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CONSTRUCTION OF THE COMBINATORIAL LIBRARIES OF 5-HYDROXYMETHYL-2-IMINO-8-METHYL-2H-PYRANO[2,3-c]PYRIDIN-3-N-ARYLCARBOXAMIDES

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Using the parallel solution-phase synthesis combinatorial libraries of 5-hydroxymetyl-2-imino-8-methyl-2H-pyrano[2,3-c]pyridin-3-N-arylcarboxamides, 5-hydroxymetyl-2-N-arylimino-methyl-2H-pyrano[2,3-c]pyridin-3-N-arylcarboxamides and their acylic derivatives were obtained.

ПОСТРОЕНИЕ КОМБИНАТОРНЫХ БИБЛИОТЕК НА ОСНОВЕ 5-ГИДРОКСИМЕТИЛ-2-ИМИНО-8-МЕТИЛ-2Н-ПИРАНО[2,3-c]ПИРИДИН-3-N-АРИЛКАРБОКСАМИДОВ
И.А.Журавель, С.Н.Коваленко, А.В.Иващенко, В.П.Черных
Методом параллельного жидкофазного синтеза получены комбинаторные библиотеки 5-гидроксиметил-2-имино-8-метил-2Н-пирано[2,3-c]пиридин-3-N-арилкарбоксамидов, 5-гидроксиметил-2-N-арилимино-8-метил-2Н-пирано[2,3-c]пиридин-3-N-арилкарбоксамидов и их ацильных производных.

ПОБУДОВА КОМБІНАТОРНИХ БІБЛІОТЕК НА ОСНОВІ 5-ГІДРОКСИМЕТИЛ-2-ІМІНО-8-МЕТИЛ-2Н-ПІРАНО[2,3-c]ПІРИДИН-3-N-АРИЛКАРБОКСАМІДІВ
І.О.Журавель, С.М.Коваленко, О.В.Іващенко, В.П.Черних
Методом паралельного рідкофазного синтезу одержані комбінаторні бібліотеки 5-гідроксиметил-2-іміно-8-метил-2Н-пірано[2,3-c]піридин-3-N-арилкарбоксамідів, 5-гідроксиметил-2-N-аріліміно-8-метил-2Н-пірано[2,3-c]піридин-3-N-арилкарбоксамідів та їх ацильних похідних.

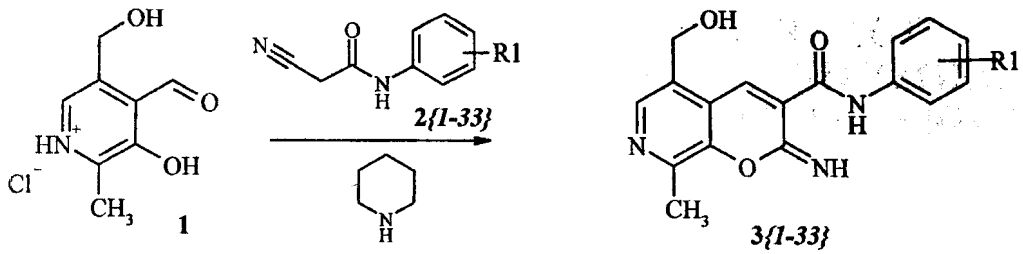
At present most of the synthetic drugs are so-called "small molecules". Generally they are heterocyclic organic compounds with certain properties, which proved selective activity to the protein targets. At the modern stage of the pharmaceutical science evolution the most part of the drug molecules is obtained by modification of active initial compounds — hits, found through bioscreening. The main sources for hits are large discovery combinatorial libraries, which are synthesized using techniques parallel solution-phase or solid-phase synthesis. The value of a compound collection is not primarily in a number of samples per se, but an uniqueness library and likelihood of detecting perspective substances and developing novel drugs from it [1, 2].

2H-Pyrano[2,3-c]pyridin-2-ones are interesting objects for the combinatorial libraries for searching biologically active substances due to the fact that they are bioisosteric analogs of well-known class coumarines, which were found in plants and act as structural subunits of more complex natural products [3].

