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Synthesis and antiviral activity of derivatives of 1-(4[1]-chlorophenyl)-3-aryl-3-hydroxy-2,5,6,7,8,9-hexahydro-*3H*-imidazo[1,2-a]azepinium for Flu A H1N1 California/07/2009 and Flu A H3N2 Brisbane/10/2007

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The respiratory illnesses in the Europe and the USA are the most common infectious illness in the general population. Respiratory illnesses are accompanied by severe complications. More then 2 billion cases of upper respiratory infections every year World Health Organization (WHO) reported; 14–15 million cases of upper respiratory infections reported in Ukraine. Influenza viruses are a family of RNA viruses that includes 3 genera: Influenza virus A, Influenza virus B, Influenza virus C. Influenza virus A among three serotypes is the most virulent and pathogenic for humans and can lead to serious disease complications. Influenza A (H1N1) virus is the subtype of influenza A virus. In 1930, subtype of A/H1N1 virus was isolated in pigs [1]. Flu A/H1N1 was attributed to endemic zoonosis [2].

In 2005, a novel swine influenza A (H1N1) caused severe respiratory illness in 50 humans who have been in contact with diseased animals [3–6]. In March–April 2009, in Mexico, a swine influenza A (H1N1) was recorded among people. In 2009 in California H1N1 (A/California/04/2009 and A/California/07/2009 (H1N1) [7]) viruses were isolated.

Only in 2009 there were reported about more than 250000 confirmed cases of influenza A (H1N1) in the world. It killed more than 2,500 patients world wide in 2009–2010 [8]. The disease spread by air-drip and contact-household. The etiotropic therapy (oseltamivir, zanamivir etc) [9–12] do not completely satisfy the clinic's requests. Therefore search for new antiviral agents (more effective and safety) is relevant now.

According to the WHO, in the 2008–2009 season in most countries of the European region the Brisbane/10/2007 strain (H3N2) was the predominant epidemic agent. In Ukraine the main cause of the flu epidemic in the 2011–2012 seasons was the strain of the influenza A virus (H3N2), accounting for 99 % of all isolated influenza viruses for this seasons [13]. The sharp rise in morbidity was accompanied by the appearance of a large number of severe forms and fatal cases. It is becoming more widespread and kills thousands of people every year around the world.

Earlier [14], we have synthesized and studied the antiviral properties of 1-(2,3-dihydro[1,4]dioxan-6-yl)-3-aryl-3-hydroxy-2,5,6,7,8,9-3H-imidazo[1,2-a] azepinium salts for Flu A H1N1 California/07/2009. In continuation of these studies we have synthesized a number of new derivatives imidazo[1,2-a] azepinium bromides to study their antiviral properties for Flu A H1N1 California / 07/2009 and Flu A H3N2 Brisbane / 10/2007.

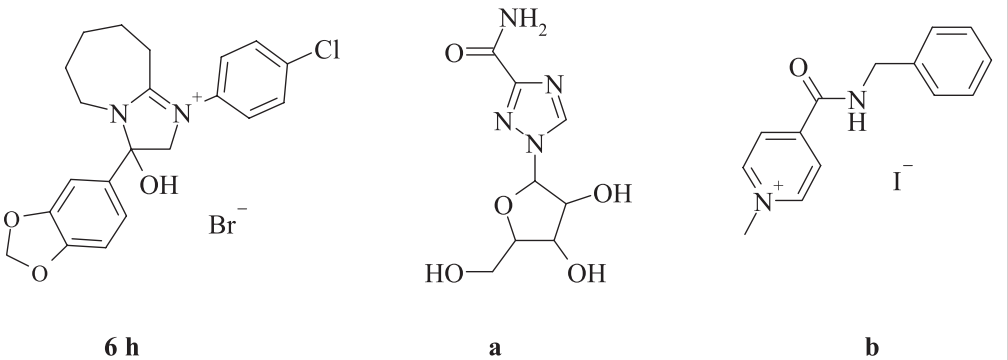
The aim of the study – to synthesize the derivatives of 1-(4[1]-chlorophenyl)-3-

aryl-3-hydroxy-2,5,6,7,8,9-hexahydro-*3H*-imidazo [1,2-a]azepinium bromides and to study the antiviral activity of 1-(4[1]-chlorophenyl)-3-(benzo[1,3]dioxol-5-yl)-3-hydroxy-2,5,6,7,8,9-hexahydro-*3H*-imidazo[1,2-a]azepinium bromide for Flu A H1N1 California/07/2009 and Flu A H3N2 Brisbane /10/2007 at primary pharmacological screening stage.

