UDC 54.057:542.951.1:547.831.9:615.28:616.441:615.212

THE SYNTHESIS AND ANALGESIC PROPERTIES OF *N*-(BENZYL)-2-HYDROXY-9-METHYL-4-OXO-4*H*-PYRIDO[1,2-*a*]PYRIMIDINE-3-CARBOXAMIDES

I.V.Ukrainets, T.V.Alexeeva, O.O.Davidenko*, V.V.Grinenko

National University of Pharmacy
53, Pushkinska str., Kharkiv, 61002. E-mail: uiv-2@mail.ru
* N.I.Pirogov Vinnitsa National Medical University, Vinnitsa, Ukraine

Key words: amidation; tricarbonylmethane heterocyclic derivatives; 2-hydroxy-4-oxo-4H-pyrido[1,2-a] pyrimidine-3-carboxamides; synthesis; bioisosteric replacements; analgesic activity

Continuing the search for new analgesics among derivatives of azahetarylcaboxylic acids by the reaction of ethyl 2-hydroxy-9-methyl-4-oxo-4H-pyrido[1,2-a]pyrimidine-3-carboxylate and benzylamines in boiling ethanol the corresponding group of N-(benzyl)-2-hydroxy-9-methyl-4-oxo-4H-pyrido[1,2-a]pyrimidine-3-carboxamides has been synthesized. The structure of the compounds obtained has been confirmed by the data of elemental analysis and NMR ^{1}H spectroscopy. It is noted that the signals of aromatic protons of pyrido-pyrimidine nuclei are shifted downfield and generally form a typical AMX spin system. At the same time, the signals of aromatic protons of benzilamide fragments on the contrary are shifted upfield in all cases and focused on very narrow segments of the spectra, thereby undergoing strong distortion. According to the results of the primary pharmacological screening it has been found that using the standard model of "acetic acid writhings" all N-(benzyl)-2-hydroxy-9-methyl-4-oxo-4H-pyrido[1,2-a]pyrimidine-3-carboxamides without exception have analgesic properties to a greater or lesser degree. Practically the same regularities of the benzylamide fragment structure –biological effect relationship as in the case of 4-hydroxyquinolin-2-ones analogues have been found. Based on it the conclusion about bioisosterism of 4-hydroxyquinolin-2-one and 2-hydroxy-9-methyl-4-oxo-4H-pyrido[1,2-a]pyrimidine nuclei has been made.

СИНТЕЗ ТА АНАЛГЕТИЧНІ ВЛАСТИВОСТІ N-(БЕНЗИЛ)-2-ГІДРОКСИ-9-МЕТИЛ-4-ОКСО-4Н-ПІРИДО[1,2-а] ПІРИМІДИН-3-КАРБОКСАМІДІВ

І.В.Українець, Т.В.Алєксєєва, О.О.Давиденко, В.В.Гріненко

Ключові слова: *амідування; гетероциклічні похідні трикарбонілметану; 2-гідрокси-4-оксо-4Н-піридо [1,2-а]піримідин-3-карбоксаміди; синтез; біоізостеричні переміщення; аналгетична активність*

Продовжуючи пошук нових аналгетиків серед похідних азагетарилкарбонових кислот, реакцією етил 2-гідрокси-9-метил-4-оксо-4Н-піридо[1,2-а]піримідин-3-карбоксилату з бензиламінами у киплячому етанолі ми здійснили синтез групи відповідних N-(бензил)-2-гідрокси-9-метил-4-оксо-4Н-піридо[1,2-а]піримідин-3-карбоксамідів. Для підтвердження будови одержаних речовин використані елементний аналіз та спектроскопія ^{1}Н ЯМР. Помічено, що сигнали ароматичних протонів піридо-піримідинового ядра зсунуті у слабке поле і в цілому утворюють типову AMX спінову систему. В той же час сигнали ароматичних протонів бензиламідних фрагментів навпаки в усіх випадках зміщені у відносно сильне поле та зосереджені на дуже вузьких відрізках спектрів, за рахунок чого піддаються досить сильному спотворенню. За результатами первинного фармакологічного скринінгу встановлено, що на стандартній моделі оцтовокислих «корчів» всі без виключення N-(бензил)-2-гідрокси-9-метил-4-оксо-4Н-піридо[1,2-а]піримідин-3-карбоксаміди в тій чи іншій мірі виявляють аналгетичні властивості. При цьому знайдені практично ті ж закономірності впливу будови бензиламідного фрагмента на біологічний ефект, що й у випадку 4-гідроксихінолін-2-онових аналогів. На підставі цього зроблено висновок щодо біоізостерності 4-гідроксихінолін-2-онового та 2-гідрокси-9-метил-4-оксо-4Н-піридо[1,2-а]піримідинового ядер.