However, there 7-azaanalogs of coumarines are considerably less investigated at present. The only few works are published on this topic. For example, starting from pyridoxal 3-substituted 2H-pyrano[2,3-c]pyridin-2-ones [4-6] and 6a,11a-dihydro-6H-benzo[4',5']thieno[2',3':4,5]pyrano[2,3-c]pyridin-6-one [7] by Knoevenagel condensation have been obtained. As a result of interaction of 3-hydroxy-4-hydroxymethylpyridine, 3-hydroxy-4-formylpyridine or 3-hydroxyisonicotinoates with malonic acid was isolated 7-azacoumarin-3-carbonic acid and the method of their decarboxylation was proposed [8], the reaction with ethoxymagnesiummalonic ether allows to obtained 4-hydroxy-7-azacoumarine [9]. By the reaction of 3-methoxy-1,4-dihydroquinolin-4-one with ethyl acrylate 3H-pyrano [2,3-c]quinolin-3-one was obtained [10], and the isomeric 6H-isochromeno[3,4-c]pyridin-6-one was isolated after the cyclization of the 3-methoxy-4-(2-carbmethoxyphenyl)pyridine [11].

It should be noticed that the biological action of the compounds obtained [4-11] has not been investigated. With regard to the above mentioned facts the combinatorial libraries of 2H-pyrano[2,3-c]pyridines are undoubtedly interesting.

In the present work the possibilities of combinatorial synthesis technologies for constructing the libraries of 5-hydroxymethyl-2-imino-8-methyl-2H-pyrano[2,3-c]



R1 = H, 2-Me, 3-Me, 4-Me, 2-Et, 4-Et, 2-OMe, 4-OMe, 3,4-diMe, 3,5-diMe, 2,4-diOMe, 2,5-diOMe, 3,5-diOMe, 2-OEt, 2-OMe-5-Me, 2-F-4-Me, 2-Cl-4-F, 3-Cl-4-Me, 3-Cl-4-OMe, 4-COOMe, 2-F, 3-F, 2-Cl, 3-Cl, 4-Cl, 3-Br, 3-CF_3, 2,3-diCl, 2,5-diCl, 3,4-diCl, 2,4-diF, 3,4-diF, 2,5-diF

Scheme 1

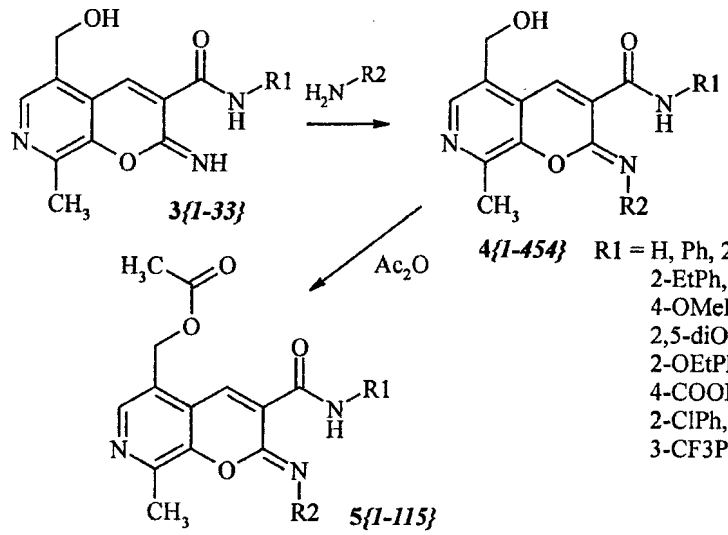
pyridin-3-carboxamides with one or two aryl substitutes in molecule were investigated.

By the interaction of pyridoxal hydrochloride 1 with a series of cyanoacetarylamides *2{1-33}* a number of 5-hydroxymethyl-2-imino-8-methyl-2H-pyrano[2,3-c] pyridin-3-N-arylcarboxamides *3{1-33}* were obtained (Scheme 1) [12].

2-Iminolactone moiety in the structure of compounds 3 provides their significant synthetic potential and allows to construct a huge series of the new substances. It is known that 2-iminocoumarines can form salts with strong acids or interact with electrophylic and nucleophylic reactants; the reactions of iminolactone cycle opening and recyclization transformations are also reported [13]. We performed the nucleophylic substitution of iminogroup with aromatic amines (Scheme 2).

Since many anilines are commercially available or synthetically accessible, these transformations may be applicable to generate a large number of 7-azacoumarin-based molecules. To accomplish of this scheme transformations we suggested the technique of solution-phase parallel synthesis using synthesizer Combi-Syn-012-3000. The reaction between the starting substances was carried out at short-time heating in glacial acetic acid medium (20 min). Glacial acetic acid is not used only as a solvent, it facilitates the interaction due to the its proton-donor properties. The condition described exclude the possibility of recyclization transformation and the hydrolysis of iminogroup, they also provide a satisfactory yields of target products (41-81%). As a result of our research work the combinatorial library of 2-N-arylimino-5-hydroxymetyl-8-methyl-2H-pyrano[2,3-c]pyridin-3-N-arylcarboxamides has been synthesized including more than 450 compounds (Fig. 1).

