The synthesis and antiviral activity of 1-(4-chlorophenyl)-4-(para-tolyl)-5,6,7,8-tetrahydro-2a,4a-diazacyclopenta[cd]-azulene-2-carboxylic acid derivatives

Aim. To synthesize, prove the structural framework and study the antiviral activity of 1-(4-chlorophenyl)-4-(para-tolyl)-5,6,7,8-tetrahydro-2a,4a-diazacyclopenta[cd]azulene-2-carboxylic acid derivatives.

Results and discussion. The antiviral activity of 1-(4-chlorophenyl)-4-(para-tolyl)-5,6,7,8-tetrahydro-2a,4a-diazacyclopenta[cd]azulene-2-carboxylic acid (4-methoxyphenyl)amide was determined in the Southern Research Institute (SRI, Birmingham, Alabama). The efficacy of this compound was expressed by EC\textsubscript{50}, IC\textsubscript{50} and SI values determined in vitro within a range of concentrations of 0.1–100 μg/mL. The antiviral drug Ribavirin (Sigma) and the active substance of Amizon – 4-(N-benzyl)aminocarboxyl-1-methylpyridinium iodide were used as the reference drugs.

Experimental part. Condensation of 2-methoxy-3,4,5,6-tetrahydro-7H-azepine with α-amino-4-methylacetonaphone hydrochloride led to 3-(4-methylphenyl)-6,7,8-tetrahydro-5H-imidazo[1,2-a]azepine. By boiling the latter with α-bromo-4-chloroacetophenone in ethyl acetate 1-[2-(4-chlorophenyl)-2-oxoethyl]-3-(para-tolyl)-6,7,8-tetrahydro-5H-imidazo[1,2-a]azepin-1-ium bromide was isolated, which in aqueous alkali solution was converted into 1-(4-chlorophenyl)-4-(para-tolyl)-5,6,7,8-tetrahydro-2a,4a-diazacyclopenta[cd]azulene. The latter while reacting with the corresponding arylisocyanate in a dry benzene gave 1-(4-chlorophenyl)-4-(para-tolyl)-5,6,7,8-tetrahydro-2a,4a-diazacyclopenta[cd]azulene-2-carboxylic acid (thio)amides. \textsuperscript{1}H NMR-spectra for the compounds synthesized were recorded on a Bruker VXR-300 spectrometer (Germany) with the operating frequency of 299.945 MHz, and also on a Bruker DRX300 (Germany) spectrometer with the operating frequency of 500.13 MHz, in DMSO-d\textsubscript{6} using tetramethylsilane (TMS) as an internal standard. The melting points were measured using a RNMK 05 apparatus (VEB Analytik, Dresden).

Conclusions. The series of new 1-(4-chlorophenyl)-4-(para-tolyl)-5,6,7,8-tetrahydro-2a,4a-diazacyclopenta[cd]azulene-2-carboxylic acid (thio)amides has been synthesized. The antiviral activity of 1-(4-chlorophenyl)-4-(para-tolyl)-5,6,7,8-tetrahydro-2a,4a-diazacyclopenta[cd]azulene-2-carboxylic acid (4-methoxyphenyl)amide has been studied in the Southern American Research Institute (SRI, Birmingham, Alabama), and the high level of the antiviral activity has been found against Flu A H1N1 California/07/2009 virus.

Key words: 1-(4-chlorophenyl)-4-(para-tolyl)-5,6,7,8-tetrahydro-2a,4a-diazacyclopenta[cd]azulene-2-carboxylic acid substituted (thio)amides; Ribavirin; Amizon; antiviral activity; Flu A H1N1 California/07/2009 virus
Висновки. Синтезовано ряд новых замещенных (тіо)амидов 1-(4-хлорфенил)-4-[(пара-толил)-5,6,7,8-тетрагидро-2а,4а-діазациклопента[cd]азулен-2-карбоновой кислоты. Противовирусную активность (4-метоксифенил)амиду 1-(4-хлорфенил)-4-[(пара-толил)-5,6,7,8-тетрагидро-2а,4а-діазациклопента[cd]азулен-2-карбоновой кислоты впервые у Південною дослідному інституту США (Southern Research Institute – SRI, Birmingham, Alabama) та встановлено високий рівень зазначеної активності щодо вірусу Flu A H1N1 California/07/2009.