СИНТЕЗ И АНАЛЬГЕТИЧЕСКИЕ СВОЙСТВА N-(БЕНЗИЛ)-2-ГИДРОКСИ-9-МЕТИЛ-4-ОКСО-4Н-ПИРИДО [1,2-а]ПИРИМИДИН-3-КАРБОКСАМИДОВ

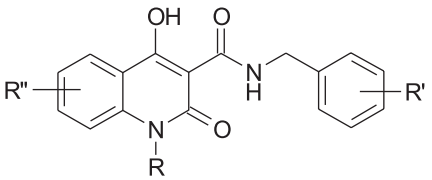
И.В.Украинец, Т.В.Алексеева, А.А.Давиденко, В.В.Гриненко

Ключевые слова: *амидирование; гетероциклические производные трикарбонилметана; 2-гидрокси-4-оксо-4Н-пиридо[1,2-а]пиримидин-3-карбоксамиды; синтез; биоизостерические перемещения; анальгетическая активность*

Продолжая поиск новых анальгетиков среди производных азагетарилкарбоновых кислот, реакцией этил 2-гидрокси-9-метил-4-оксо-4Н-пиридо[1,2-а]пиримидин-3-карбоксилата с бензиламинами в кипящем этаноле мы осуществили синтез группы соответствующих N-(бензил)-2-гидрокси-9-метил-4-оксо-4Н-пиридо[1,2-а] пиримидин-3-карбоксамидов. Для подтверждения строения полученных веществ использованы элементный анализ и спектроскопия ^{1}Н ЯМР. Отмечено, что сигналы ароматических протонов пиридо-пиримидинового ядра сдвинуты в слабое поле и в целом образуют типичную AMX спиновую систему. В то же время сигналы ароматических протонов бензиламидных фрагментов наоборот во всех случаях смещены в относительно сильное поле и сосредоточены на очень узких отрезках спектров, за счет чего претерпевают сильное искажение. По результатам первичного фармакологического скрининга установлено, что на стандартной модели уксуснокислых «корчей» все без исключения N-(бензил)-2-гидрокси-9-метил-4-оксо-4Н-пиридо[1,2-а]пиримидин-3-карбоксамиды в той или иной степени обладают анальгетическими свойствами. При этом обнаружены практически те же закономерности влияния строения бензиламидного фрагмента на биологический эффект, что и в случае 4-гидроксихинолин-2-оновых аналогов. На этом основании сделан вывод о биоизостерности 4-гидроксихинолин-2-онового и 2-гидрокси-9-метил-4-оксо-4Н-пиридо[1,2-а]пиримидинового ядер.

Among the world population it is almost impossible to find someone who would be unfamiliar with frightening and something paradoxical sensation of pain. On the one hand, the pain in its nature has a specific and necessary role for the survival – it instantly signals the occurrence of external or internal factors that can cause harm to the body. However, on the other hand, pain is able to exhaust the resources of the body very quickly and lead to serious disorders of its vital functions. This explains why the mankind is searching for means of dealing with pain throughout the history of its existence, and the desire to create an "ideal analgesic", which would meet all modern requirements for efficacy and safety, have not lost their relevance today [1-6].

The interesting objects of study in this respect are the numerous *N*-(benzyl)-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxamides of the general formula (**1**) and their heterocyclic analogues studied earlier. Among them promising lead compounds far exceeding the analgesic effect of narcotic analgesics officially recognized and with a much lower toxicity have been identified [7-10].