Materials and methods. The investigated compounds – 1-(4[1]-chlorophenyl)-3-aryl-3-hydroxy-2,5,6,7,8,9-hexahydro-*3H*-imidazo [1,2-a]azepinium bromides **(6 a-i)** and the substance of the drug «Amizon» were synthesized in the department of medical chemistry Institute of Pharmacology and Toxicology of National Academy of Medical Sciences (Fig. 1–2).

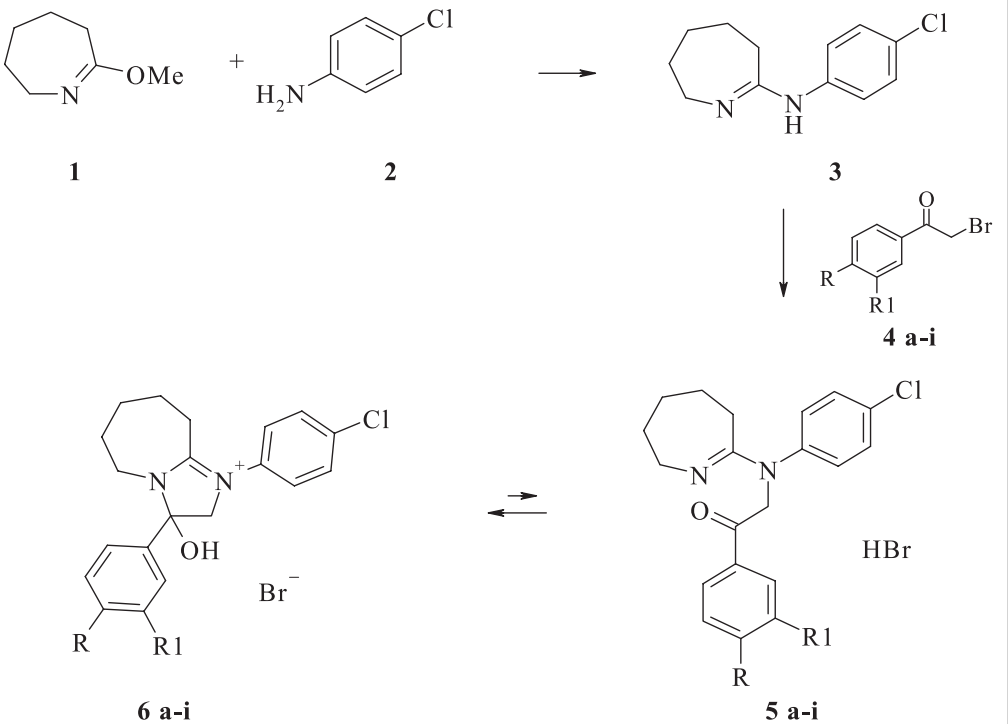
The investigated compounds **(6 a-i)** were synthesized according to the scheme on Fig. 2.

2-Methoxy-3,4,5,6-tetrahydro-7H-azepine **1** was obtained by alkylating caprolactam with dimethyl sulfate using



6 h **a** **b**

*Fig. 1. Structural formulas for active ingredients of Ribavirin (**a**), Amizon (**b**) and 1-(4[1]-chlorophenyl)-3-(benzo[1,3]dioxol-5-yl)-3-hydroxy-2,5,6,7,8,9-hexahydro-3H-imidazo[1,2-a] azepinium bromide (**6 h**)*



1 **2** **3** **4 a-i** **6 a-i** **5 a-i**

*Fig. 2. where **4–6**: **a**) R=R[1]=H; **b**) R=F, R[1]=H; **c**) R=Cl, R[1]=H; **d**) R=Br, R[1]=H; **e**) R=OCH[3], R[1]=H; **f**) R=CH[3], R[1]=H; **g**) R=NO[2], R[1]=H; **h**) RR[1]= -OCH[2]O-; **i**) RR[1]= -OCH[2]CH[2]O-*

the method [15]. Derivatives of α-bromoacetophenones 4 i was obtained by bromination of the corresponding acetophenones with bromine in acetic acid medium [16, 17]. ^{1}H-NMR spectra were recorded on the Varian Gemini 400 MHz (Germany) in DMSO-d6 using tetramethylsilane (TMS) as an internal standard. Chemical shifts are reported in ppm units with use of the δ scale.

