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The synthesis and antiviral activity of 1-(4-chlorophenyl)-4-(*para*-tolyl)-5,6,7,8-tetrahydro-2*a*,4*a*-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-2*a*,4*a*-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-2*a*,4*a*-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_{50}, IC_{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)aminocarbonyl-1-methylpyridinium iodide were used as the reference drugs.

Experimental part. Condensation of 2-methoxy-3,4,5,6-tetrahydro-7*H*-azepine with α-amino-4-methylacetophenone hydrochloride led to 3-(4-methylphenyl)-6,7,8,9-tetrahydro-5*H*-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)-6,7,8,9-tetrahydro-5*H*-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-2*a*,4*a*-diazacyclopenta[*cd*]azulene. The latter while reacting with the corresponding aryliso(thio)cyanates in a dry benzene gave 1-(4-chlorophenyl)-4-(*para*-tolyl)-5,6,7,8-tetrahydro-2*a*,4*a*-diazacyclopenta[*cd*]azulene-2-carboxylic acid (thio)amides. ^{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_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-2*a*,4*a*-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-2*a*,4*a*-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-2*a*,4*a*-diazacyclopenta[*cd*]azulene-2-carboxylic acid substituted (thio)amides; Ribavirin; Amizone; antiviral activity; Flu A H1N1 California/07/2009 virus

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Синтез та противірусна активність похідних 1-(4-хлорофеніл)-4-(*пара*-толіл)-5,6,7,8-тетрагідро-2*а*,4*а*-діазациклопента[*cd*]азулен-2-карбонової кислоти

Мета роботи. Синтезувати, довести структуру та дослідити противірусну активність заміщених амідів 1-(4-хлорофеніл)-4-(*пара*-толіл)-5,6,7,8-тетрагідро-2*а*,4*а*-діазациклопента[*cd*]азулен-2-карбонової кислоти.

Результати та їх обговорення. Визначення противірусної активності (4-метоксифеніл)аміду 1-(4-хлорофеніл)-4-(*пара*-толіл)-5,6,7,8-тетрагідро-2*а*,4*а*-діазациклопента[*cd*]азулен-2-карбонової кислоти здійснено у Південному дослідному інституті США (Southern Research Institute – SRI, Birmingham, Alabama). Ефективність зазначеної сполуки виражали показниками EC_{50}, IC_{50} та SI, які визначали в дослідах *in vitro* в діапазоні концентрацій від 0,1 до 100 мкг/мл. Як сполуки порівняння використано противірусний засіб Рибавірин (Sigma) та діючу речовину препарату Амізон – 4-(N-бензил)амінокарбоніл-1-метилпіридинію йодид.

Експериментальна частина. Конденсацією 2-метокси-3,4,5,6-тетрагідро-7*H*-азепіну з гідрохлоридом α-аміно-4-метилацетофенону одержано 3-(4-метилфеніл)-6,7,8,9-тетрагідро-5*H*-імідазо[1,2-*а*]азепін. При кип'ятінні останнього з α-бромо-4-хлороацетофеноном в етилацетаті виділено 1-[2-(4-хлорофеніл)-2-оксоетил]-3-(*пара*-толіл)-6,7,8,9-тетрагідро-5*H*-імідазо[1,2-*а*]азепінію-1 бромід, який у водному розчині лугу циклізується у 1-(4-хлорофеніл)-4-(*пара*-толіл)-5,6,7,8-тетрагідро-2*а*,4*а*-діазациклопента[*cd*]азулен. При взаємодії останнього з арилізо(тіо)ціанатами в сухому бензені одержано (тіо)аміди 1-(4-хлорофеніл)-4-(*пара*-толіл)-5,6,7,8-тетрагідро-2*а*,4*а*-діазациклопента[*cd*]азулен-2-карбонової кислоти. ^{1}Н ЯМР-спектри синтезованих сполук було записано на спектрометрі Bruker VXR-300 (Німеччина), робоча частота – 299,945 МГц та на спектрометрі Bruker DRX300 (Німеччина), робоча частота – 500,13 МГц, в DMSO-d_6, використовуючи як внутрішній стандарт тетраметилсилан (TMS). Температури плавлення вимірювали за допомогою пристрою RNMK 05 (VEB Analytik, Dresden).