I

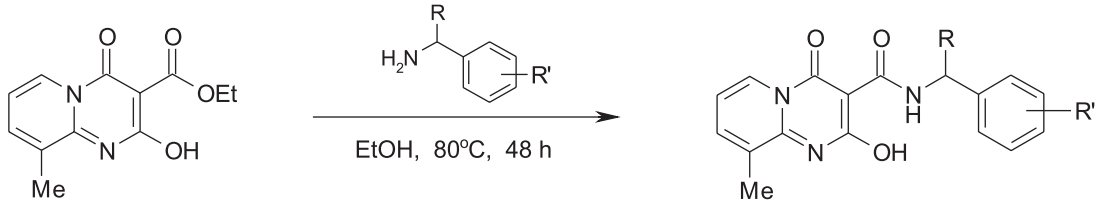
Continuing research in this area we considered replacement of the 4-hydroxyquinoline-2-ones base with 2-hydroxy-4-oxopyrido[1,2-*a*]pyrimidine nucleus that is similar by its structure as one of the possible ways to optimize analgesics of formula (**1**). The theoretical precondition for such modification was the methodology of bioisosteric replacements widely and effectively used by modern medical chemistry, involving the replacement of one group in the molecule close to it by the properties [11, 12]. It should be remembered that the bioisosteric groups are groups that are the same not only in size or volume, but have similar physical and chemical properties, and therefore, reveal a similar pharmacological effect [13-15]. In other words, the structural similarity of 4-hydroxyquinoline-2-ones and 2-hydroxy-4-oxopyrido[1,2-*a*] pyrimidine heterocycles itself does not guarantee their bioisosterism. Only the experimental study will show whether the compounds synthesized can exhibit the real analgesic effect.

The synthesis of the objects of research was carried out by the reaction of ethyl 2-hydroxy-9-methyl-4-oxo-4H-pyrido[1,2-*a*]pyrimidine-3-carboxylate (**2**) and benzylamines in boiling ethanol. As known, pyrido[1,2-*a*]pyrimidine esters of type (**2**) not only form rather stable salts with the primary amines, but also lose much in the reactivity [16]. Therefore, for successful amidation it is necessary to introduce at least a double excess of amine in the synthesis and significantly increase duration of the reaction.

It is interesting to note that in contrast to the initial ester (**2**) *N*-(benzyl)-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxamides (**3a-n**) obtained do not form stable salts with the excess of the corresponding amine in the reaction mixture (apparently due to decrease of the 2-OH-group acidity [16]), and no additional procedures are required for their isolation.

All *N*-(benzyl)-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxamides (**3a-n**) synthesized are colourless crystals with a sharp melting points (Table 1), moderately soluble in DMF and DMSO at room temperature, and practically insoluble in water. To confirm their structure the data of the elemental analysis and ^{1}H NMR spectroscopy were used (Table 2).

As a characteristic feature of the ^{1}H NMR spectra of N-(benzyl)-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxamides (**3a-n**) it should be noted a great shift downfield the doublet signals of aromatic protons in position 6 of the pyrido-pyrimidine ring; it is caused by the proximity with a cyclic nitrogen atom. Their nearest neighbours – H-7 and H-8 – also resonate in the strongly (about 0.7 ppm) distinct areas, generally forming a typical AMX spin system (see Fig.). At the same time, the signals of aromatic protons of benzylamide fragments are shifted in a relatively strong field in all cases and focused on very narrow segments of the spectra, thereby undergoing strong distortion (see, for example, almost a singlet signal of the protons of H-5 'and H-6' piperonylamide **3k**).



2 **3a-n**

2: R = H – **a** R' = H; **b** R' = 4-F; **c** R' = 2-Cl; **d** R' = 4-Cl; **e** R' = 2-Me; **f** R' = 3-Me; **g** R' = 4-Me; **h** R' = 2-OMe; **i** R' = 4-OMe; **j** R' = 3,4-$(OMe)_2$; **k** R' = 3-O-CH_2-O-4. R = Me – **l** R' = H, (±); **m** R' = H, *S*(–); **n** R' = H, *R*(+)