*Synthesis of (4^1-chlorophenyl)-4,5,6,7-tetrahydro-3H-azepin-2-yl)-amine (**3**).* A mixture of 3.83 g (0.03 M) of para-chloroaniline **2** and 3.94 g (0.031 M) of 2-methoxy-3,4,5,6-tetrahydro-7H-azepine **1** in 30 ml of toluene is refluxed for 3 hours. After cooling, the precipitate formed is filtered off, washed with hexane, dried. Yield 5.55 g (83 %). M. p. = 129–130 °C (from propanol-2). Anal. Calc. for $C_{12}H_{15}ClN_2$, %: N = 12.6; Cl = 15.9. Found, %: N = 12.5; Cl = 15.7. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.44–1.63 (m, 6H, -$CH_2CH_2CH_2$-), 2.35 (m, 2H, CH_2), 3.15 (m, 2H, CH_2), 6.14–6.70 (d-d, 4H, C_6H_4).

*Synthesis of 1-(4^1-chlorophenyl)-3-phenyl-3-hydroxy-2,5,6,7,8,9-hexahydro-3H-imidazo[1,2-a]azepinium bromide (**6a**).* To solution of 2.23 g (0.01 M) (4^1-chlorophenyl)-4,5,6,7-tetrahydro-3*H*-azepin-2-yl)-amine **3** in 50 ml of ethyl acetate was added with stirring 1.99 g (0.01 M) of α-bromoacetophenone **4a**. The mixture was refluxed for 1 hour. The reaction mixture was cooled. The precipitate was filtered off and crystallized from ethanol. Yield 3.29 g (78 %). M. p. = 232-233 °C. Anal. Calc. for $C_{20}H_{22}BrClN_2O$, %: N = 6.64. Found, %: N = 6.73. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.60–1.82 (m, 6H, -CH_2CH_2 CH_2-), 2.79 (m, 2H, CH_2), 3.27 (m, 2H, CH_2), 4.37 and 4.56 (д-д, 2H, 2-CH_2, J = 12.4 Hz), 7.49 – 7.74 (m, 9H, aromatic protons), 8.12 (s, 1H, OH).

1-(4^1-Chlorophenyl)-3-(4^2-fluorophenyl)-3-hydroxy-2,5,6,7,8,9-hexahydro-3H-imidazo[1,2-a]azepinium bromide **6 b** was obtained as bromide 6a from 2.23 g (0.01 M) of amine **3** and 2.17 g (0.01 M) of α-bromo-4-fluoroacetophenone **4 b**. Yield 3.03 g (69 %). M. p. = 254–255 °C. Anal. Calc. for $C_{20}H_{21}BrClFN_2O$, %: N = 6.37. Found, %: N = 6.48. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.60–1.85 (m, 6H, -CH_2CH_2 CH_2-), 2.77 (m, 2H, CH_2), 3.26–3.32 (m, 2H, CH_2), 4.36 and 4.57 (d-d, 2H, 2-CH_2, J = 12.7 Hz), 7.65 and 7.71 (d-d, 4H, C_6H_4, J = 8.3 Hz), 7.33–7.82 (m, 4H, C_6H_4), 8.19 (s, 1H, OH).

1,3-Di-(4^1-chlorophenyl)-3-hydroxy-2,5,6,7,8,9-hexahydro-3H-imidazo [1,2-a] azepinium bromide **6 c** was obtained as bromide **6a** from 2.23 g (0.01 M) of amine **3** and 2.33 g (0.01 M) of α-bromo-4-chloroacetophenone **4 c**. Yield 3.51 g (77 %). M. p. = 227–229 °C. Anal. Calc. for $C_{20}H_{21}BrCl_2N_2O$, %: N = 6.14. Found, %: N = 5.98. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.60–1.84 (m, 6H, -CH_2CH_2 CH_2-), 2.76 (m, 2H, CH_2), 3.28 (m, 2H, CH_2), 4.36 and 4.56 (d-d, 2H, 2-CH_2, J = 13.1 Hz), 7.58 and 7.77 (d-d, 4H, C_6H_4, J = 8.8 Hz), 7.64 and 7.71 (d-d, 4H, C_6H_4, J = 9.0 Hz), 8.23 (c, 1H, OH).

