3, 127.0, 126.3, 124.0, 123.5, 120.3, 114.5, 113.0, 111.0.

2-(2-Chlorophenyl)-$N$-[3-(3,4-dichlorophenyl)-1H-indazol-5-yl]quinazolin-4-amine hydrochloride 39. Yield 65 %. $^1$H NMR (302 MHz, DMSO-$_d$$_6$) $\delta$ 13.47 (br s, 1H), 10.14 (br s, 1H), 8.76 (s, 1H), 8.66 (d, J = 8.1 Hz, 1H), 8.11 (s, 1H), 7.86 (d, J = 7.0 Hz, 2H), 7.72 (d, J = 7.3 Hz, 1H), 7.65 (d, J = 7.2 Hz, 2H), 7.59 (d, J = 9.1 Hz, 2H), 7.50 (d, J = 7.7 Hz, 1H), 7.46–7.39 (m, 2H), 7.37 (d, J = 7.3 Hz, 1H); $^{13}$C NMR (76 MHz, DMSO-$_d$$_6$) $\delta$ 161.1, 158.3, 150.3, 141.1, 139.6, 139.4, 134.9, 133.8, 133.6, 132.2, 131.9, 131.8, 131.4, 130.4, 130.3, 128.3, 127.3, 126.9, 126.7, 123.9, 123.5, 120.2, 114.2, 113.3, 111.1.

$N$-[3-(3,4-Dichlorophenyl)-1H-indazol-5-yl]-6-methylquinazolin-4-amine hydrochloride 40. Yield 64 %. $^1$H NMR (302 MHz, DMSO-$_d$$_6$) $\delta$ 13.65 (br s, 1H), 11.09 (br s, 1H), 8.70 (s, 1H), 8.63 (s, 1H), 8.41 (s, 1H), 8.09 (s, 1H), 7.92 (d, J = 7.8 Hz, 1H), 7.83–7.67 (m, 4H), 7.63 (d, J = 7.6 Hz, 1H), 2.48 (s, 3H); $^{13}$C NMR (76 MHz, DMSO-$_d$$_6$) $\delta$ 159.2, 151.8, 141.1, 140.9, 140.1, 138.1, 136.8, 134.6, 132.1, 131.5, 130.5, 128.1, 126.8, 124.7, 123.6, 122.6, 120.0, 115.4, 114.3, 111.2, 21.6.

3-(3,4-Dichlorophenyl)-$N$-(6-phenylpyrimidin-4-yl)-1H-indazol-5-amine 41. Yield 80 %. $^1$H NMR (400 MHz, DMSO-$_d$$_6$) $\delta$ 13.65 (s, 1H), 11.60 (s, 1H), 8.84 (s, 1H),
8.41 (s, 1H), 8.07 (s, 1H), 8.00–7.85 (m, 3H), 7.73 (d, J = 8.2 Hz, 1H), 7.67 (s, 1H), 7.63 (d, J = 9.3 Hz, 1H), 7.58 (d, J = 6.8 Hz, 3H), 7.43 (s, 1H). 13C NMR (101 MHz, DMSO-d6) δ 162.0, 154.3, 154.2, 141.2, 139.8, 134.6, 132.4, 132.2, 131.7, 131.6, 130.5, 129.8, 128.3, 127.6, 126.9, 122.9, 120.2, 113.3, 111.9, 104.3, 103.2.

N-[3-(3,4-Dichlorophenyl)-1H-indazol-5-yl]-6,7-dimethoxy-2-(trifluoromethyl)quinazolin-4-amine 42. Yield 68 %. 1H NMR (400 MHz, DMSO-d6) δ 13.49 (br s, 1H), 9.99 (br s, 1H), 8.72 (s, 1H), 8.13 (s, 1H), 7.97 (d, J = 7.2 Hz, 2H), 7.75 (d, J = 8.7 Hz, 1H), 7.69 (d, J = 8.3 Hz, 1H), 7.64 (d, J = 8.8 Hz, 1H), 7.33 (s, 1H), 3.98 (s, 3H), 3.93 (s, 3H). 13C NMR (101 MHz, DMSO-d6) δ 157.5, 155.3, 150.7, 147.5, 146.3, 141.0, 139.4, 134.9, 133.4, 132.2, 131.3, 130.4, 128.1, 126.7, 123.6, 122.0, 120.1, 113.0, 111.1, 109.5, 108.3, 102.6, 56.9, 56.5.