Ключові слова: заміщенні (тіо)аміди 1-(4-хлорфенил)-4-[(пара-толил)-5,6,7,8-тетрагидро-2а,4а-діазациклопента[cd]азулен-2-карбонової кислоти; рібавірин; амізон; противірусна активність; вірус Flu A H1N1 California/07/2009

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Синтез и противовирусная активность производных 1-(4-хлорфенил)-4-[(пара-толил)-5,6,7,8-тетрагидро-2а,4а-діазациклопента[cd]азулен-2-карбоновой кислоты

Цель работы. Синтезировать, доказать строение и исследовать противовирусную активность замещенных (тіо)амидов 1-(4-хлорфенил)-4-[(пара-толил)-5,6,7,8-тетрагидро-2а,4а-діазациклопента[cd]азулен-2-карбоновой кислоты.

Результаты и их обсуждение. Определение противовирусной активности (4-метоксифенил)амид 1-(4-хлорфенил)-4-[(пара-толил)-5,6,7,8-тетрагидро-2а,4а-діазациклопента[cd]азулен-2-карбоновой кислоты проведено в Южном исследовательском институте США (Southern Research Institute – SRI, Birmingham, Alabama). Эффективность данного соединения выражались показателями EC50, IC50 и SI, которые определяли в опытах in vitro в диапазоне концентраций от 0,1 до 100 мкг/мл. В качестве препаратов сравнения использованы противовирусное средство Рибавирин (Sigma) и действующее вещество препарата Амизон – 4-(N-бензил)аминокарбонил-1-метилпиридиний йодид.

Экспериментальная часть. Конденсацией 2-метокси-3,4,5,6-тетрагидро-7Н-азепина с солянокислым а-амино-4-метилацидофеноном синтезирован 3-(4-метилфенил)-6,7,8,9-тетрагидро-5Н-имидазо[1,2-а]-азепин. При кипячении последнего с а-бром-4-хлорацидофеноном в этаноле выпал 1-(4-хлорфенил)-2-оксазол-3-[(пара-толил)-6,7,8,9-тетрагидро-5Н-имидазо[1,2-а]-азепин-1 бромид, который в водном растворе щелочи циклизуется в 1-(4-хлорфенил)-4-[(пара-толил)-5,6,7,8-тетрагидро-2а,4а-діазациклопента[cd]азулен. При взаимодействии последнего с соответствующими арилизо(тио)цианатами в сухом бензоле получены (тіо)амиды 1-(4-хлорфенил)-4-[(пара-толил)-5,6,7,8-тетрагидро-2а,4а-діазациклопента[cd]азулен-2-карбоновой кислоты. 1H ЯМР-спектры синтезированных соединений были записаны на спектрометре Bruker VXR-300 (Германия), рабочая частота – 299,945 МГц и спектрометре Bruker DRX300 (Германия), рабочая частота – 500,13 МГц, в DMSO-d6, используя в качестве внутреннего стандарта тетраметилсилан (TMS). Температуры плавления измеряли с помощью устройства RNMK 05 (VEB Analytik, Dresden).

Выводы. Синтезирована серия новых (тіо)амидов 1-(4-хлорфенил)-4-[(пара-толил)-5,6,7,8-тетрагидро-2а,4а-діазациклопента[cd]азулен-2-карбоновой кислоты. В Южном исследовательском институте США (Southern Research Institute – SRI, Birmingham, Alabama) изучена противовирусная активность (4-метоксифенил)амид 1-(4-хлорфенил)-4-[(пара-толил)-5,6,7,8-тетрагидро-2а,4а-діазациклопента[cd]азулен-2-карбоновой кислоты и установлен высокий уровень указанной активности в отношении вируса Flu A H1N1 California/07/2009.

Ключевые слова: замещённые (тіо)амиды 1-(4-хлорфенил)-4-[(пара-толил)-5,6,7,8-тетрагидро-2а,4а-діазациклопента[cd]азулен-2-карбоновой кислоты; рібавірин; амізон; противірусна активність; вірус Flu A H1N1 California/07/2009

The H1N1 virus strain, the influenza A [1] virus subtype, caused the epidemic of Spanish flu in 1918, became the cause of influenza outbreak in 2005/2006 and 2009/2010 seasons. According to the data of the Ministry of Health of Ukraine, just only within the period of influenza and acute respiratory viral infections outbreak (as from October 2009 until May 2010) more than 7.7 million of people or 16.87% of population contracted the disease in Ukraine.