For the expansion of the searching area of potentially biologically active compounds the reaction of acetylation of diarylsubstituted products was carried out. As a result the library of correspondent acetyl derivatives (115 compounds) has been obtained (Scheme 2, Fig. 2).



4{1-454} R1 = H, Ph, 2-MePh, 3-MePh, 4-MePh, 2-EtPh, 4-EtPh, 2-OMePh, 4-OMePh, 3,4-diMePh, 2,5-diOMePh, 3,5-diOMePh, 2-OEtPh, 2-OMe-5-MePh, 4-COOMePh, 2-FPh, 3-FPh, 2-ClPh, 3-ClPh, 3-BrPh, 3-CF3Ph, 3,4-diFPh, 2,5-diFPh

R2 = Ph, 2-MePh, 3-MePh, 4-MePh, 2-EtPh, 3-EtPh, 4-EtPh, 4-PhPh, 4-OPhPh, 2-OMePh, 3-OMePh, 4-OMePh, 3-SMePh, 2-OEtPh, 4-OEtPh, 1-naphthyl, 2-ClPh, 4-ClPh, 2-FPh, 3-FPh, 4-FPh, 3-BrPh, 4-BrPh, 2-IPh, 4-IPh, 3,4-diMePh, 3,5-diMePh, 2,4-diOMePh, 2,5-diOMePh, 3,5-diOMePh, 3,4-diOMePh, 2,5-diOEtPh, 3,4,5-triOMePh, 3,4-diClPh, 3,4-diBrPh, 3-Cl-4-FPh, 3-Cl-4-MePh, 3-Cl-4-OMePh, 2-Cl-4-MePh, 2-OMe-5-ClPh, 2-OMe-5-MePh, 2,4-diOMe-5-ClPh, 3,4-OCH_2OPh, 3-CF_3Ph, 4-CF_3Ph, 4-CNPh, 4-COOEtPh, 3-COMePh, 3-$CONH_2$Ph, 4-COOMePh, 4-COOEtPh, 4-COMePh, 4-$CONH_2$Ph