Scheme

Table 1

Characteristics of benzylamides **3a-n**

Compound	Empirical formula	Found, % / Calculated, %			Mp, °C	Yield, %
		C	H	N		
3a	$C_{17}H_{15}N_3O_3$	65.94 / 66.01	4.77 / 4.89	13.62 / 13.58	161-163	89
3b	$C_{17}H_{14}FN_3O_3$	62.30 / 62.38	4.24 / 4.31	12.76 / 12.84	190-192	90
3c	$C_{17}H_{14}ClN_3O_3$	59.31 / 59.40	4.15 / 4.10	12.30 / 12.22	187-189	86
3d	$C_{17}H_{14}ClN_3O_3$	59.46 / 59.40	4.17 / 4.10	12.14 / 12.22	196-198	92
3e	$C_{18}H_{17}N_3O_3$	66.93 / 66.86	5.25 / 5.30	12.91 / 13.00	176-178	86
3f	$C_{18}H_{17}N_3O_3$	66.95 / 66.86	5.34 / 5.30	12.95 / 13.00	133-135	90
3g	$C_{18}H_{17}N_3O_3$	66.78 / 66.86	5.37 / 5.30	13.06 / 13.00	162-164	91
3h	$C_{18}H_{17}N_3O_4$	63.80 / 63.71	4.97 / 5.05	12.29 / 12.38	200-202	83
3i	$C_{18}H_{17}N_3O_4$	63.78 / 63.71	5.03 / 5.05	12.44 / 12.38	171-173	87
3j	$C_{19}H_{19}N_3O_5$	61.70 / 61.78	5.26 / 5.18	11.31 / 11.38	168-170	88
3k	$C_{18}H_{15}N_3O_5$	61.11 / 61.19	4.35 / 4.28	11.78 / 11.89	195-197	91
3l	$C_{18}H_{17}N_3O_3$	66.94 / 66.86	5.39 / 5.30	12.91 / 13.00	141-144	81
3m*	$C_{18}H_{17}N_3O_3$	66.95 / 66.86	5.57 / 5.30	12.94 / 13.00	144-146	84
3n**	$C_{18}H_{17}N_3O_3$	66.78 / 66.86	5.24 / 5.30	13.08 / 13.00	144-146	82

* $[\alpha]^{20}_D$ = + 23.2; *c* = 5; DMF.
** $[\alpha]^{20}_D$ = – 23.2; *c* = 5; DMF.

All biological experiments were carried out in full accordance with the European Convention on the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes and the Ukrainian Law No. 3447-IV "On protection of animals from severe treatment" (2006).

The analgesic activity of the compounds synthesized was studied on nonlinear white mice weighing 18-23 g (10 animals per each substance tested) using the standard model of "acetic acid writhings" [17]. The nociceptive effect was reproduced by intraperitoneal injection of 0.6% acetic acid solution in the amount of 0.1 ml per 10 g of the body weight 1 hour after administration of the test sample. The animals were observed for 20 min, counting the number of "writhings". The analgesic effect was assessed by the

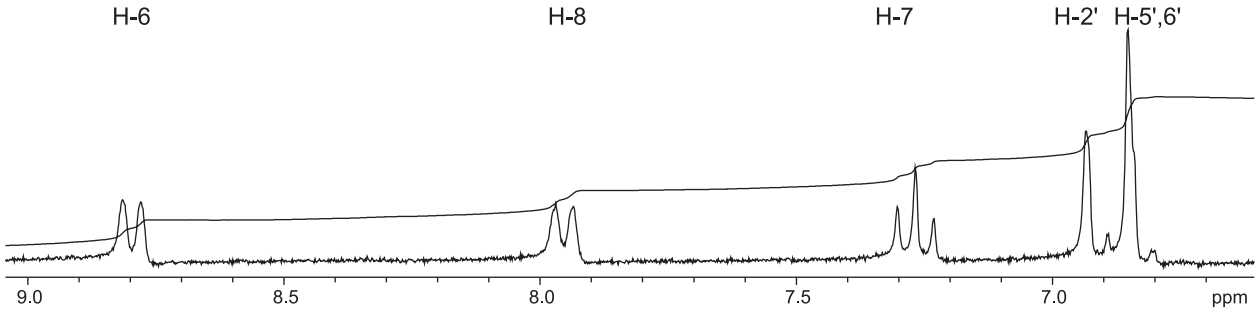


Fig. The fragment of ^{1}H NMR spectra (signals of aromatic protons) of amide **3k**.