1-(4^1-Chlorophenyl)-3-(4^2-bromophenyl)-3-hydroxy-2,5,6,7,8,9-hexahydro-3H-imidazo[1,2-a]azepinium bromide **6 d** was obtained as bromide **6a** from 2.23 g (0.01 M) of amine **3** and 2.78 g (0.01 M) of α-bromo-4-bromoacetophenone **4 d**. Yield 4.06 g (81 %). M. p. = 232–233 °C. Anal. Calc. for $C_{20}H_{21}Br_2ClN_2O$, %: N = 5.59. Found, %: N = 5.41. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.64–2.02 (m, 6H, -CH_2CH_2 CH_2-), 2.77–2.87 (m, 2H, CH_2), 3.37 (m, 2H, CH_2), 4.43 and 4.48 (d-d, 2H, 2-CH_2, J = 12.8 Hz), 7.53 and 7.78 (d-d, 4H, C_6H_4, J = 8.0 Hz), 7.58 and 7.90 (d-d, 4H, C_6H_4, J = 8.0 Hz), 8.23 (s, 1H, OH).

1-(4^1-Chlorophenyl)-3-(4^2-methoxyphenyl)-3-hydroxy-2,5,6,7,8,9-hexahydro-3H-imidazo[1,2-a]azepinium bromide **6 e** was obtained as bromide **6a** from 2.23 g (0.01 M) of amine **3** and 2.29 g (0.01 M) of α-bromo-4-methoxyacetophenone **4 e**. Yield 2.89 g (64 %). M. p. = 234–235 °C. Anal. Calc. for $C_{21}H_{24}BrClN_2O_2$, %: N = 6.20. Found, %: N = 6.36. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.60–1.83 (m, 6H, -CH_2CH_2 CH_2-), 2.76 (m, 2H, CH_2), 3.29 (m, 2H, CH_2), 3.81 (s, 3H, OCH_3), 4.32 and 4.55 (d-d, 2H, 2-CH_2, J = 11.7 Hz), 7.04 and 7.62 (d-d, 4H, C_6H_4, J = 8.0 Hz), 7.66 (s, 4H, C_6H_4), 8.04 (s, 1H, OH).

1-(4^1-Chlorophenyl)-3-(4^2-methylphenyl)-3-hydroxy-2,5,6,7,8,9-hexahydro-

3H-imidazo[1,2-a]azepinium bromide **6 f** was obtained as bromide **6a** from 2.23 g (0.01 M) of amine **3** and 2.13 g (0.01 M) of α-bromo-4-methylacetophenone 4 f. Yield 2.66 g (61 %). M. p. = 243–245 °C. Anal. Calc. for $C_{21}H_{24}BrClN_2O$, %: N = 6.42. Found, %: N = 6.60. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.60–2.04 (m, 6H, -CH_2CH_2 CH_2-), 2.36 (s, 3H, CH_3), 2.74 (m, 2H, CH_2), 3.37 (m, 2H, CH_2), 4.31 and 4.49 (d-d, 2H, 2-CH_2, J = 12.4 Hz), 7.21 and 7.50 (d-d, 4H, C_6H_4, J = 8.0 Hz), 7.66 and 7.95 (d-d, 4H, C_6H_4, J = 8.0 Hz), 8.06 (s, 1H, OH).

1-(4^1-Chlorophenyl)-3-(4^2-nitrophenyl)-3-hydroxy-2,5,6,7,8,9-hexahydro-3H-imidazo[1,2-a]azepinium bromide **6 g** was obtained as bromide **6a** from 2.23 g (0.01 M) of amine **3** and 2.44 g (0.01 M) of α-bromo-4-nitroacetophenone 4 g. Yield 3.13 g (67 %). M. p. = 298–300 °C. Anal. Calc. for $C_{20}H_{21}BrClN_3O_3$, %: N = 9.00. Found, %: N = 9.16. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.67–1.89 (m, 6H, -CH_2CH_2 CH_2-), 2.76–2.87 (m, 2H, CH_2), 3.31–3.37 (m, 2H, CH_2), 4.44 and 4.55 (d-d, 2H, 2-CH_2, J = 13.3 Hz), 7.59–7.80 (d-d, 4H, C_6H_4, J = 7.4 Hz), 8.11–8.30 (d-d, 4H, C_6H_4, J = 8.0 Hz), 8.41 (s, 1H, OH).

1-(4^1-Chlorophenyl)-3-(benzo[1,3]dioxol-5-yl)-3-hydroxy-2,5,6,7,8,9-hexahydro-3H-imidazo[1,2-a]azepinium bromide **6 h** was obtained as bromide **6a** from 2.23 g (0.01 M) of amine **3** and 2.43 g (0.01 M) of 1-benzo[1,3]dioxol-5-yl-2-bromomethanone **4 h**. Yield 3.77 g (81 %). M. p. = 217–218 °C. Anal. Calc. for $C_{21}H_{22}BrClN_2O_3$, %: N = 6.01. Found, %: N = 6.17. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.64 – 2.05 (m, 6H, -CH_2CH_2 CH_2-), 2.76–2.83 (m, 2H, CH_2), 3.28 (m, 2H, CH_2), 4.38 and 4.46 (d-d, 2H, 2-CH_2, J = 12 Hz), 6.04 (m, 4H, -OCH_2O-), 6.85–7.32 (m, 3H, C_6H_3), 7.53 and 7.90 (d-d, 4H, C_6H_3, J =8.9 Hz), 8.09 (s, 1H, OH).