N-[3-(3,4-Dichlorophenyl)-1H-indazol-5-yl]quinolin-4-amine hydrochloride 43. Yield 38 %. 1H NMR (302 MHz, DMSO-d6) δ 14.73 (br s, 1H), 13.86 (br s, 1H), 11.26 (br s, 1H), 8.90 (d, J = 8.5 Hz, 1H), 8.43 (d, J = 6.7 Hz, 1H), 8.21 (s, 1H), 8.12 (s, 1H), 8.09 (d, J = 8.7 Hz, 1H), 7.99 (t, J = 8.1 Hz, 2H), 7.79 (d, J = 8.8 Hz, 1H), 7.75 (d, J = 7.8 Hz, 1H), 7.69 (d, J = 8.4 Hz, 1H), 7.49 (d, J = 9.0 Hz, 1H), 6.69 (d, J = 6.9 Hz, 1H); 13C NMR (76 MHz, DMSO-d6) δ 156.2, 142.8, 141.5, 141.0, 138.6, 134.3, 134.2, 132.2, 131.6, 131.4, 130.7, 128.3, 127.3, 127.1, 125.5, 124.3, 120.6, 120.5, 118.3, 117.4, 112.9, 100.2.

N-[3-(3,4-Dichlorophenyl)-1H-indazol-5-yl]-2,3-dihydro-1H-cyclopent[a]b]quinolin-9-amine hydrochloride 44. Yield 84 %. 1H NMR (400 MHz, DMSO-d6) δ 15.42 (br s, 1H), 13.63 (br s, 1H), 10.73 (s, 1H), 8.72 (d, J = 8.5 Hz, 1H), 8.18 (d, J = 8.7 Hz, 1H), 8.13 (d, J = 1.9 Hz, 1H), 7.94 (dd, J = 10.5, 1.9 Hz, 2H), 7.92–7.86 (m, 1H), 7.68 (d, J = 8.5 Hz, 2H), 7.63 (d, J = 8.4 Hz, 1H), 7.37 (dd, J = 8.9, 1.5 Hz, 1H), 3.19 (t, J = 7.6 Hz, 2H), 2.20 (t, J = 7.3 Hz, 2H), 1.97 (p, J = 7.8 Hz, 2H). 13C NMR (101 MHz, DMSO-d6) δ 158.4, 156.3, 150.5, 147.3, 137.7, 137.2, 135.9, 134.0, 132.6, 132.3, 131.4, 130.4, 129.5, 129.5, 129.1, 128.4, 127.5, 119.0, 117.9, 116.6, 99.5.

N-[3-(3,4-Dichlorophenyl)-1H-indazol-5-yl]thieno[2,3-d]pyrimidin-4-amine hydrochloride 45. Yield 27 %. 1H NMR (400 MHz, DMSO-d6) δ 10.81 (br s, 1H), 8.53 (s, 1H), 8.45 (d, J = 1.9 Hz, 1H), 8.15 (d, J = 1.8 Hz, 1H), 8.11–8.06 (m, 1H), 7.97 (dd, J = 8.4, 1.9 Hz, 1H), 7.75 (dd, J = 8.8, 1.7 Hz, 1H), 7.69 (d, J = 5.9 Hz, 1H), 7.67 (d, J = 3.4 Hz, 1H), 7.65 (d, J = 3.9 Hz, 1H). 13C NMR (101 MHz, DMSO-d6) δ 164.7, 156.2, 154.7, 150.6, 150.5, 134.0, 132.3, 131.4, 130.4, 129.5, 129.5, 127.5, 126.1, 121.0, 120.9, 120.5, 117.5, 113.6, 101.5.

N-[3-(3,4-Dichlorophenyl)-1H-indazol-5-yl]-1-methyl-pyrazolo[3,4-d]pyrimidin-4-amine hydrochloride 46. Yield 57 %. 1H NMR (400 MHz, DMSO-d6) δ 13.53 (br s, 1H), 10.30 (br s, 1H), 8.52 (s, 1H), 8.41 (s, 1H), 8.15 (d, J = 1.7 Hz, 1H), 7.97 (dd, J = 8.4, 1.7 Hz, 1H), 7.81 (dd, J = 10.8, 6.9 Hz, 2H), 7.66 (d, J = 9.0 Hz, 1H), 7.58 (t, J = 9.5 Hz, 1H), 3.95 (s, 3H). 13C NMR (101 MHz, DMSO-d6) δ 158.0, 155.7, 151.5, 150.5, 148.4, 134.0, 132.3, 131.4, 130.6, 130.4, 129.5, 129.5, 129.4, 127.5, 118.9, 116.9, 101.6, 99.4, 33.4.