The level of children hospitalization during influenza epidemic is significantly higher (84–93%) than that of adults [2]. According to the evaluation of the WHO experts the pandemic of 2009/2010 years led to the death of more than 500 thousand people. During this period, 1128 of those lethal cases were registered in Ukraine. Over 80% of deaths from influenza characterizing the Californian strain were registered in the age category of 18–50 years.

At the background of accompanying conditions (obesity, diabetes, chronic lung diseases, cardiovascular diseases, etc.) the fatal double hemorrhagic pneumonia is reliably observed [3].

Flu A H1N1 virus was first discovered in 1931 by the American scientist Richard Shope, and was later classified as endemic zoonosis [5, 6].

The strain of pandemic H1N1 (“Pandemic (H1N1) 09 Virus”) became known as “Swine Influenza” in media [1]. A/California/04/2009 (H1N1) and A/Cali-
fornia/07/2009 (H1N1) influenza virus strains were registered in California in 2009 and spread by means of aerosol and contact transmissions.

Modern antiviral medications are classified by the mechanism of action as those that directly damage the replication of virus, and those that modulate the immune system of the host organism. The group of drugs of this action registered and allowed to use in Ukraine includes Amizom, Amantadin, Arbidol, Zanamivir, Inozin pranobecs, Ozeltamivir, Rimantadin, etc. [8 – 15].

In Ukraine for curing conditions caused by the strain of H1N1 virus, 4-(N-benzyl)aminocarbonyl-1-methylpyridinium iodide (Amizom) is currently used. It was developed by the Institute of Pharmacology and Toxicology of Ukraine. Amizom possesses the anti-inflammatory, analgesic and antipyretic effects [11]. The analgesic effect is manifested with participation of the reticular formation of the brain stem [12]. Amizom has interferonogenic properties, causes the inhibiting effect on influenza viruses, and increases the body resistance to viral infections [14]. All these make Amizom a promising drug for prevention and treating different virus diseases [13].

However, from position of evidence-based medicine, there is no single opinion regarding indubitable effectiveness of certain drugs (Arbidol, Amixin, Amizom, Kagocel, Immunofam, etc.) used as immunomodulators with the anti-influenza activity [15].

Therefore, the search for new antiviral compounds is still relevant.

A series of amide and thioamide derivatives of 1-(4-chlorophenyl)-4-(para-tolyl)-5,6,7,8-tetrahydro-2,a,4a-diazacyclopenta[cd]azulene-2-carboxylic acid by interaction of 1-(4-chlorophenyl)-4-(para-tolyl)-5,6,7,8-tetrahydro-2,a,4a-diazacyclopenta[cd]azulene with the corresponding arylisothiocyanates in a dry benzene (Scheme) has been synthesized.

The antiviral effect of 1-(4-chlorophenyl)-4-(para-tolyl)-5,6,7,8-tetrahydro-2,a,4a-diazacyclopenta[cd]azulene-2-carboxylic acid (4-methoxyphenyl)amide 9d was compared to that of active compounds of Amizom and Ribavirin used for the treatment of infections caused by the respiratory syncytial virus, hepatitis C virus, etc. [16].

Among the side effects of Ribavirin there is dose-dependent anemia. In the case of kidney, cardiovascular diseases, this medication must be used only after thorough examination [17], which makes search for new antiviral compounds even more relevant.

Scheme. The synthesis of 1-(4-chlorophenyl)-4-(para-tolyl)-5,6,7,8-tetrahydro-2,a,4a-diazacyclopenta[cd]azulene-2-carboxylic acid derivatives 9a–j, 10k–m
The antiviral activity of 1-(4-chlorophenyl)-4-(para-tolyl)-5,6,7,8-tetrahydro-2а,4а-diazacyclopenta[cd]azulene-2-carboxylic acid (4-methoxyphenyl)amide 9d against Flu A H1N1 California/07/2009 virus strain

| Compound | Structure | Type of virus | EC₅₀ μg/mL | IC₅₀ μg/mL | SI |
|----------|-----------|--------------|------------|------------|----|
| 9d       | ![Structure of 9d](image1) | Flu A H1N1 California/07/2009 | 3.4 | >100 | >29 |
| Ribavirin | ![Structure of Ribavirin](image2) | Flu A H1N1 California/07/2009 | 8.7 | >320 | >37 |
| Amizone  | ![Structure of Amizone](image3) | Flu A H1N1 California/07/2009 | 47 | >100 | >2.1 |

Notes: EC₅₀ — the effective concentration determined by the dose/effect curve, and is a compound concentration, in which effect is observed in 50% of the population after a definite period of time passed, μg/mL; IC₅₀ — the concentration, in which inhibition of cells by a compound is 50%, μg/mL; SI — the index of selectivity, which is the indicator of the compound efficacy, expressed in IC₅₀/EC₅₀ ratio.

