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SYNTHESIS OF NEW 2-ARYLQUINOLINE AMIDES

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Annotatsiya: 6'-aminodubamin va turli alifatik kislotalarga asoslangan xinolin amidlari sintez qilingan. Sintezlangan birikmalarning tuzilishi IR, massa, 1H va 13C NMR spektrlari bilan isbotlangan. Amidlar sintezi ikki xil usulda amalga oshirilgan.

Kalit so'zlar: xinolin alkaloidlari, 6'-aminodubamin, amidlar, alifatik kislotalar.

Аннотация: Синтезированы хинолиновые амиды на основе 6’-аминодубамина и различных алифатических кислот. Строение синтезированных соединений подтверждено данными ИК, масс, ЯМР 1Н и 13С спектров. Синтез амидов проводили двумя разными методами.

Ключевые слова: хинолиновые алкалоиды, 6'-аминодубамин, амиды, алифатические кислоты.

Abstract: Quinoline amides based on 6’-aminodubamine and various aliphatic acids were synthesized. The structure of the synthesized compounds was proved by IR, mass, ^{1}H and ^{13}C NMR spectra. The synthesis of amides was carried out using two different methods.

Keywords: quinoline alkaloids, 6'-aminodubamine, amides, aliphatic acids.

Introduction. It is important to note that one of the tasks of modern organic and bioorganic chemistry is the creation of low-toxic compounds with high biological activity and another one is the study of their physicochemical and pharmacological properties.Today, there are more than 100 drugs based on quinoline used in practical medicine, while more than 400 drugs in which quinoline derivatives are used as dietary supplements (biologically active additives) [1].

2- Substituted quinoline alkaloids have antitumor [2], wound healing [3], antibacterial [4] and other types of activity.

It is given in this work that the alkaloid dubamine, known as one of the 2-arylquinoline alkaloids, was isolated from the plants *Dictamnus angustifolius*,

Haplophyllum latifolium, Haplophyllum dubium and *Haplophyllum griffithianum* [5-6]. In our previous works, we reported on the nitration of dubamine, the reduction of the obtained nitro derivative to the amine, on the interaction of 6'-aminodubamine with various aromatic aldehydes, as well as information on the cytotoxic activity of the synthesized compounds [7 - 8].

According to the data from the literature amides of some 2-arylquinoline alkaloids, representing a new class of tubulin polymerization inhibitors, also exhibit anti-inflammatory, analgesic, antimalarial, anticancer, and antimicrobial activity [9-11]. An example is the drug Saquinavir, which is currently used in practical medicine [1].

Materials and method. In this regard, IR spectra were recorded on a System 2000 Fourier spectrometer (Perkin-Elmer) in KBr tablets. ^{1}H and ^{13}C NMR spectra were recorded on Unity-400 + Varian spectrometers (400 MHz, TMS internal standard, δ-scale). High-resolution mass spectra were recorded on an Agilent Technologies 6420 Triplequad LC / MS instrument. The progress of the reaction and the purity of the obtained compounds were monitored by TLC on Sigma-Aldrich, Silufol L/W 10×20 cm plates (Germany) in a solvent system: hexane: chloroform: methanol, (5:5:0.2).

General Method for synthesizing 3a-c.

Method A. To a solution of 6'-aminodubamine (0.38 mmol) in 3 ml of chloroform was added the corresponding acid (0.45 mmol) to form an alkaloid salt. The chloroform was removed in vacuum and then the alkaloid salt was heated in an oil bath for 2-4 hours at different temperatures. After cooling, the reaction mixture was dissolved in 100 ml of chloroform, washed with 2% NaOH solution, then with water until neutral. The chloroform extract was dried over anhydrous Na_2SO_4, and the solvent was distilled off in vacuum. All obtained products was crystallized from ethanol.

Method B. A solution of 0.45 mmol of acid chloride in 1 ml of chloroform was added drop by drop to the reaction mixture of 0.1 g (0.38 mmol) of 6'-aminodubamine and 0.157 g (1.14 mmol) of K_2CO_3 in 3 ml of chloroform and stirred on a magnetic stirrer for 3-5 minutes at room temperature. After the completion of the reaction (TLC), the solution was alkalized with NaOH to pH 9-10 and extracted with chloroform (3×15 ml). After the solvent was removed, the reaction products were crystallized from ethanol.

2-[4′,5′-Methylenedioxy-2′-(*N*-monochloroethanamido)phenyl]quinoline (3a). $C_{18}H_{13}N_2O_3Cl$. Prepared from 0.100 g (0.38 mmol) amine **1** and 0.45 mmol monochloroethanoic acid or chloroanhydride (**2a**). Yield **3a** according to the method A - 0.019 g (15.0%), according to the method B - 0.120 g (93.1%), mp 170°C (dec.) (C_2H_5OH), R_f 0.70.

IR spectrum (KBr, ν, cm^{-1}): 2885, 1671 (C=O), 1630, 1598, 1530, 1497, 1478, 1431, 1363, 1256, 1228, 1101, 1038, 971, 930, 870, 842.