Висновки. Синтезовано ряд нових заміщених (тіо)амідів 1-(4-хлорофеніл)-4-(*пара*-толіл)-5,6,7,8-тетрагідро-2*a*,4*a*-діазациклопента[*cd*]азулен-2-карбонової кислоти. Противірусну активність (4-метоксифеніл)аміду 1-(4-хлорофеніл)-4-(*пара*-толіл)-5,6,7,8-тетрагідро-2*a*,4*a*-діазациклопента[*cd*]азулен-2-карбонової кислоти вивчено у Південному дослідному інституті США (Southern Research Institute – SRI, Birmingham, Alabama) та встановлено високий рівень зазначеної активності щодо вірусу Flu A H1N1 California/07/2009.

***Ключові слова*:** заміщені (тіо)аміди 1-(4-хлорофеніл)-4-(*пара*-толіл)-5,6,7,8-тетрагідро-2*a*,4*a*-діазациклопента[*cd*]азулен-2-карбонової кислоти; рибавірин; 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-2*a*,4*a*-диазациклопента[*cd*]азулен-2-карбоновой кислоты

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

Результаты и их обсуждение. Определение противовирусной активности (4-метоксифенил)амида 1-(4-хлорфенил)-4(*пара*-толил)-5,6,7,8-тетрагидро-2*a*,4*a*-диазациклопента[*cd*]азулен-2-карбоновой кислоты проведено в Южном исследовательском институте США (Southern Research Institute – SRI, Birmingham, Alabama). Эффективность данного соединения выражали показателями EC_{50}, IC_{50} 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-метилпиридиния йодид.

Экспериментальная часть. Конденсацией 2-метокси-3,4,5,6-тетрагидро-7*H*-азепина с солянокислым α-амино-4-метилацетофеноном синтезирован 3-(4-метилфенил)-6,7,8,9-тетрагидро-5*H*-имидазо[1,2-*a*]-азепин. При кипячении последнего с α-бром-4-хлорацетофеноном в этилацетате выделен 1-[2-(4-хлорфенил)-2-оксоэтил]-3-(*пара*-толил)-6,7,8,9-тетрагидро-5*H*-имидазо[1,2-*a*]азепиния-1 бромид, который в водном растворе щелочи циклизуется в 1-(4-хлорфенил)-4-(*пара*-толил)-5,6,7,8-тетрагидро-2*a*,4*a*-диазациклопента[*cd*]азулен. При взаимодействии последнего с соответствующими арилизо(тио)цианатами в сухом бензоле получены (тио)амиды 1-(4-хлорфенил)-4(*пара*-толил)-5,6,7,8-тетрагидро-2*a*,4*a*-диазациклопента[*cd*]азулен-2-карбоновой кислоты. ^{1}H 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-d_6, используя в качестве внутреннего стандарта тетраметилсилан (TMS). Температуры плавления измеряли с помощью устройства RNMK 05 (VEB Analytik, Dresden).

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

***Ключевые слова*:** замещённые (тио)амиды 1-(4-хлорфенил)-4-(*пара*-толил)-5,6,7,8-тетрагидро-2*a*,4*a*-диазациклопента[*cd*]азулен-2-карбоновой кислоты; рибавирин; амизон; противовирусная активность; вирус 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 Amizon, 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-methylpiridinium iodide (Amizon) is currently used. It was developed by the Institute of Pharmacology and Toxicology of Ukraine. Amizon 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]. Amizon has interferonogenic properties, causes the inhibiting effect on influenza viruses, and increases the body resistance to viral infections [14]. All these make Amizon a promising drug for prevention and treating different virus diseases [13].