The antiviral activity of compound 9d against virus Flu A H1N1 California/07/2009 was studied in the Southern Research Institute (SRI, Birmingham, Alabama). The results obtained are given in Table below. The efficacy of compounds was expressed with EC₅₀, IC₅₀ and SI values determined in the experiments in vitro when studying the effects of compounds. Compounds were dissolved in dimethyl sulfoxide within a range of concentrations of 0.1 – 100 μg/mL. Together with the compound declared for studying the antiviral activity we sent the active compound of Amizon to the Southern Research Institute. The research revealed the high level of the antiviral activity of compound 9d against Flu A H1N1 California/07/2009 virus strain.

The results obtained indicate that the antiviral activity of 1-(4-chlorophenyl)-4-(para-tolyl)-5,6,7,8-tetrahydro-2а,4а-diazacyclopenta[cd]azulene-2-carboxylic acid (4-methoxyphenyl)amide 9d is observed in 2.56 times lower dose than that for Ribavirin substance and in 13.8 times lower dose than for Amizone substance. The selectivity index of the compound under research appeared to be more than 29 and IC₅₀ > 100 μg/mL. At the same time, the selectivity index of Ribavirin was more than 37 and IC₅₀ > 320 μg/mL. It should be noted that if IC₅₀ for those two compounds was the same, then SI for amide 9d would be three times higher and would be equal to SI > 92.8.

**Experimental part**

2-Methoxy-3,4,5,6-tetrahydro-7H-azepine 1 was obtained by alkylation caprolactam with dimethyl sulfate using the method [18]. α-Amino-4-methylacetophenone hydrochloride salt 2 was obtained by the interaction of α-bromo-4-methylacetophenone with hexamethylenetetramine using the method [19]. 3-(4-Methylphenyl)-6,7,8,9-tetrahydro-5H-imidazo [1,2-а]azepine 3 was obtained by the method described in [20].

¹H NMR spectra for compounds 9a–j were recorded using a Bruker VXR-300 (Germany) spectrometer with the operating frequency of 299.945 MHz and a Bruker DRX300 (Germany) spectrometer with the operating frequency of 500.13 MHz for compounds 10l–m; DMSO-d₆ was used as a solvent; tetramethylsilane (TMS) was used as an internal standard. Chemical shifts were reported in ppm using the δ scale.

The melting points were measured on a small-sized heating table with a RNMK 05 observation device (VEB Analytik, Dresden).
The synthesis of 1-[2-(4-chlorophenyl)-2-oxoethyl]-3-(para-tolylo)-6,7,8,9-tetrahydro-5H-imidazo[1,2-a]azepine-1-ium bromide 5. To the solution of 3-(4-methylphenyl)-6,7,8,9-tetrahydro-5H-imidazo[1,2-a]azepine 3 (9.04 g, 0.04 mole) in 150 mL of ethyl acetate add α-bromo-4-methylacetophenone 4 (9.43 g, 0.04 mole). Reflux the reaction mixture for 1 hour. After cooling filter the solid product 5, wash with ethyl acetate, then dry in air. Yield: 16.0 g (87%).

M. p. 239–240°C (from ethanol). Anal. Calcld. for C_{25}H_{25}BrClN,O: %: N 6.09. Found, %: N 6.16.

The synthesis of 1-(4-chlorophenyl)-4-(para-tolyl)-5,6,7,8-tetrahydro-2a,4a-diazacyclopenta[c]azulene 6. To the suspension of 1-(4-chlorophenyl)-2-oxoethyl]-3-(para-tolyl)-6,7,8,9-tetrahydro-5H-imidazo[1,2-a]azepine-1-ium bromide 5 (4.60 g, 0.01 mole) in 50 mL of water add 5% NaOH in 20 mL. Reflux the reaction mixture for 3 hours. After cooling filter the solid product 6, wash with water, then dry in air and recrystallize from benzene. Yield – 1.73 g (48%).