Table 2

^{1}H NMR Spectra of benzylamides **3a-n**

Compound	Chemical shifts, δ, ppm (*J*, Hz)
3a	15.89 (1H, s, 2-OH); 9.97 (1H, t, *J* = 5.9, NH); 8.82 (1H, d, *J* = 7.0, H-6); 7.97 (1H, d, *J* = 7.0, H-8); 7.39-7.33 (5H, m, Ph); 7.28 (1H, t, *J* = 7.0, H-7); 4.60 (2H, d, *J* = 5.8, CONHC$\underline{H}_2$); 2.43 (3H, s, 9-Me)
3b	15.84 (1H, s, 2-OH); 9.96 (1H, t, *J* = 5.8, NH); 8.80 (1H, d, *J* = 7.0, H-6); 7.96 (1H, d, *J* = 7.0, H-8); 7.40 (2H, dd, *J* = 7.7 and 5.4, H-3′,5′); 7.27 (1H, t, *J* = 7.1, H-7); 7.16 (2H, t, *J* = 8.9, H-2′,6′); 4.57 (2H, d, *J* = 5.8, CONHC$\underline{H}_2$); 2.41 (3H, s, 9-Me)
3c	15.68 (1H, s, 2-OH); 10.03 (1H, t, *J* = 6.0, NH); 8.83 (1H, d, *J* = 7.1, H-6); 7.97 (1H, d, *J* = 6,9, H-8); 7.51-7.24 (5H, m, H-7 + H-3′,4′,5′,6′); 4.66 (2H, d, *J* = 6.2, CONHC$\underline{H}_2$); 2.42 (3H, s, 9-Me)
3d	15.82 (1H, s, 2-OH); 9.99 (1H, t, *J* = 6.0, NH); 8.81 (1H, d, *J* = 7.0, H-6); 7.97 (1H, d, *J* = 6.9, H-8); 7.41-7.37 (4H, m, H-2′,3′,5′,6′); 7.28 (1H, t, *J* = 7.0, H-7); 4.58 (2H, d, *J* = 6.0, CONHC$\underline{H}_2$); 2.42 (3H, s, 9-Me)
3e	15.82 (1H, s, 2-OH); 9.85 (1H, t, *J* = 5.8, NH); 8.77 (1H, d, *J* = 6,9, H-6); 7.93 (1H, d, *J* = 6.9, H-8); 7.29-7.10 (5H, m, H-7 + H-3′,4′,5′,6′); 4.57 (2H, d, *J* = 5.8, CONHC$\underline{H}_2$); 2.40 (3H, s, 9-Me); 2.31 (3H, s, 2′-Me)
3f	15.91 (1H, s, 2-OH); 9.94 (1H, t, *J* = 6.1, NH); 8.80 (1H, d, *J* = 7.1, H-6); 7.95 (1H, d, *J* = 7.1, H-8); 7.32-7.04 (5H, m, H-7 + H-2′,4′,5′,6′); 4.55 (2H, d, *J* = 6.1, CONHC$\underline{H}_2$); 2.41 (3H, s, 9-Me); 2.28 (3H, s, 3′-Me)
3g	15,88 (1H, s, 2-OH); 9,87 (1H, t, *J* = 5,8, NH); 8,76 (1H, d, *J* = 7,1, H-6); 7,93 (1H, d, *J* = 7,1, H-8); 7,25 (1H, t, *J* = 6,9, H-7); 7,20 (2H, d, *J* = 8,0, H-2′,6′); 7,13 (2H, d, *J* = 8,0, H-7 + H-3′,5′); 4,52 (2H, d, *J* = 5,9, CONHC$\underline{H}_2$); 2,39 (3H, s, 9-Me); 2,25 (3H, s, 4′-Me)
3h	15.93 (1H, s, 2-OH); 9.95 (1H, t, *J* = 6.0, NH); 8.81 (1H, d, *J* = 7.1, H-6); 7.95 (1H, d, *J* = 7.1, H-8); 7.33-7.21 (3H, m, H-7 + H-3′,5′); 7.03 (1H, d, *J* = 8.0, H-6′); 6.91 (1H, t, *J* = 7.6, H-4′); 4.54 (2H, d, *J* = 6.0, CONHC$\underline{H}_2$); 3.83 (3H, s, OMe); 2.41 (3H, s, 9-Me)
3i	15,94 (1H, s, 2-OH); 9,87 (1H, t, *J* = 5,8, NH); 8,78 (1H, d, *J* = 7,1, H-6); 7,95 (1H, d, *J* = 7,0, H-8); 7,32-7,20 (3H, m, H-7 + H-3′,5′); 6,89 (2H, d, *J* = 8,7, H-2′,6′); 4,50 (2H, d, *J* = 5,8, CONHC$\underline{H}_2$); 3,71 (3H, s, OMe); 2,41 (3H, s, 9-Me)
3j	15.96 (1H, s, 2-OH); 9.89 (1H, t, *J* = 6.0, NH); 8.80 (1H, d, *J* = 7,0, H-6); 7.95 (1H, d, *J* = 7.0, H-8); 7.27 (1H, t, *J* = 6.9, H-7); 6.99 (1H, s, H-2′); 6.92-6.87 (2H, m, H-5′,6′); 4.50 (2H, d, *J* = 6.0, CONHC$\underline{H}_2$); 3.73 (3H, s, OMe); 3.71 (3H, s, OMe); 2.42 (3H, s, 9-Me)
3k	15.90 (1H, s, 2-OH); 9.89 (1H, t, *J* = 6.0, NH); 8.80 (1H, d, *J* = 7.1, H-6); 7.95 (1H, d, *J* = 7.0, H-8); 7.27 (1H, t, *J* = 7.0, H-7); 6.93 (1H, s, H-2′); 6.88-6.82 (2H, m, H-5′,6′); 5.98 (2H, s, O-CH_2-O); 4.48 (2H, d, *J* = 6.0, CONHC$\underline{H}_2$); 2.40 (3H, s, 9-Me)
3l	15.73 (1H, s, 2-OH); 9.98 (1H, d, *J* = 7.3, NH); 8.82 (1H, d, *J* = 7.1, H-6); 7.96 (1H, d, *J* = 7.0, H-8); 7.44-7.28 (6H, m, H-7 + Ph); 5.17 (1H, q, *J* = 7.3, CONHC$\underline{H}$); 2.41 (3H, s, 9-Me); 1.53 (3H, d, *J* = 7.3, CH-$\underline{Me}$)
3m	15.73 (1H, s, 2-OH); 9.98 (1H, d, *J* = 7.3, NH); 8.82 (1H, d, *J* = 7.1, H-6); 7.96 (1H, d, *J* = 7.0, H-8); 7.44-7.28 (6H, m, H-7 + Ph); 5.17 (1H, q, *J* = 7.3, CONHC$\underline{H}$); 2.41 (3H, s, 9-Me); 1.53 (3H, d, *J* = 7.3, CH-$\underline{Me}$)
3n	15.73 (1H, s, 2-OH); 9.98 (1H, d, *J* = 7.3, NH); 8.82 (1H, d, *J* = 7.1, H-6); 7.96 (1H, d, *J* = 7.0, H-8); 7.44-7.28 (6H, m, H-7 + Ph); 5,17 (1H, q, *J* = 7.3, CONHC$\underline{H}$); 2.41 (3H, s, 9-Me); 1.53 (3H, d, *J* = 7.3, CH-$\underline{Me}$)