^{1}H NMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 4.18 (2H, s, H-2′′), 6.04 (2H, s, 4′-OCH_2O-5′), 7.22 (1H, s, H-6′), 7.55 (1H, td, *J* = 7.5, 1.2, H-6), 7.69 (1H, d, *J* = 8.8, H-3), 7.74 (1H, td, *J* = 7.7, 1.5, H-7), 7.83 (1H, dd, *J* = 8.1,1.2, H-5), 8.14 (1H, s, H-3′), 8.16 (1H, d, *J* = 8.5, H-8), 8.26 (1H, d, *J* = 8.8, H-4), 13.15 (1H, s, NH).

^{13}C NMR spectrum (100 MHz, CDCl3, δ, ppm): 43.5 (C-2′′), 101.8 (C-3′), 103.9 (4′-OCH_2O-5′), 108.8 (C-6′), 120.7 (C-3), 120.9 (C-2′), 126.5 (C-10), 126.8 (C-6), 127.7 (C-5), 128.7 (C-8), 130.4 (C-7), 132.2 (C-1′), 137.9 (C-4), 144.6 (C-5′), 146.4 (C-4′), 148.7 (C-9), 157.5 (C-2), 165.1 (C-1′′).

HR-MS *m/z* ^{35}Cl – 341.0755 $[M+H]^+$, ^{37}Cl – 343.0755 $[M+H]^+$, calcd for $C_{18}H_{14}N_2O_3Cl$: ^{35}Cl-341.3220, ^{37}Cl-343.3220.

2-[4′,5′-Methylenedioxy-2′-(*N*-pentanamido)phenyl]quinoline (3b). $C_{21}H_{20}N_2O_3$. Prepared from 0.100 g (0.38 mmol) amine **1** and 0.45 mmol pentanic acid or chloroanhydride (**2b**). Yield **3b** according to the method A - 0.030 g (22.9%), according to the method B - 0.122 g (92.7%), mp 133-135°C (C_2H_5OH), R_f 0.7.

IR spectrum (KBr, ν, cm^{-1}): 2947, 2867, 1676 (C=O), 1626, 1613, 1597, 1542, 1507, 1480, 1432, 1395, 1353, 1249, 1225, 1210,1094, 1033, 961,921, 871, 819.

^{1}H NMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.89 (3H, t, *J* = 7.5, H-5′′), 1.33-1.43 (2H, m, H-4′′), 1.69-1.77 (2H, m, H-3′′), 2.44 (2H, t, *J* = 7.6, H-2′′), 6.01 (2H, s, 4′-OCH_2O-5′), 7.26 (1H, s, H-6′), 7.56 (1H, td, *J* = 7.6, 1.3, H-6), 7.74 (1H, d, *J* =9.1, H-3), 7.76 (1H, td, *J* = 7.7, 1.5, H-7), 7.84 (1H, dd, *J* = 8.4, 1.4, H-5), 8.00 (1H, d, *J* = 8.9, H-8), 8.24 (1H, d, *J* = 9.2, H-4), 8.28 (1H, s, H-3′), 13.03 (1H, s, NH).

^{13}C NMR spectrum (100 MHz, CDCl3, δ, ppm): 13.9 (C-5′′), 22.5 (C-4′′), 27.9 (C-3′′), 38.6 (C-2′′),101.7 (C-3′), 103.4 (4′-OCH_2O-5′), 108.3 (C-6′), 118.3 (C-2′), 120.7 (C-3), 126.3 (C-10), 126.8 (C-6), 127.7 (C-5), 128.1 (C-8), 130.4 (C-7), 134.4 (C-1′), 137.6 (C-4), 143.7 (C-5′), 146.1 (C-4′), 149.0 (C-9), 158.0 (C-2), 171.9 (C-1′′).

HR-MS *m/z* 349.1599 $[M+H]^+$, calcd for $C_{21}H_{21}N_2O_3$: 349.4106.

2-[4′,5′-Methylenedioxy-2′-(*N*- octadecanamido)phenyl]quinoline (3c). $C_{34}H_{46}N_2O_3$. Prepared from 0.100 g (0.38 mmol) amine **1** and 0.45 mmol octadecanoic acid or chloroanhydride (**2c**). Yield **3c** according to the method A - 0.101 g (50%), method B - 0.176 g (87.4%), mp 95-96°C (C_2H_5OH), R_f 0.75, mp 95-96°C (C_2H_5OH), R_f 0.75.

IR spectrum (KBr, ν, cm–1): 2918, 2848, 1673 (C=O), 1626, 1615, 1598, 1536, 1505, 1480, 1471, 1428, 1397, 1355, 1221, 1205, 1095, 1033, 960, 922, 874, 819.