N-[3-(3,4-Dichlorophenyl)-1H-indazol-5-yl]-1,3-dimethyl-pyrazolo[3,4-d]pyrimidin-4-amine hydrochloride 47. Yield 48 %. 1H NMR (400 MHz, DMSO-d6) δ 13.25 (br s, 1H), 8.69 (s, 1H), 8.32 (s, 1H), 8.19 (s, 1H), 8.16 (d, J = 1.9 Hz,
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1H), 7.96 (dd, J = 8.4, 1.9 Hz, 1H), 7.92 (s, 1H), 7.68 (dd, J = 8.8, 1.5 Hz, 2H), 7.67 (d, J = 8.4 Hz, 2H), 7.57 (d, J = 8.9 Hz, 1H), 3.91 (s, 3H), 2.71 (s, 3H). 13C NMR (101 MHz, DMSO-d6) δ 156.1, 155.5, 154.4, 140.8, 140.3, 139.8, 134.9, 133.4, 132.1, 131.5, 130.3, 128.1, 126.8, 125.3, 120.2, 114.4, 111.0, 100.0, 33.5, 15.0.

3-Bromo-N-[3-(3,4-dichlorophenyl)-1H-indazol-5-yl]-1-methyl-pyrazolo[3,4-d]pyrimidin-4-amine 48. Yield 73 %. 1H NMR (400 MHz, DMSO-d6) δ 13.47 (br s, 1H), 10.21 (br s, 1H), 8.50 (s, 1H), 8.42 (s, 1H), 8.17 (d, J = 1.8 Hz, 1H), 7.98 (dd, J = 8.4, 1.9 Hz, 1H), 7.89–7.74 (m, 3H), 7.69 (d, J = 8.8 Hz, 1H), 3.96 (s, 3H).

13C NMR (101 MHz, DMSO-d6) δ 156.6, 154.3, 152.2, 150.5, 149.1, 134.0, 132.3, 131.4, 130.4, 129.5, 129.4, 127.5, 119.8, 116.9, 113.6, 101.8, 100.3, 33.6.

N-[3-(3,4-Dichlorophenyl)-1H-indazol-5-yl]-1,6-dimethyl-pyrazolo[3,4-d]pyrimidin-4-amine hydrochloride 49. Yield 62 %. 1H NMR (400 MHz, DMSO-d6) δ 13.57 (br s, 1H), 10.45 (br s, 1H), 8.93 (s, 1H), 8.17 (d, J = 1.8 Hz, 1H), 7.99 (dd, J = 8.3, 1.1 Hz, 1H), 7.78 (d, J = 8.1 Hz, 1H), 7.75–7.62 (m, 3H), 3.92 (s, 3H), 2.59 (s, 3H). 13C NMR (101 MHz, DMSO-d6) δ 159.2, 155.1, 153.8, 150.5, 149.1, 134.0, 132.3, 131.4, 130.4, 129.5, 129.4, 127.5, 119.8, 116.9, 113.6, 101.8, 100.3, 33.6.

LogP calculation

LogP values were calculated using Marvin Sketch 19.12 (https://www.chemaxon.com).

Results and Discussion

Earlier we have found new promising CK2 inhibitors among the 4-quinazoline derivatives of 5-amino-3-arylindazoles 1-3 [29]. The inhibitory activity of these compounds against CK2 was tested in in vitro assay with radiolabeled ATP [30]. They have shown IC50 values in a range 0.007–0.1 µM [29]. The structures and inhibitory activity of 1-3 are represented in Figure 2.

Besides the high IC50 values all three compounds 1-3 also have a significant disadvantage. They have too high lipophilicity (LogP>5) and as a result – poor water solubility. We have tried to modify chemical structure to overcome this disadvantage. We have selected the 3,4-dichlorophenyl substituent in the 3-position as a substituent of the most active compound 3 and left it unchanged. Meanwhile, we have focused on varying of available heterocyclic residues attached to the 5-amino-group. The 5-amino-3-(3,4-dichlorophenyl)-1H-indazole 6 interme-

![Compound 1](image1.png)  
**Compound 1**  
IC50 = 0.007 µM

![Compound 2](image2.png)  
**Compound 2**  
IC50 = 0.016 µM

![Compound 3](image3.png)  
**Compound 3**  
IC50 = 0.1 µM

Fig. 2. Chemical structure of the 5-(4-quinazolylamino)-3-aryindazole derivatives 1-3.
diate has been synthesized following Scheme 1.