ability of compounds to reduce the number of "writhings" in the groups under study compared to the control and expressed in percentage (Table 3). Testing was carried out in comparison with such known non-narcotic analgesics as Piroxicam (Jenapharm, Germany), Diclofenac (KRK, Slovenia) and Nabumetone (Smith-Kline Beecham, Germany). All substances under study were administered orally in the screening dose of 20 mg/kg as a thin aqueous suspension stabilized with Tween-80. Medicines were used similarly or as aqueous solutions in the doses corresponding to their ED_{50} for this experimental model [18]. The animals of the control group received an equivalent amount of water and Tween-80. The results of all biological tests were statistically processed using the Student's *t*-test [19].

The analysis of the experimental data presented in Table 3 shows that the replacement of 4-hydroxyquinoline-2-one nucleus on the 2-hydroxy-4-oxopyrido[1,2-*a*]pyrimidine one was really bioisosteric since all compounds, without exception, revealed a more or less pronounced analgesic effect.

A comparative analysis with the parameters of the corresponding benzylamides of 1*H*- and 1-allylsubstituted 4-hydroxy-6,7-dimethoxy-2-oxo-1,2-dihydroquinoline-3-carboxylic acids studied under similar conditions shows approximately the same structural and biological regularities – the similar effect of the nature and location of substituents in the aromatic ring of the benzylamide moiety of the molecule can be traced in most of the examples (Table 3). Methylation of the methylene bridge separating phenyl and amide nitrogen – amides **3l-n** – regardless of the peculiarities of the spatial structure of the chiral fragment formed leads to the almost complete loss of analgesic properties, and therefore, it is undesirable. Of all groups of the compounds tested *N*-(benzyl)-