^{1}H NMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.85 (3H, t, *J* = 6.7, H-18′′), 0.84-1.29 (28H, m, H-4′′-17′′), 1.69-1.76 (2H, m, H-3′′), 2.32 (2H, t, *J* = 7.5, H-2′′), 6.00 (2H, s, 4′-OCH_2O-5′), 7.25 (1H, s, H-6′), 7.54 (1H, td, *J* = 7.5, 1.1, H-6), 7.72 (1H, d, *J* =8.8, H-3), 7.74 (1H, td, *J* = 7.7, 1.4, H-7), 7.82 (1H, dd, *J* = 8.2, 1.1 , H-5), 7.98 (1H, d, *J* = 8.9, H-8), 8.23 (1H, d, *J* = 8.7, H-4), 8.25 (1H, s, H-3′), 12.9 (1H, s, NH).

^{13}C NMR spectrum (100 MHz, CDCl3, δ, ppm): 14.3 (C-18′′), 22.5 (C-17′′), 24.8-34.1 (C-3′′-16′′), 38.9 (C-2′′), 101.7 (C-3′), 103.5 (4′-OCH_2O- 5′), 108.3 (C-6′), 118.5 (C-2′), 120.7 (C-3), 126.4 (C-10), 126.8 (C-6), 127.8 (C-5), 128.2 (C-8), 130.4 (C-7), 134.4 (C-1′), 137.7 (C-4), 143.7 (C-5′), 146.1 (C-4′), 149.0 (C-9), 158.0 (C-2), 172.1 (C-1′′).

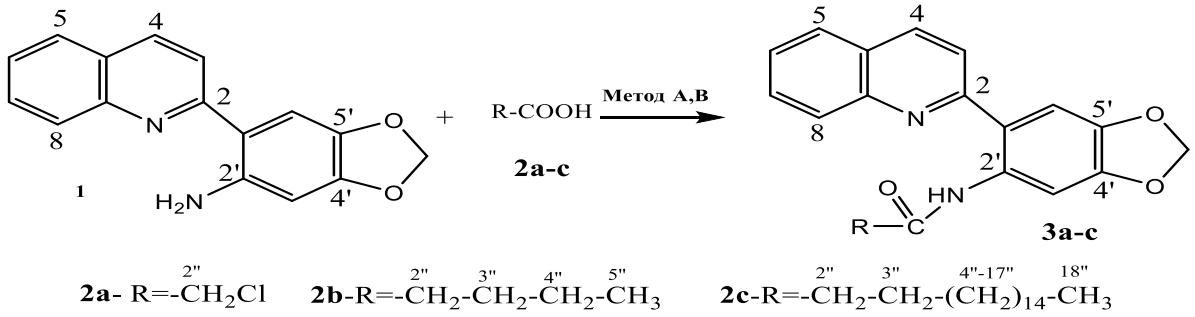
HR-MS *m/z* 531.4030 $[M+H]^+$, calcd for $C_{34}H_{47}N_2O_3$: 531.7603.

Results and its discussion. In order to obtain target amides of 6'-aminoduabamine (1), we used two methods of its interaction with aliphatic acids **2a-c.** (**Scheme 1**)

The first method (method A) differs from generally accepted by the fact that it is not a mixture of substances, but a pre-obtained salt from the acid taken in equivalent amounts of acid and 6'-aminoduurbamine. The reaction is carried out "one pot".

When using the traditional method (method B) of the interaction of amine 1 with chloride hydrhydrides, amides outputs were relatively higher (**Table 1**).

The structure of the synthesized compounds is proved with the help of physicochemical spectral methods. In NMR, the spectrum of 1H compounds **3a-b** besides the signals of protons of the original 6'-aminodubamin molecule, there is a presence of signals of aliphatic protons - a two-terminal singlet at 4.18 md (-CH_2-, 3a), a triplet at 0.83-0.92 ppm (CH_3, 3b, 3c), multiplets of the group CH_2 1.34-1.78 ppm (3b, 3c), and a triplet of groups CH_2-2″ at 2.30-2.46 ppm. It should also be noted that the presence of a hydrogen bond between the N-1 atom and the proton NH amide leads to a proton shift NH into a weak field (δ 12.99-13.15 ppm) and the absence of the absorption band NH amides in the region 3460-3420 cm^{-1} IR spectra of **3a-3c** bonds.



Scheme 1. Reactions of 6'-aminodubamine with various aliphatic acids

Table 1. Products of the reaction of 6'-aminodubamine with **2a-c** acid, obtained by methods A, B.

Product	Method **A**			Method **B**		T. pl., °C
	T.reac, °C	Time, h.	Yield, %	Time, h.	Yield, %	
3a	130-140	2	15	5	93.1	170(dec.)
3b	160-170	4	22.9	5	92.7	133-135
3c	170-180	3	60	5	87.4	95-96

Conclusion. To sum up, the synthesis of 3 new quinoline amides based on 6'-aminodubamine and various aliphatic acids was carried out. The structure of synthesized compounds was proved by the data of physicochemical methods of research (IR, masses, ^{1}H and ^{13}C NMR spectra). Synthesized amides were obtained

using two different methods (A and B). When using the method, the yield of finite reaction products was 15-50%. And with the method B it was 84.7–93.1%.

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