Scheme 2

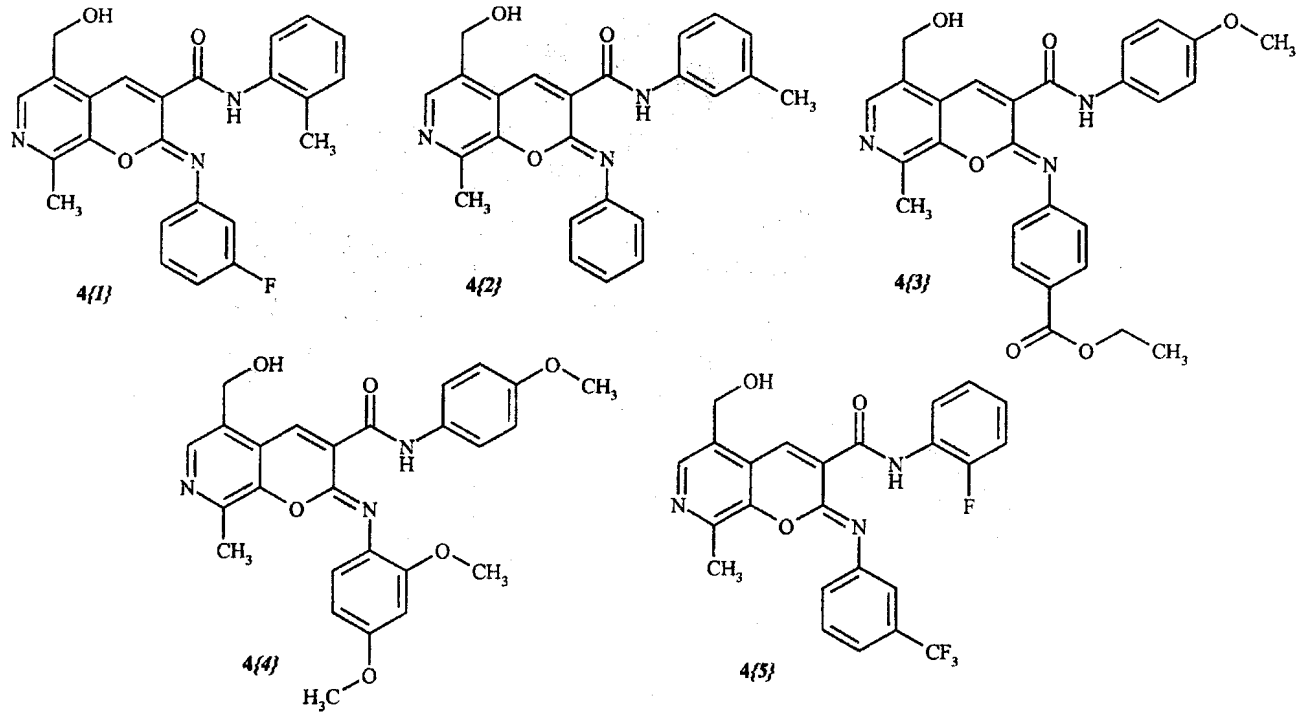


Fig. 1. Examples of substances of library of 2-N-arylimino-5-hydroxymetyl-8-methyl-2H-pyrano[2,3-c]pyridin-3-N-arylcarboxamides.

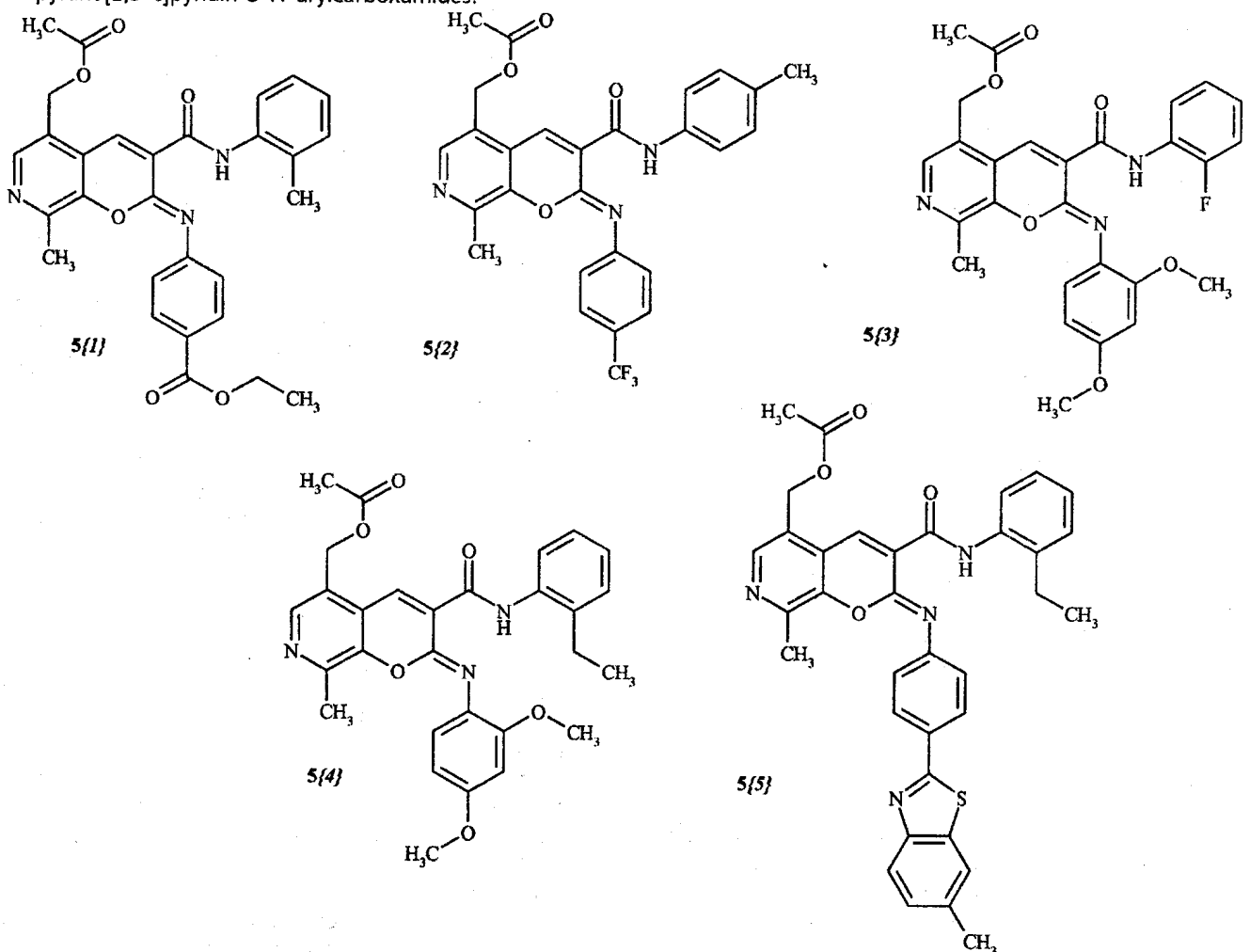


Fig. 2. Examples of substances of library of acetyl derivatives of 2-N-arylimino-5-hydroxymetyl-8-methyl-2H-pyrano[2,3-c]pyridin-3-N-arylcarboxamides.