Table 3

The analgesic properties of benzylamides **3a-n**

Compound	Analgesic activity	
	Average number of "acetic acid writhing"	%*
3a	39.7±1.3	52.3 (66.6 & 30.9)
3b	56.9±2.2	31.5 (44.5 & 15.6)
3c	55.9±1.1	32.7 (45.5 & 14.4)
3d	40.6±1.4	51.2 (54.0 & 56.9)
3e	73.3±1.8	11.8
3f	68.8±1.6	17.1
3g	69.5±2.5	16.4 (12.4 & 24.3)
3h	60.9±1.2	26.7 (37.7 & 10.8)
3i	61.9±1.4	25.6 (36.5 & 26.3)
3j	47.8±1.0	42.4 (53.6 & 39.4)
3k	59.0±1.7	29.1 (53.4 & 15.4)
3l	68.1±1.3	18.2 (40.7 & 9.50)
3m	69.1±1.5	16.9
3n	68.6±1.1	17.5
Piroxicam (92 mg/kg)	41.6±1.8	50.0
Diclofenac (5 mg/kg)	40.1±2.3	51.6
Nabumetone (50 mg/kg)	41.0±3.3	50.6
Control	83.2±1.3	–

* In parentheses there are the indices of the analgesic activity of the corresponding benzylamides of 1*H*- and 1-allylsubstituted 4-hydroxy-6,7-dimethoxy-2-oxo-1,2-dihydroquinoline-3-carboxylic acids studied under similar conditions [20 & 9].

4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxamide (**3a**) and its 4-chloro-substituted analogue (**3d**) exhibiting the analgesic activity at the level of Piroxicam and Nabumetone but in much lower dose are of the most interest.

Experimental Part

The ^{1}H NMR spectra were recorded on a Varian Mercury-400 spectrometer (400 MHz) in DMSO-d_6 solution, the internal standard was TMS. Elemental analysis was carried out on a EuroVector EA-3000 microanalyzer. Melting points were determined in capillaries on a SMP10 Stuart digital melting point analyzer. The values of specific rotation of the optically active amides **3m,n** were determined on a Polamat A polarimeter. These syntheses use commercially *S(–)*- and *R(+)*-1-phenyl- and 1-(4-methoxyphenyl)ethylamines from Fluka with the optical purity of at least 99.5 and 99.0%, respectively. The starting ethyl 2-hydroxy-9-methyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylate (**2**) was synthesized according to the literature procedure [21].

***N*-(Benzyl)-2-hydroxy-9-methyl-4-oxo-4H-pyrido[1,2-a]pyrimidine-3-carboxamides (3a-n). The general procedure.** Add the corresponding benzylamine (0.02 Mol) to 2.48 g (0.01 Mol) of the solution of ethyl ester (**2**) in 10 mL of ethanol and heat at reflux for 30 h. Then cool the reaction mixture and allow to stand at a temperature of about 0°C for 10-12 h. Filter the precipitate of benzylamide (3a-n) obtained, wash thoroughly with hexane, then with cold water and dry in the air. Crystallize from the DMF – ethanol mixture (1:1).

Conclusions

1. A new series of *N*-(benzyl)-2-hydroxy-9-methyl-4-oxo-4H-pyrido[1,2-*a*]pyrimidine-3-carboxamides has been synthesized as potential analgesics, their structure has been confirmed by elemental analysis and ^{1}H NMR spectra.

2. According to pharmacological studies it has been found that 2-hydroxy-9-methyl-4-oxopyrido[1,2-*a*]pyrimidine and 4-hydroxyquinoline-2-one are bioisosteric heterocycles and are of undoubted interest as the basis for obtaining highly effective analgesics.

References

1. *Kesmati M., Torabi M. Basic and Clinical Neuroscience, 2014, Vol. 5, No.1, pp.80-87.*
2. *Ondachi P. W., Castro A. H., Bartkowiak J. M., Luetje C. W., Damaj M. I., Mascarella S. W., Navarro H. A., Carroll F. I. Journal of Medicinal Chemistry, 2014, Vol. 57, No.3, pp.836-848. DOI: 10.1021/jm401602p.*
3. *Dulu T. D., Kanui T. I., Towett P. K., Maloiy G. M., Abelson K. S. In Vivo, 2014, Vol. 28, No.1, pp.39-48.*
4. *Tao P. L., Law P. Y., Loh H. H. International Union of Biochemistry and Molecular Biology Life, 2010, Vol. 62, No.2, pp.103-111. DOI: 10.1002/iub.292.*