1-(4^1-Chlorophenyl)-3-(2,3-dihydrobenzo[1,4]dioxan-6-yl)-3-hydroxy-2,5,6,7,8,9-hexahydro-3H-imidazo[1,2-a]azepinium bromide **6 i** was obtained as bromide **6a** from 2.23 g (0.01 M) of amine **3** and 2.57 g (0.01 M) of 2-bromo-1-(2,3-dihydrobenzo[1,4]dioxan-6-yl)ethanone **4 i**. Yield 3.02 g (63 %). M. p. = 194–195 °C. Anal. Calc. for $C_{22}H_{24}BrClN_2O_4$, %: N = 5.84. Found, %: N = 5.71. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.76–1.90 (m, 6H, -CH_2CH_2 CH_2-), 3.00 (m, 2H, CH_2), 3.24 (m, 2H, CH_2), 4.20 (s, 2H, 2-CH_2), 4.32 (m, 4H, -OCH_2CH_2O-), 6.95–7.11 (m, 3H, C_6H_3), 7.65–7.77 (d-d, 4H, C_6H_4, J = 8.0 Hz), 7.95 (s, 1H, OH).

The antiviral activity of new substance (against the Flu A H1N1 California/ 07/2009 and Flu A H3N2 Brisbane/10/2007) was examined in Southern Research Institute – SRI, Birmingham, Alabama. The trial was conducted within the framework of an international program to search new antiviral drugs. According to agreement of collaboration between Institute of Pharmacology and Toxicology of NAMS of Ukraine and Southern Research Institute there were studied the substance **6 h** and active ingredient of Amizon (4-(N-benzyl) aminocarbonyl-1-methylpyridinium iodide). 1-(4^1-Chlorophenyl)-3-(benzo[1,3]dioxol-5-yl)-3-hydroxy-2,5,6,7,8,9-hexahydro-*3H*-imidazo[1,2-a]azepinium bromide was selected among other new compounds as substance that contains a natural pharmacophore – (benzo[1,3]dioxol-5-yl) for Flu A H1N1 California / 07/2009 and Flu A H3N2 Brisbane/10/2007. Amizon is an original development of SI «Institute of Pharmacology and Toxicology of NAMS of Ukraine» [18], with analgesic, anti-inflammatory and antipyretic activity.

It is indicated that Amizon has interferonogenic properties [19]. It is noted that Amizon increases the body's resistance to viral infections and its widespread use in Ukraine for the treatment of influenza [20].

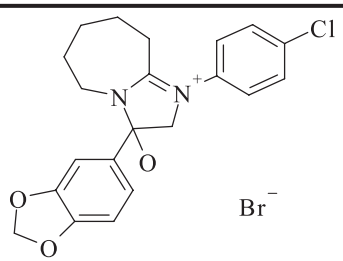
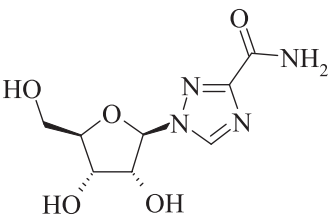
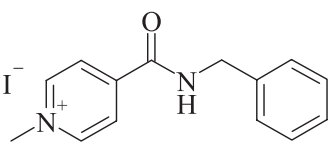
The antiviral activity was studied *in vitro*, using MDCK cell culture [21]. According to this procedure, Ribavirin is always used at the stage of primary antiviral activity screening as positive control in this test. Confluent monolayers of MDCK cells were grown in 96-well plates. Residual cultural medium was completely removed and plates were washed once with phosphate buffered saline (PBS) and then infected with influenza Flu A H1N1 or Flu A H3N2 viruses in dimethylsulfoxide (DMSO) at 0.1–10 μg / ml. Sub-

stance **6 h** or active ingredient of Amizon, or Ribavirin (Sigma) in DMSO was added to each well at a final concentration of 0.1 to 10 μg/ml. There were cultured for 48 hours and observed in microscope to evaluate the state MDCK cell culture. Then 100 μl of 70 % acetone was added and each plate well was kept at −20 ° C for 1 hour. After drying 100 μl of 0.4 % (w/v) SRB solution (sulforhodamine B) dissolved in 1 % (v/v) acetic acid. After 30 minutes of staining the SRB solution, not bound to the cells, was washed 4 times with 1 % (v/v) acetic acid. After drying, 100 μl 10 mM Tris solution (pH 10.5) was added to each well to dissolve the colored substance at the bottom of the well. Optical density was measured to assess antiviral activity. Cells treated with DMSO alone and cells treated with DMSO and the Flu A H1N1 or Flu A H3N2 viruses were used for control.