M. p. 216–218°C. Anal. Calcld. for C_{25}H_{25}ClN,O: %: N 7.76. Found, %: N 7.62.

The general procedure for the synthesis of 1-(4-chlorophenyl)-4-(para-tolyl)-5,6,7,8-tetrahydro-2a,4a-diazacyclopenta[c]azulene-2-carboxylic acid 9a–j. Reflux the mixture of 1-(4-chlorophenyl)-4-(para-tolyl)-5,6,7,8-tetrahydro-2a,4a-diazacyclopenta[c] azulene 6 (0.005 mole) and the appropriate arylisocyanate 7a–j (0.005 mole) in 50 mL of a dry benzene for 2 hours. After cooling filter the solid products 9a–j, wash with benzene, then dry in air and recrystallize from benzene or propanol-2.

1-(4-Chlorophenyl)-4-(para-tolyl)-5,6,7,8-tetrahydro-2a,4a-diazacyclopenta[c]azulene-2-carboxylic acid phenylamide 9a. Yield – 1.90 g (79%).

M. p. 212–213°C (from benzene). Anal. Calcld. for C_{31}H_{28}ClN,O: %: Cl 7.40, N 8.75. Found, %: Cl 7.56, N 8.53. H NMR (300 MHz, DMSO-d_6), δ ppm: 1.88–2.01 (2H, m, CH), 2.03–2.11 (2H, m, CH), 2.42 (3H, s, CH), 2.39–2.70 (2H, m, CH), 3.80–4.08 (2H, m, CH), 6.97 (1H, s, NH), 6.89–7.24 (5H, m, CH), 7.31 (2H, d, J = 8.3 Hz, C_H), 7.43 (2H, d, J = 8.3 Hz, C_H), 7.47 (2H, d, J = 8.8 Hz, C_H), 7.56 (2H, d, J = 8.8 Hz, C_H), 7.84 (1H, s, CH).

1-(4-Chlorophenyl)-4-(para-tolyl)-5,6,7,8-tetrahydro-2a,4a-diazacyclopenta[c]azulene-2-carboxylic acid phenylamide 9b. Yield – 1.76 g (69%).

M. p. 230–231°C (from benzene). Anal. Calcld. for C_{32}H_{29}ClN,O: %: Cl 6.96, N 8.24. Found, %: Cl 6.81, N 8.39. H NMR (300 MHz, DMSO-d_6), δ ppm: 1.87–1.98 (2H, m, CH), 2.03–2.15 (2H, m, CH), 2.43 (3H, s, CH), 2.35–2.64 (2H, m, CH), 3.50 (3H, s, OCH), 3.85–4.05 (2H, m, CH), 7.45 (1H, s, NH), 6.75–8.43 (4H, m, CH), 7.31 (2H, d, J = 8.3 Hz, C_H), 7.56 (2H, d, J = 8.3 Hz, C_H), 7.48 (2H, d, J = 8.8 Hz, C_H), 7.56 (2H, d, J = 8.8 Hz, C_H), 7.91 (1H, s, CH).

1-(4-Chlorophenyl)-4-(para-tolyl)-5,6,7,8-tetrahydro-2a,4a-diazacyclopenta[c]azulene-2-carboxylic acid 2-methoxyphenylamide 9c. Yield – 1.86 g (73%).

M. p. 203–204°C (from benzene). Anal. Calcld. for C_{31}H_{28}ClN,O_2: %: Cl 6.96, N 8.24. Found, %: Cl 7.08, N 8.41. H NMR (300 MHz, DMSO-d_6), δ ppm: 1.89–1.99 (2H, m, CH), 2.04–2.14 (2H, m, CH), 2.43 (3H, s, CH), 2.40–2.70 (2H, m, CH), 3.72 (3H, s, OCH), 3.82–4.12 (2H, m, CH), 6.43–7.06 (4H, m, C_H), 7.01 (1H, s, NH), 7.31 (2H, d, J = 7.8 Hz, C_H), 7.45 (2H, d, J = 7.8 Hz, C_H), 7.48 (2H, d, J = 8.3 Hz, C_H), 7.59 (2H, d, J = 8.3 Hz, C_H), 7.86 (1H, s, CH).

1-(4-Chlorophenyl)-4-(para-tolyl)-5,6,7,8-tetrahydro-2a,4a-diazacyclopenta[c]azulene-2-carboxylic acid 4-(methoxyphenyl)amide 9d. Yield – 1.94 g (76%).