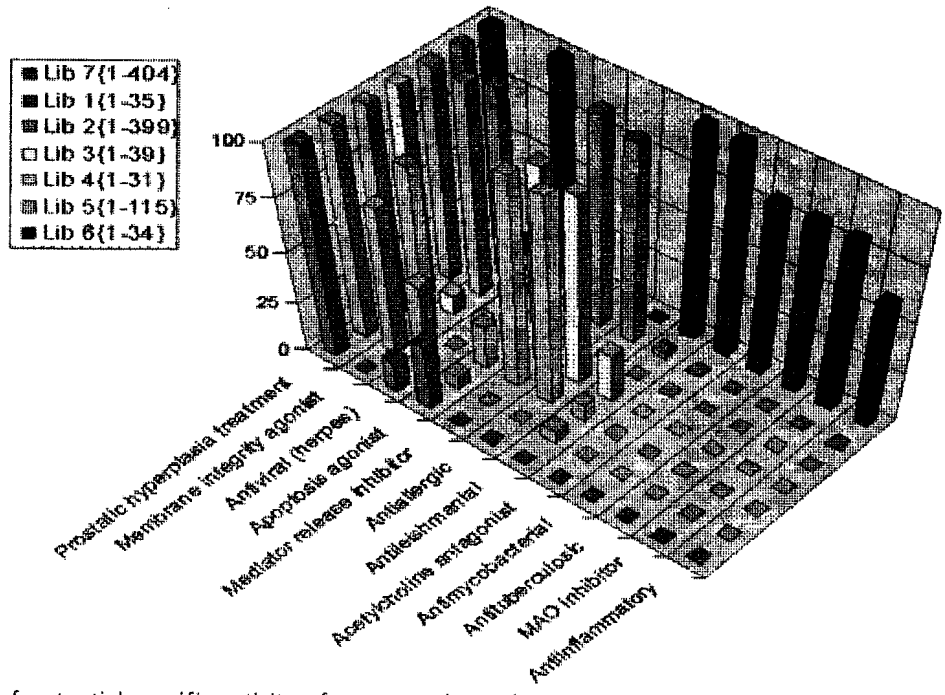


Fig. 3. Prediction of potential specific activity of compounds synthesized.

The structures of the substances obtained have been confirmed with the elemental analysis, IR-, PMR-spectroscopy, in some cases — mass-spectrometry and RSA [14].

One of the most important approaches for new effective compounds search is the utilization of virtual screening methods.

As a part of our investigation work the prediction of potential specific activity of all compounds synthesized using the PASS program package (Prediction Activity Spectra for Substances) [15] has been carried out. The analysis showed that for all of the compounds classes from 3 to 8 types of the pharmacological action can be expected. With a high degree of probability the antiviral, antimycobacterial, antiallergical activity have been predicted. These substances can be of interest as potential MAO inhibitors or medicines for treatment prostate hyperplasia (Fig. 3).

Conclusions

As a consequence of our research work the combinatorial libraries of the new 2H-pyrano[2,3-c]pyridine derivatives have been synthesized. Their promising potential as objects for biologically activity investigations has been shown using the virtual screening methods.

Experimental Section

All solvents and reagents were obtained from the commercial sources and used without purification. Melting points (°C) were measured with the melting point apparatus of Buchi firm (Switzerland) model B-520. ^{1}H NMR spectra were recorded on spectrometer of Varian firm WXR-400 (200 MHz) in DMSO-D_6 or $CDCl_3$ using TMS as an internal standard (chemical shifts in ppm). IR spectra were recorded on the spectrophotometer "Specord M80" in tablets KBr. UV/Vis spectra were registered on the spectrophotometer "Specord M40" in ethanol.

Thin-layer chromatography (TLC) was performed on silica gel on aluminium sheets Silufol UV_{254} (5 sm x 15 sm) (Kavalier, Czech Republic) or on glass plates with 0,25 mm silica gel 60 F_{254} layer (Merck, Germany), eluent is the mixture of solvents: chloroform — triethylamine — methanol 90:5:5. The content of the main substance was controlled using HPLC in Shimadzu 10-AV apparatus (Luna-C18 column, Phenomenex, 25 sm x 4,6 mm, UV detection at 215 and 254 nm) and LC-MS on Applied Biosystems apparatus (Shimadzu 10-AV LC, Gilson-215 the automatic supply of the samples, mass-spectrometre API 150EX, detectors UV (215 and 254 nm) and ELS, Luna-C18 column, Phenomenex, 5 sm x 2 mm). According to LC/MS data, all compounds have purity more than 95%.