Results and discussion. For initial screening of the antiviral activity, each compound was tested by plaque inhibition assay in MDCK cells at a fixed concentration (against virus Flu A H1N1 California/07/2009). 1-(4^1-Chlorophenyl)-3-(benzo[1,3]dioxol-5-yl)-3-hydroxy-2,5,6,7,8,9-hexahydro-*3H*-imidazo[1,2-a]azepinium bromide **6 h** inhibitory effect was observed in concentration by 2.9 times less than for ribavirin, and in 15.7 times less than for Amizon. The selectivity index of compound **6 h** SI > 33 (IC_{50} > 100 μg/ml). The selectivity index of ribavirin is higher (SI > 37), but at the same time IC_{50} > 320 μg/ml. It should be noted, that if IC_{50} for these two substances were the same, then the SI for compound **6h** would be three times greater. Antiviral activity of «Amizon» was lower then **6 h** and ribavirin (Table).

Table

The Antiviral activity of 1-(4^1-chlorophenyl)-3-(benzo[1,3]dioxol-5-yl)-3-hydroxy-2,5,6,7,8,9-hexahydro-3H-imidazo[1,2-a]azepinium bromide 6 h against FLU A H1N1 California/ 07/2009 and Flu A (H3N2) Brisbane/10/2007

Substance	Structure	Type of virus	EC_{50}, μg/ml	IC_{50}, μg/ml	SI
6 h		Flu A (H1N1) California/07/2009	3	> 100	> 33
		Flu A (H3N2) Brisbane/10/2007	10	61	6.1
Ribavirin		Flu A (H1N1) California/07/2009	8.7	> 320	> 37
		Flu A (H3N2) Brisbane/10/2007	6.7	> 320	> 48
Amizon (active ingredient)		Flu A (H1N1) California/07/2009	47	> 100	> 2.1
		Flu A (H3N2) Brisbane/10/2007	> 100	> 100	0

Notes. 1. EC_{50} (half maximal effective concentration) refers to the concentration of a drug, antibody or toxicant which induces a response halfway between the baseline and maximum after a specified exposure time. It is commonly used as a measure of a drug's potency. EC_{50} is expressed in μg / ml. 2. IC_{50} – is a measure of a compound's inhibition (50 % inhibition). IC_{50} is expressed in μg / ml. 3. SI – selectivity index (IC_{50} / EC_{50}).

The selectivity index of **6 h** compound as to the Flu A (H3N2) Brisbane /10/2007 is 6.1 (IC_{50} = 61 μg/ml). This indicator of activity is less than such of Ribavirin, but more than of the Amizon substance (Table).

Thus, the proposed new compound provides high antiviral activity against Flu A H1N1 Californiya / 07/2009 and somewhat less activity for Flu A H3N2 Brisbane /10/2007.

The data obtained substantiate the expediency of further studies of 1-(4^1-chlorophenyl)-3-aryl-3-hydroxy-2,5,6,7,8,9-hexahydro-*3H*-imidazo[1,2-a] azepinium derivatives as potential antiviral agents.

Conclusions

1. Under *in vitro* assay on MDCK cell culture 1-(4^1-Chlorophenyl)-3-(benzo[1,3]dioxol-5-yl)-3-hydroxy-2,5,6,7,8,9-hexahydro-*3H*-imidazo[1,2-a]azepinium bromide demonstrates high antiviral activity for Flu A H1N1 California/07/2009: EC_{50} 3.0 μg /ml (lower in 2.9 times than ribavirin) and selectivity index SI > 33.
2. 1-(4^1-Chlorophenyl)-3-(benzo[1,3] dioxol-5-yl)-3-hydroxy-2,5,6,7,8,9-hexahydro-*3H*-imidazo[1,2-a]azepinium bromide has antiviral activity for Flu A H3N2 Brisbane/10/2007: EC_{50} 10 μg /ml and selectivity index (SI) > 6.1.
3. The data obtained substantiate the expediency of further studies of derivatives of 1-(4^1-chlorophenyl)-3-aryl-3-hydroxy-2,5,6,7,8,9-hexahydro-*3H*-imidazo[1,2-a]azepinium as potential antiviral agents.