M. p. 202–204°C (from benzene). Anal. Calcld. for C_{32}H_{29}ClN,O: %: Cl 6.96, N 8.24. Found, %: Cl 6.85, N 8.33. H NMR (300 MHz, DMSO-d_6), δ ppm: 1.85–1.95 (2H, m, CH), 2.02–2.13 (2H, m, CH), 2.43 (3H, s, CH), 2.41–2.74 (2H, m, CH), 3.71 (3H, s, OCH), 3.81–4.18 (2H, m, CH), 6.97 (1H, s, NH), 6.74 (2H, d, J = 9.3 Hz, C_H), 7.06 (2H, d, J = 9.3 Hz, C_H), 7.30 (2H, d, J = 8.3 Hz, C_H), 7.44 (2H, d, J = 8.3 Hz, C_H), 7.48 (2H, d, J = 8.8 Hz, C_H), 7.56 (2H, d, J = 8.8 Hz, C_H), 7.84 (1H, s, CH).
1-(4-Chlorophenyl)-4-(para-tolyl)-5,6,7,8-tetrahydro-2a,4a-diazacyclopenta[c]azulene-2-carboxylic acid (3-chlorophenyl)amide 9h. Yield – 1.98 g (87%). M. p. 205–206 °C (from propanol-2). Anal. Calcld. for C_{25}H_{20}ClNO, %: Cl 13.80, N 8.16. Found, %: Cl 13.50, N 8.24. \(^1H\) NMR (300 MHz, DMSO-d_6), \(\delta\), ppm: 1.81–1.93 (2H, m, CH_2), 2.03–2.15 (2H, m, CH_2), 2.39 (3H, s, CH_3), 2.37–2.67 (2H, m, CH_2), 2.78–4.08 (2H, m, CH), 7.47 (1H, s, NH), 6.86–7.60 (12H, m, 3\times \text{CH}), 7.82 (1H, s, 3-CH).

1-(4-Chlorophenyl)-4-(para-tolyl)-5,6,7,8-tetrahydro-2a,4a-diazacyclopenta[c]azulene-2-carboxylic acid (4-chlorophenyl)amide 9i. Yield – 2.08 g (81%). M. p. 245–246 °C (from propanol-2). Anal. Calcld. for C_{26}H_{22}Cl_2N_2O, %: Cl 13.80, N 8.16. Found, %: Cl 13.50, N 8.24. \(^1H\) NMR (300 MHz, DMSO-d_6), \(\delta\), ppm: 1.85–1.95 (2H, m, CH_2), 2.03–2.15 (2H, m, CH_2), 2.41 (3H, s, CH_3), 2.35–2.65 (2H, m, CH), 3.80–4.10 (2H, m, CH), 7.37 (1H, s, NH), 7.32 (2H, d, \(J = 7.8\) Hz, CH_2), 7.46 (2H, d, \(J = 7.8\) Hz, CH), 7.45 (2H, d, \(J = 8.3\) Hz, CH), 7.53 (2H, d, \(J = 8.3\) Hz, CH), 7.51 (2H, d, \(J = 8.6\) Hz, CH), 7.61 (2H, d, \(J = 8.6\) Hz, CH), 7.89 (1H, s, 3-CH).

The general procedure for the synthesis of 1-(4-chlorophenyl)-4-(para-tolyl)-5,6,7,8-tetrahydro-2a,4a-diazacyclopenta[c]azulene-2-carbothioic acid arylamides 10k–m. Ref. m. p. 196–197 °C (from propanol-2). Anal. Calcld. for C_{25}H_{20}ClN_2O, %: Cl 13.8, N 8.24. \(^1H\) NMR (500 MHz, DMSO-d_6), \(\delta\), ppm: 1.88–1.96 (2H, m, CH), 2.19 (3H, s, CH_3), 2.38–2.68 (2H, m, CH), 3.84–3.14 (2H, m, CH), 7.21 (4H, s, CH_2), 7.29 (2H, d, \(J = 7.9\) Hz, CH), 7.41 (2H, d, \(J = 7.9\) Hz, CH), 7.36 (2H, d, \(J = 8.1\) Hz, CH), 7.51 (2H, d, \(J = 8.1\) Hz, CH), 7.36 (2H, d, \(J = 8.4\) Hz, CH), 7.48 (2H, d, \(J = 8.4\) Hz, CH), 8.52 (1H, s, 3-CH), 8.75 (1H, s, NH).