General method of synthesis of 5-hydroxymethyl-2-imino-8-methyl-2H-pyrano[2,3-c]pyridin-3-N-arylcarboxamides 3*{1-33}*.

The parallel synthesis of combinatorial libraries were accomplished using a laboratory synthesizer CombiSyn-012-3000. The solution of pyridoxal hydrochloride 1 (2,44 g, 0,012 mol) in 60 mL of absolutely methanol containing piperidine (0,25 mL, 0,025 mol) was dispensed to 12 combinatorial vials (5 mL per vial). To this portion 5 mL of absolutely methanol containing 0.001 mol of correspondent substituted amide of cyanoacetic acid 2 was added by injection while stirring. Resulting mixtures were heated at 40-50°C for 30 minutes while stirring. The solids of 5-hydroxymethyl-2-imino-8-methyl-2H-pyrano[2,3-c] pyridin-3-N-arylcarboxamides 3 obtained were filtered, washed with water, methanol and crystallized from mixture of DMF — methanol. The yields of the

products are 47-89%. The combinatorial library including 12 compounds was obtained. It contains: **5-hydroxymethyl-2-imino-8-methyl-2H-pyrano[2,3-c] pyridin-3-N-phenylcarboxamide 3***{1}*: was obtained with yield 76%, m.p. 230-31°C, ^{1}H NMR ($CDCl_3$), δ (ppm): 12,58 (s, 1H), 9,41 (s, 1H), 8,61 (s, 1H), 8,23 (s, 1H), 7,64 (dd, 2H) 7,39 (t, 2H), 7,13 (dt, 1H), 5,41 (t, 1H), 4,71 (d, 2H), 2,54 (s, 3H); IR (KBr), ν (cm^{-1}): 3300, 3202, 1689, 1634; **5-hydroxymethyl-2-imino-8-methyl-2H-pyrano[2,3-c]pyridin-3-N-(2-fluorophenyl)carboxamide 3***{2}*: was obtained with yield 48%, m.p. 254-55°C, ^{1}H NMR ($CDCl_3$), δ (ppm): 12,92 (s, 1H), 9,43 (s, 1H), 8,58 (s, 1H), 8,26 (s, 1H), 8,38 (dt, 1H) 7,20 (m, 3H), 5,38 (t, 1H), 4,63 (d, 2H), 2,52 (s, 3H); IR (KBr), ν (cm^{-1}): 3314, 3196, 1691, 1643; **5-hydroxymethyl-2-imino-8-methyl-2H-pyrano[2,3-c]pyridin-3-N-(3,4-dimethylphenyl)carboxamide 3***{3}*: was obtained with yield 81%, m.p. 232-33°C, ^{1}H NMR ($CDCl_3$), δ (ppm): 12,46 (s, 1H), 9,43 (s, 1H), 8,61 (s, 1H), 8,25 (s, 1H), 7,44 (d, 1H), 7,39 (s, 1H), 7,12 (d, 1H), 5,39 (t, 1H), 4,70 (d, 2H), 2,53 (s, 3H), 2,21 (s, 6H); IR (KBr), ν (cm^{-1}): 3428, 3185, 1677, 1630; **5-hydroxymethyl-2-imino-8-methyl-2H-pyrano[2,3-c]pyridin-3-N-(3-trifluoromethylphenyl)carboxamide 3***{4}*: was obtained with yield 60%, m.p. 239°C, ^{1}H NMR ($CDCl_3$), δ (ppm): 12.84 (s, 1H), 9.45 (s, 1H), 8.61 (s, 1H), 8.22 (s, 1H), 8.18 (s, 1H), 7.77 (d, 1H), 7.59 (t, 1H), 7.46 (d, 1H), 5.42 (t, 1H), 4.68 (d, 2H), 2.52 (s, 3H); IR (KBr), ν (cm^{-1}): 3340, 3200, 1693, 1642; **5-hydroxymethyl-2-imino-8-methyl-2H-pyrano[2,3-c] pyridin-3-N-(4-methoxy-3-chlorophenyl)carboxamide 3***{5}*: was obtained with yield 70%, m.p. 258-60°C, ^{1}H NMR ($CDCl_3$), δ (ppm): 12,51 (s, 1H), 9,38 (s, 1H), 8,56 (s, 1H), 8,21 (s, 1H), 7,86 (d, 1H), 7,46 (dd, 1H), 7,13 (d, 1H), 5,39 (t, 1H), 4,70 (d, 2H), 3,83 (s, 3H), 2,50 (s, 3H); IR (KBr), ν (cm^{-1}): 3315, 3235, 1687, 1624.