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Synthesis and antiviral activity of derivatives of 1-(4^1-chlorophenyl)-3-aryl-3-hydroxy-2,5,6,7,8,9-hexahydro-*3H*-imidazo[1,2-a]azepinium for Flu A H1N1 California/07/2009 and Flu A H3N2 Brisbane/10/2007

The problem of acute respiratory viral infections (ARVIs) and flu therapy, especially influenza caused by virus H1N1, because of the prevalence of disease incidence and complications is one of the urgent medical and social problems.

According to the WHO, in the 2008–2009 season in most countries of the European region, the Brisbane / 10/2007 strain (H3N2) was the predominant epidemic agent. In Ukraine, the main cause of the flu epidemic in the 2011–2012 seasons was the strain of the influenza A virus (H3N2), accounting for 99 % of all isolated influenza viruses these seasons.

The aim of the study – to synthesize the derivatives of 1-(4^1-chlorophenyl)-3-aryl-3-hydroxy-2,5,6,7,8,9-hexahydro-*3H*-imidazo [1,2-a]azepinium bromides and to study the antiviral activity of 1-(4^1-chlorophenyl)-3-(benzo[1,3]dioxol-5-yl)-3-hydroxy-2,5,6,7,8,9-hexahydro-3H-imidazo[1,2-a]azepinium bromide for Flu A H1N1 California/07/2009 and Flu A H3N2 Brisbane /10/2007 at primary pharmacological screening stage.

By the reaction of (4^1-chlorophenyl)-4,5,6,7-tetrahydro-*3H*-azepin-2-yl)amine with substituted α-bromoacetophenones 1-(4^1-chlorophenyl)-3-aryl-3-hydroxy-2,5,6,7,8,9-hexahydro-*3H*-imidazo[1,2-a]azepinium bromides were obtained. The antiviral activity of 1-(4^1-chlorophenyl)-3-(benzo[1,3] dioxol-5-yl)-3-hydroxy-2,5,6,7,8,9-hexahydro-*3H*-imidazo[1,2-a]azepinium bromide and active substance of Amizon was determined *in vitro* on MDCK cell culture with Ribavirin as positive control in this test.

It is shown that the analyzed substances have antiviral activity against the virus Flu A H1N1 California/07/2009 and virus Flu A H3N2 Brisbane/10/2007 in test *in vitro* on cell culture MDCK. The results obtained substantiate the expediency of further studies of 1-(4^1-chlorophenyl)-3-aryl-3-hydroxy-2,5,6,7,8,9-hexahydro-*3H*-imidazo[1,2-a] azepinium based compounds as potential antiviral agents.

Key words: antiviral activity, Ribavirin, Flu A H1N1 California/07/2009 virus, Flu A H3N2 Brisbane/10/2007 virus, Amizon, 1-(4^1-chlorophenyl)-3-aryl-3-hydroxy-2,5,6,7,8,9-hexahydro-3H-imidazo[1,2-a]azepinium based compounds

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Синтез і противірусна активність похідних 1-(4^1-хлорофеніл)-3-арил-3-гідрокси-2,5,6,7,8,9-гексагідро-*3H*-імідазо[1,2-а]азепінію відносно вірусів грипу А H1N1 та H3N2

Проблема лікування гострих респіраторних вірусних інфекцій (ГРВІ) і грипу, особливо грипу, викликаного вірусами H1N1 і H3N2, з огляду на поширеність захворювань, тяжкість перебігу та ускладнення, є однією з актуальних медичних та соціальних проблем сучасності.

За даними ВООЗ, у сезоні 2008–2009 років у більшості країн Європейського регіону переважним збудником епідемічного підйому був штам Brisbane/10/2007 (H3N2). В Україні головним збудником епідемії грипу в сезоні 2011–2012 років був штам вірусу грипу А(H3N2), який склав 99 % усіх виділених вірусів грипу в тому сезоні.

Мета дослідження – синтезувати та вивчити противірусну активність похідних бромідів 1-(4^1-хлорофеніл)-3-арил-3-гідрокси-2,5,6,7,8,9-гексагідро-*3H*-імідазо[1,2-а]азепінію на етапі первинного фармакологічного скринінгу.