1-(4-Chlorophenyl)-4-(para-tolyl)-5,6,7,8-tetrahydro-2a,4a-diazacyclopenta[c]azulene-2-carbothioic acid (4-chlorophenyl)amide 9m. Yield – 2.12 g (80%). M. p. 216–217 °C (from propanol-2). Anal. Calcld. for C_{26}H_{22}ClN_2S, %: Cl 7.92. Found, %: N 8.08. \(^1H\) NMR (500 MHz, DMSO-d_6), \(\delta\), ppm: 1.88–1.96 (2H, m, CH), 2.19 (3H, s, CH_3), 2.38–2.68 (2H, m, CH), 3.84–3.14 (2H, m, CH), 7.21 (4H, s, CH_2), 7.29 (2H, d, \(J = 7.9\) Hz, CH), 7.41 (2H, d, \(J = 7.9\) Hz, CH), 7.36 (2H, d, \(J = 8.1\) Hz, CH), 7.51 (2H, d, \(J = 8.1\) Hz, CH), 7.36 (2H, d, \(J = 8.4\) Hz, CH), 7.48 (2H, d, \(J = 8.4\) Hz, CH), 8.57 (1H, s, 3-CH), 9.11 (1H, s, NH).

Conclusions

1. A series of new 1-(4-chlorophenyl)-4-(para-tolyl)-5,6,7,8-tetrahydro-2a,4a-diazacyclopenta[c]azulene-2-carboxylic acid arylamides and 1-(4-chlorophenyl)-4-(para-tolyl)-5,6,7,8-tetrahydro-2a,4a-diazacyclopenta[c]azulene-2-carbothioic acid arylamides have been synthesized.

2. The high level of the antiviral activity for 1-(4-chlorophenyl)-4-(para-tolyl)-5,6,7,8-tetrahydro-2a,4a-diazacyclopenta[c]azulene-2-carboxylic acid (4-methoxyphenyl)amide against Flu A H1N1 California/07/2009 virus strain (Southern American Research Institute, Birmingham, Alabama) has been found.

Conflict of interests: authors have no conflict of interests to declare.

References

1. Shope, R. E. Swine influenza: III. Filtration experiments and etiology / R. E. Shope // J. Exp. Med. – 1931. – Vol. 54, Issue 3. – P. 373–385. https://doi.org/10.1084/jem.54.3.373

2. Sporadic occurrence of zoonotic swine influenza virus infections / C. C. Dacso, R. B. Couch, H. R. Six et al. // J. Clin. Microbiol. – 1984. – Vol. 20, Issue 4. – P. 833–835.

3. The prevalence of influenza viruses in swine and the antigenic and genetic relatedness of influenza viruses from man and swine / V. S. Hinshaw, W. J. Bean, R. G. Webster et al. // Virology. – 1978. – Vol. 84, Issue 1. – P. 51–62. https://doi.org/10.1016/0042-6822(78)90217-9

4. Are swine workers in the United States at increased risk of infection with zoonotic influenza virus? / K. P. Myers, C. W. Olsen, S. F. Setterquist et al. // Clin. Infect. Dis. – 2006. – Vol. 42, Issue 1. – P. 14–20. https://doi.org/10.1086/498977

5. Swine workers and swine influenza virus infections / G. C. Gray, T. McCarthy, A. W. Capuano et al. // Emerg. Infect. Dis. – 2007. – Vol. 13, Issue 12. – P. 1871–1878. https://doi.org/10.3201/eid1312.061323
References

1. Shope, R. E. (1931). Swine influenza: III. Filtration experiments and etiology. Journal of Experimental Medicine, 54 (3), 373–385. https://doi.org/10.1084/jem.54.3.373

2. Dacso, C. C., Couch, R. B., Six, H. R., Young, J. F., Quarles, J. M., Kasel, J. A. (1984). Sporadic occurrence of zoonotic swine influenza virus infections. Journal of Clinical Microbiology, 20 (4), 833–835.