General method of synthesis of 5-hydroxymethyl-8-methyl-2-N-arylimino-2H-pyrano[2,3-c]pyridin-3-N-arylcarboxamides 4*{1-454}*.

The solution of correspondent aniline (0,012 mol) in 60 mL of glacial acetic acid was dispensed to 12 combinatorial vials of the synthesizer (5 mL per vial) and heated at 50-65°C. To this portion 5 mL of glacial acetic acid containing 0,001 mol of correspondent 2H-pyrano[2,3-c]pyridin-3-N-arylcarboxamides 3 was added by injection while stirring. Resulting mixtures were refluxed for 20 minutes while stirring. After cooling the solids of 2-N-arylimino-2H-pyrano[2,3-c] pyridin-3-N-arylcarboxamides 4 were filtered, washed with ethanol and crystallized from mixture of DMF — ethanol. The yields of the products are 41-81%. The combinatorial library including 12 compounds was obtained. It contains: **5-hydroxymethyl-2-N-(3-fluorophenyl)imino-8-methyl-2H-pyrano[2,3-c]pyridin-3-N-(2-methylphenyl)carboxamide 4***{1}*: was obtained with yield 69%, m.p. 244-45°C, ^{1}H NMR ($CDCl_3$), δ (ppm): 11,91 (s, 1H), 8,80 (s, 1H), 8,31 (s, 1H), 8,24 (dd, 1H), 7,47 (m, 1H), 7,24 (m, 4H), 7,05 (m, 2H), 5,47 (t, 1H), 4,77 (d, 2H), 2,30 (s, 3H); **5-hydroxymethyl-2-N-phenylimino-8-methyl-2H-pyrano[2,3-c]pyridin-3-(N-3-methylphenyl)carboxamide 4***{2}*: was obtained with yield 72%, m.p. 245°C, ^{1}H NMR (CDCl3), δ (ppm): 12,09 (s, 1H), 8,77 (s, 1H), 8,29 (s, 1H), 7,48 (m, 6H), 7,24 (m, 2H), 6,97 (d, 1H), 5,42 (t, 1H), 4,71 (d, 2H), 2,30 (s, 3H); **5-hydroxymethyl-2-N-(4-carbethoxyphenyl)imino-8-methyl-2H-pyrano[2,3-c] pyridin-3-N-(4-methoxyphenyl)carboxamide 4***{3}*: was obtained with yield 53%, m.p. 241-42°C, ^{1}H NMR ($CDCl_3$), δ (ppm): 11,70 (s, 1H), 8,65 (s, 1H), 8,30 (s, 1H), 8,02 (d, 2H), 7,65 (d, 2H), 7,48 (d, 2H), 6,92 (d, 2H), 5,40 (t, 1H), 4,72 (d, 2H), 4,30 (q, 2H), 3,71 (s, 3H), 2,30 (s, 3H), 1,32 (t, 3H); **5-hydroxymethyl-2-N-(2,4-dimethoxyphenyl)imino-8-methyl-2H-pyrano [2,3-c]pyridin-3-(N-4-methoxyphenyl)carboxamide 4***{4}*: was obtained with yield 61%, m.p. 229°C, ^{1}H NMR ($CDCl_3$), δ (ppm): 12,71 (s, 1H), 8,64 (s, 1H), 8,27 (s, 1H), 7,65 (m, 3H), 6,97 (d, 2H), 6,65 (m, 2H), 5,40 (t, 1H), 4,70 (d, 2H), 3,75 (m, 9H), 2,45 (s, 3H); **5-hydroxymethyl-2-N-(4-trifluoromethylphenyl)imino-8-methyl-2H-pyrano[2,3-c]pyridin-3-(N-2-fluorophenyl)carboxamide 4***{5}*: was obtained with yield 50%, m.p. 229°C, ^{1}H NMR ($CDCl_3$), δ (ppm): 12,70 (s, 1H,), 8,81 (s, 1H), 8,31 (s, 1H), 8,45 (dt, 1H), 7,79 (d, 2H), 7,60 (d, 2H), 7,10-7,34 (m, 3H), 5,49 (t, 1H), 4,77 (d, 2H), 2,38 (s, 3H).