Взаємодією (4[1]-хлорофеніл)-4,5,6,7-тетрагідро-3Н-азепін-2-їл)аміну з заміщеними α-бромацетофенонами отримані броміди 1-(4[1]-хлорофеніл)-3-арил-3-гідрокси-2,5,6,7,8,9-гексагідро-*3Н*-імідазо[1,2-а]азепінію. Оцінено противірусну активність броміду 1-(4[1]-хлорофеніл)-3-(бензо[1,3] діоксол-5-їл)-3-гідрокси-2,5,6,7,8,9-гексагідро-*3Н*-імідазо[1,2-а]азепінію та субстанції препарату «Амізон» *in vitro* на культурі клітини MDCK з рибавірином як позитивним контролем у цьому тесті.

Показано, що досліджувані речовини мають противірусну активність відносно вірусів Flu A H1N1 California/07/2009 та Flu A H3N2 Brisbane /10/2007 в тесті *in vitro* на культурі клітини MDCK. Отримані дані обґрунтовують доцільність подальшого вивчення похідних 1-(4[1]-хлорофеніл)-3-арил-3-гідрокси-2,5,6,7,8,9-гексагідро-*3Н*-імідазо[1,2-а]азепінію як потенційних противірусних засобів.

Ключові слова: противірусна активність, рибавірин, вірус Flu A H1N1 California/07/ 2009, вірус Flu A H3N2 Brisbane/10/2007, Амізон, похідні 1-(4[1]-хлорофеніл)-3-арил-3-гідроксі-2,5,6,7,8,9-гексагідро-3Н-імідазо[1,2-а]азепінію

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Синтез и противовирусная активность производных 1-(4[1]-хлорфенил)-3-арил-3-гидрокси-2,5,6,7,8,9-гексагидро-*3Н*-имидазо[1,2-а]азепиния по отношению к вирусам гриппа А H1N1 и H3N2

Проблема лечения острых респираторных вирусных инфекций (ОРВИ) и гриппа, особенно гриппа, вызванного вирусами H1N1 или H3N2, из-за распространенности заболеваний, тяжести протекания и осложнений является одной из актуальнейших медициских и социальных проблем современности.

По данным ВООЗ, в сезоне 2008–2009 годов в большинстве стран Европейского региона преобладающим возбудителем эпидемии был штамм Brisbane/10/2007 (H3N2). В Украине основным возбудителем эпидемии гриппа в сезоне 2011–2012 годов также был штамм вируса гриппа А (H3N2), который составил 99 % от всех выделенных видов вирусов в том сезоне.

Цель исследования – синтезировать, изучить противирусную активность производных бромидов 1-(4[1]-хлорфенил)-3-арил-3-гидрокси-2,5,6,7,8,9-гексагидро-*3Н*-имидазо[1,2-а]азепиния по отношению к вирусам Flu A H1N1 California/07/ 2009 и Flu A H3N2 Brisbane/10/2007 на этапе первичного фармакологического скрининга.

Взаимодействием (4[1]-хлорфенил)-4,5,6,7-тетрагидро-*3Н*-азепин-2-ил) амина с замещенными α-бромацетофенонами получены бромиды 1-(4[1]-хлорфенил)-3-арил-3-гидрокси-2,5,6,7,8,9-гексагидро-*3Н*-имидазо[1,2-а]азепиния. Оценена противирусная активность бромида 1-(4[1]-хлорфенил)-3-(бензо[1,3] диоксол-5-ил)-3-гидрокси-2,5,6,7,8,9-гексагидро-*3Н*-имидазо[1,2-а]азепиния и субстанции препарата «Амизон» *in vitro* на культуре клеток MDCK с рибавирином в качестве позитивного контроля.

Показано, что исследованные соединения проявляют противирусное действие по отношению к вирусам Flu A H1N1 California/07/ 2009 и Flu A H3N2 Brisbane/10/2007 в тесте *in vitro* на культуре клеток MDCK. Полученные данные обосновывают целесообразность дальнейшего изучения производных 1-(4[1]-хлорфенил)-3-арил-3-гидрокси-2,5,6,7,8,9-гексагидро-*3Н*-имидазо[1,2-а]азепиния в качестве потенциальных противовирусных средств.

Ключевые слова: противовирусная активность, рибавирин, вирус Flu A H1N1 California/07/ 2009, вирус Flu A H3N2 Brisbane/10/2007, Амизон, производные 1-(4[1]-хлорфенил)-3-арил-3-гидрокси-2,5,6,7, 8,9-гексагидро-3Н-имидазо[1,2-а]азепиния

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