2-Chloro-5-nitrobenzoic acid 4 was converted into acid chloride and immediately used for Friedel-Crafts acylation of 1,2-dichlorobenzene. The heating of obtained ketone 5 with hydrazine hydrate in dimethylformamide caused chlorine substitution and indazole ring closure. The reduction of nitro-group with hydrazine hydrate in the presence of Raney nickel gave 5-amino-3-(3,4-dichlorophenyl)-1H-indazole 6.

Following starting heteroaromatic derivatives: (3H-quinazolin-4-one 8 [31], 2-isopropyl-3H-quinazolin-4-one 9 [32], 2-trifluoromethyl-3H-quinazolin-4-one [33], 2-phenyl-3H-quinazolin-4-one 10, 2-(2-chlorophenyl)-3H-quinazolin-4-one 11 [34], 6-methyl-3H-quinazolin-4-one 12 [31], 6-phenyl-3H-pyrimidin-4-one 13 [35], 6,7-dimethoxy-2-(trifluoromethyl)-3H-quinazolin-4-one 14 [36], 1H-quinolin-4-one 15 [37], 1,2,3,4-tetrahydrocyclopenta[b]quinolin-9-one 16 [38], 1H-thieno[2,3-d]pyrimidin-4-one 17 [39], 1-methyl-7H-pyrazolo[3,4-d]pyrimidin-4-one 18, 1,3-dimethyl-7H-pyrazolo[3,4-d]pyrimidin-4-one 19 [40], 3-bromo-1-methyl-7H-pyrazolo[3,4-d]pyrimidin-4-one 20 [41], 1,6-di-
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Besides additional quinazoline derivatives – the quinoline and thieno[2,3-d]pyrimidine derivatives of similar structure but different polarity were obtained. Also a series of 1-methylpyrazolo[3,4-d]pyrimidine derivatives with decreased lipophilicity was synthesized.

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The synthesis of 5-hetarylamino-3-aryl-1H-indazoles as inhibitors of protein kinase CK2

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Мета. В продовження пошуку нових інгібіторів протеїнкинази CK2 ґрунтуючись на раніше виявлених нами інгібіюючій активності похідних 5-(4-хіназоліламіно)-3-ариліндазолу було виконано синтез нових азотвмісних гетероциклічних похідних 5-аміно-3-ариліндазолу.

Методи. Органічний синтез, спектроскопія ЯМР. Результати. Було синтезовано низку 4-хлорхіназолінів, 4-хлорпіразоло[3,4-d]піримідинів та 4-хлоротієно[2,3-d]піримідинів. Взаємодію цих інтермедіатів з 5-аміно-3-(3,4-дихлорфеніл)-індазолом було одержано 14 нових гетероциклічних похідних 5-аміно-3-(3,4-дихлорфеніл)-індазолу.

Висновки. Крім нових похідних хіназолину, було отримано похідні хіноліну та тієно[2,3-d]піримідину близькі за структурою, але відмінні за полярністю. Також було синтезовано низку 1-метилпіразоло[3,4-d]піримідинових похідних з нижчою ліпофільністю.

Ключові слова: синтез, індазол, хіназолін, тієно[2,3-d]піримідин, піразоло[3,4-d]піримідин, інгібітор протеїнкинази CK2

Синтез 5-гетариламіно-3-арил-1H-індазолів як інгібіторів протеїнкинази CK2

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Цель. В продолжение поиска новых ингибиторов протеинкиназы СК2 пошлаясь на ранее выявленную нами
ингибитирующую активность производных 5-(4-хиназо- 
лиламино)-3-арилидазола были синтезированы новые 
азотсодержащие гетероциклические производные 5-ами- 
но-3-арил-индазола. Методы. Органический синтез, 
спектроскопия ЯМР. Результаты. Была синтезирована 
серия 4-хлорхиназолинов, 4-хлорхинолинов, 4-хлорпи- 
разоло[3,4-d]пиримидинов и 4-хлортиено[2,3-d]пирими- 
дин. Взаимодействием этих интермедиатов с 5-ами- 
но-3-(3,4-дихлорфенил)-индазолом было получено 14 
новых гетероциклических производных 5-ами- 
но-3-(3,4-дихлорфенил)-индазола. Выводы. Помимо 
новых производных хиназолина, были получены произ- 
водные хинолина и тиено[2,3-d]пиримидина близкие по 
структуре, но другой полярности. Также была синтези- 
рована серия 1-метилпиразоло[3,4-d]пиримидиновых 
производных с пониженной липофильностью.

Ключевые слова: синтез, индазол, хиназолин, 
тиено[2,3-d]пиримидин, пиразоло[3,4-d]пиримидин, 
ингибитор протеинкиназы CK2

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