General method of synthesis of (2-N-arylimino-8-methyl-3-N-arylcarboxamido-8-methyl-2H-pyrano[2,3-c] pyridin-5-yl)methylacetates 5*{1-115}*.

The solids of 5-hydroxymethyl-8-methyl-2-N-arylimino-2H-pyrano[2,3-c]pyridin-3-N-arylcarboxamides 4 (without excretion as it is described above) were dissolved in 10 mL of acetic anhydride while stirring. Resulting mixtures were refluxed for 1,5 hours. After cooling, each portion was diluted with 10 mL of water. The solids were filtered, washed with water (3 x 5 mL), ethanol (2 x 5 mL), and crystallized from mixture of DMF — ethanol. The yields of the products are 51-85%. The combinatorial library including 12 compounds was obtained. It contains: **[2-(4-carbethoxyphenyl)imino-8-methyl-3-N-(2-methylphenyl)carboxamido-2H-pyrano[2,3-c]pyridin-5-yl]methylacetate 5***{1}*: was obtained with yield 79%, m.p. 202-203°C, ^{1}H NMR ($CDCl_3$), δ (ppm): 11,79 (s, 1H), 8,69 (s, 1H), 8,40 (s, 1H), 8,21 (d, 1H), 8,03 (d, 2H), 7,46 (d, 2H), 7,23 (t, 2H), 7,07 (dt, 2H), 5,40 (s, 2H), 4,32 (q, 2H), 2,29 (s, 6H), 2,00 (s, 3H), 1,31 (t, 3H); **[2-(4-trifluoromethylphenyl)imino-8-methyl-3-N-(4-methylphenyl)carboxamido-2H-pyrano[2,3-c]pyridin-5-yl]methylacetate 5***{2}*: was obtained with yield 68%, m.p. 212-214°C, ^{1}H NMR ($CDCl_3$), δ (ppm): 11,69 (s, 1H), 8,54 (s, 1H), 8,38 (s, 1H), 7,78 (d, 2H), 7,57 (dd, 4H), 7,16 (d, 2H), 5,39 (s, 2H), 2,30 (s, 3H), 2,22 (s, 3H); **[2-(2,4-dimetoxyphenyl)imino-8-methyl-3-N-(2-fluorophenyl)carboxamido-2H-pyrano[2,3-c] pyridin-5-yl]methylacetate 5***{3}*: was obtained with yield 81%, m.p. 183-184°C, ^{1}H NMR ($CDCl_3$), δ (ppm): 12,80 (s, 1H), 8,57 (s, 1H), 8,36 (s, 1H), 8,21 (m, 1H), 7,42 (d, 1H), 7,18-7,29 (m, 3H), 6,72 (d, 1H), 6,58 (dd, 1H), 5,39 (s, 2H), 3,80 (s, 3H), 3,71 (s, 3H), 2,39 (s, 3H), 2,01 (s, 3H); **[2-(2,4-dimethoxy-**

phenyl)imino-8-methyl-3-N-(2-ethylphenyl)carboxamido-2H-pyrano[2,3-c]pyridin-5-yl]methylacetate 5*{4}*: was obtained with yield 67%, m.p. 182°C, ^{1}H NMR ($CDCl_3$), δ (ppm): 12,40 (s, 1H), 8,60 (s, 1H), 8,32 (s, 1H), 8,05 (d, 1H), 7,35 (d, 1H), 7,10-7,25 (m, 3H), 6,68 (d, 1H), 6,60 (dd, 1H), 5,40 (s, 2H), 3,81 (s, 3H), 3,71 (s, 3H), 2,70 (q, 2H), 2,32 (s, 3H), 2,03 (s, 3H), 1,04 (t, 3H); **{2-[4-(6-methyl-benzothyazolyl-2)phenyl]imino-8-methyl-3-N-(2-ethylphenyl)carboxamido-2H-pyrano[2,3-c]pyridin-5-yl}methylacetate 5***{5}*: was obtained with yield 70%, m.p. 191-193°C, ^{1}H NMR ($CDCl_3$), δ (ppm): 11,90 (s, 1H), 8,68 (s, 1H), 8,39 (s, 1H), 8,22 (d, 1H), 8,13 (d, 2H), 7,89 (d, 2H), 7,51 (d, 2H), 7,33 (d, 1H), 7,23 (t, 2H), 7,10 (t, 1H), 5,40 (t, 1H), 2,70 (q, 2H), 2,44 (s, 3H), 2,30 (s, 3H), 2,05 (s, 3H), 1,11 (t, 3H).

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