5. *Zor F., Ozturk S., Bilgin F., Isik S., Cosar A. Burns: Journal of the International Society for Burn Injuries, 2010, Vol. 36, No.4, pp.501-505. DOI: 10.1016/j.burns.2009.08.007.*
6. *Keri R. S., Patil M. R., Patil S. A., Budagumpi S. European Journal of Medicinal Chemistry, 2015, Vol. 89, pp.207-251. DOI: 10.1016/j.ejmech.2014.10.059.*
7. *Ukrainets I. V., Gorokhova O. V., Nidal Amin Jaradat, Petrushova L. A., Mospanova E. V., Savchenkova L. V., Kuz'min V. E., Lyahovsky A. V. 4-Hydroxyquinolin-2-ones and their Close Structural Analogues as a New Source of Highly Effective Pain-killers. In book: Pain and Treatment, Racz G. B. and Noe C. E. (Ed.), Rijeka: InTech, 2014, pp.21-73.*
8. *Ukrainets I. V., Gorokhova O. V., Andreeva K. V. Russian Journal of Organic Chemistry, 2013, Vol. 49, No.6, pp.867-871. DOI:10.1134/S1070428013060122.*
9. *Ukrainets I. V., Mospanova E. V., Jaradat N. A., Bevz O. V., Turov A. V. Chemistry of Heterocyclic Compounds, 2012, Vol. 48, No.9, pp.1347-1356. DOI:10.1007/s10593-012-1143-1147.*
10. *Ukrainets I. V., Gorokhova O. V., Andreeva K. V., Davidenko A. A. Zhurnal Organichnoi ta Farmatsevtichnoi Khimii – Journal of Organic and Pharmaceutical Chemistry, 2014, Vol. 12, No.1(45), pp.51-55.*
11. *Dhiman R., Sharma S., Singh G., Nepali K., Singh Bedi P. M. Archiv der Pharmazie (Weinheim). 2013, Vol. 346, No.1, pp.7-16. DOI: 10.1002/ardp.201200296.*
12. *Chatzopoulou M., Bonovolias I. D., Nicolaou I., Demopoulos V. J., Vizirianakis I. S. Tsiftsoglou A. S. European Journal of Medicinal Chemistry, 2012, Vol. 50, pp.75-80. DOI: 10.1016/j.ejmech.2012.01.041.*
13. *Pegklidou K., Koukoulitsa C., Nicolaou I., Demopoulos V. J. Bioorganic & Medicinal Chemistry, 2010, Vol. 18. No.6, pp.2107-2114. DOI: 10.1016/j.bmc.2010.02.010.*
14. *Vijayan R. S., Bera I., Prabu M., Saha S., Ghoshal N. Journal of chemical information and modeling, 2009, Vol. 49, No.11, pp.2498-2511. DOI: 10.1021/ci900309s.*
15. *Tosco P., Lolli M. L. Journal of molecular modeling, 2008, Vol. 14, No.4, pp.279-291. DOI: 10.1007/s00894-008-0269-0.*
16. *Ukrainets I. V., Tugaibei I. A., Bereznyakova N. L., Kravchenko V. N., Turov A. V. Chemistry of Heterocyclic Compounds, 2008, Vol. 44, No.5, pp.565-575. DOI: 10.1007/s10593-008-0076-7.*
17. *Vogel H. G. Drug Discovery and Evaluation: Pharmacological Assays. Berlin, Springer; 2008, pp.1030-1032.*
18. *Sigidin Ya. A., Shvarts G. Ya., Arzamastsev A. P., Liberman S. S. Lekarstvennaya terapiya vospalitel'nogo protsessa (Drug Therapy of the Anti-inflammatory Process). Moscow, Meditsina; 1988, pp.60-63.*
19. *Sernov L. N., Gatsura V. V. Elementy experimentalnoi pharmakologii (Elements of Experimental Pharmacology). Moscow, Nauka, 2000, pp.308-316.*
20. *Mospanova Ye. V., Ukrainets I. V., Bevz O. V., Savchenkova L. V., Yankovich S. I. Zhurnal Organichnoi ta Farmatsevtichnoi Khimii – Journal of Organic and Pharmaceutical Chemistry, 2012, Vol. 10, No.2(38), pp.50-53.*
21. *Ukrainets I. V., Bereznyakova N. L., Petyunin G. P., Tugaibei I. A., Rybakov V. B., Chernyshev V. V., Turov A. V. Chemistry of Heterocyclic Compounds, 2007, Vol. 43, No.6, pp.729-739. DOI: 10.1007/s10593-007-0119-5.*

Надійшла до редакції 17.06.2015 р.