3. Hinshaw, V. S., Bean, W. J., Webster, R. G., Easterday, B. C. (1978). The prevalence of influenza viruses in swine and the antigenic and genetic relationships of influenza viruses from man and swine. Virology, 84 (1), 51–62. https://doi.org/10.1016/0042-6822(78)90217-9

4. Myers, K. P., Olsen, C. W., Setterquist, S. F., Capuano, A. W., Donham, K. J., Thacker, E. L., Merchant, J. A., Gray, C. G. (2006). Are Swine workers in the United States at increased risk of infection with zoonotic influenza virus? Clinical Infectious Diseases, 42 (1), 14–20. https://doi.org/10.1086/498977

5. Gray, G. C., McCarthy, T., Capuano, A. W., Setterquist, S. F., Olsen, C. W., Alwanaja, M. C., Lynch, C. F. (2007). Swine workers and swine influenza virus infections. Emerging Infectious Diseases, 13 (12), 1871–1878. https://doi.org/10.3201/eid1312.061323

6. Wells, D. L., Hopfen,berger, D. J., Arden, N. H., Harmon, M. W., Davis, J. P., Tipple, M. A., Schonberger, L. B. (1991). Swine influenza virus infections: transmission from ill pigs to humans at a Wisconsin agricultural fair and subsequent probable person-to-person transmission. JAMA, 265 (4), 478–481. https://doi.org/10.1001/jama.265.4.478

7. Olsen, C. W. (2002). The emergence of novel swine influenza virus in North America. Virus Research, 85 (2), 199–210. https://doi.org/10.1016/S0168-1702(02)00227-8

8. Bartlett, J. G. (2009). H1N1 influenza — just the facts: what's new and what to expect. Published: 09/25/2009. Available at: http://www.medscape.com

9. Dawood, F. S., Jain, S., Finelli, L., Shove, W., Lindstrom, S., Garten, R. J., Gubareva, L. V., Xu, X., Bridges, C. B., Uyeki, T. M. (2009) Emergence of novel swine-origin influenza A (H1N1) virus in human. The New England Journal of Medicine, 360 (25), 2605–2615. https://doi.org/10.1056/NEJMoa0903810

10. MMWR Mortal Mortal Wkly Rep. (2009). Update: drug susceptibility of swine-origin influenza A (H1N1) viruses, April 2009. Centers for Disease Control and Prevention (CDC), 58, 433–435. https://doi.org/10.1558/ijc.v47i3.3373

11. FDA. (2002). Antiviral Drug Advisory Committee. Gaithersburg: Centre for Drug Evaluation and Research, 266.

12. Hayden, F. (2002). WHO Guidelines on the Use of Vaccines and Antivirals during Influenza. Annex 5 – Considerations for the Use of Antivirals during an Influenza pandemic. Geneva, 2–4 October, 2002. Available at : https://www.who.int/influenza/resources/documents/11_29_01_A.pdf

13. Peifen, Yu. Синтез хлоргидрата α-аминоацетофенона и его паразамещенных производных / Yu. Peifeng // Chem. Reagents, 8 (5), 302–325.

14. References

15. Amizono, Z. (n.d.). Available at: http://www.jci.org.uk/node/91 (дата звернення: 10.09.2019).

16. Фармацевтична практика

17. Effektivnost Amizona v lechenii i profilaktike virusnykh infektsiy (k 10-letiiu primeneniia preparata v klinicheskoy praktike).

18. Amіzon zharoznizhuyuchyi zasіb z іnterferonogennimi, протизапальними та жарознижуючими властивостями / Трінус Ф. П, Даниленко В. П, Бухтіарова Т. А та ін. – №92808942; заявл. 02. 03. 93; опубл. 29. 12. 94, Бюл. №8-1/1994. – 7с.

19. Ribavirin. [Електронний ресурс]. – Режим доступу : https://ru.wikipedia.org/wiki/Рибавирин. (дата звернення: 10.09.2019).

20. References

21. Reiteng, Yu. Sintez khlorgidrata α-aminoaczetofenona i ego parazameshhenny`kh proizvodny`kh.

22. Granik, V. G., Zhidkova, A. M., Kuryatov, N. S., Pakhomov, V. P., Glushkov, R. G. (1973). Lactam acetals. VII. A study of the alkylation of N-methyllactams and lactim ethers with dimethyl sulfate. Chemistry of Heterocyclic Compounds, 8 (11), 1387–1390. https://doi.org/10.1007/BF00470348

23. Reiteng, Yu. (1986). Sintez khlorgidrata α-aminoaczetofenona i ego parazameshhenny`kh proizvodny`kh. Chem. Reagents, 8 (5), 302–325.

24. Claxton, G. P., Girsch, J., Wiech, N. L. (1974). Cyclization of lactamide ketones to imidazo[1,2-α]azacycloalkanes with hypoglycemic activity. Journal of Medicinal Chemistry, 17 (3), 364–367. https://doi.org/10.1021/jm0249a027

Nадійшла до редакції 29.09.2019 р.