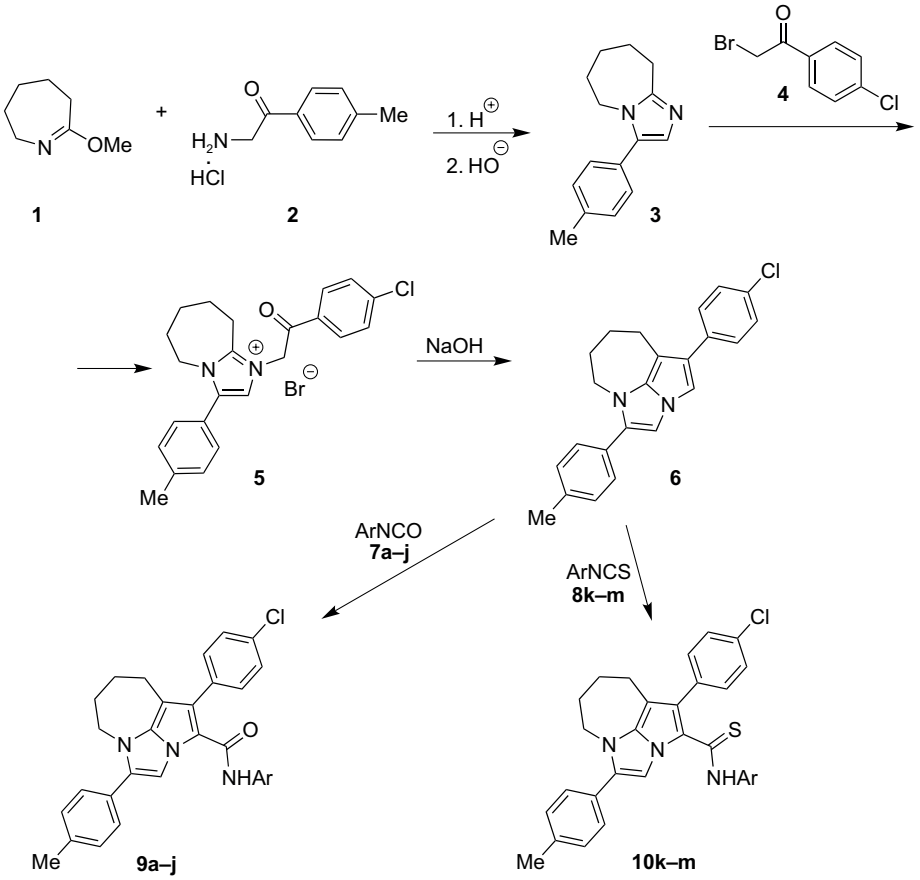
However, from position of evidence-based medicine, there is no single opinion regarding indubitable effectiveness of certain drugs (Arbidol, Amixin, Amizon, Kagocel, Immunofam, etc.) used as immunomodulators with the anti-influenza activity [15].

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*,4*a*-diazacyclopenta[*cd*]azulene-2-carboxylic acid by interaction of 1-(4-chlorphenyl)-4-(*para*-tolyl)-5,6,7,8-tetrahydro-2*a*,4*a*-diazacyclopenta[*cd*]azulene with the corresponding arylisо-(thio)cyanates 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*,4*a*-diazacyclopenta[*cd*]azulene-2-carboxylic acid (4-methoxyphenyl)amide **9d** was compared to that of active compounds of Amizon 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.

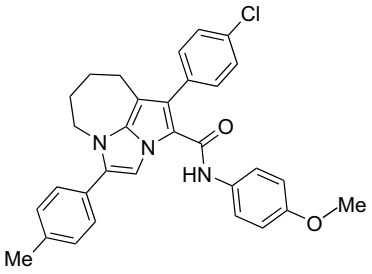
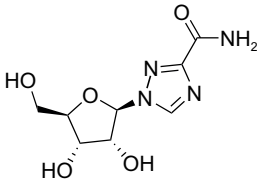
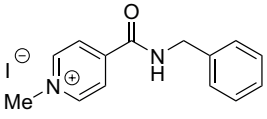


9a Ar = Ph, **9b** Ar = 2-MeO–C_6H_4, **9c** Ar **=** 3-MeO–C_6H_4, **9d** Ar **=** 4-MeO–C_6H_4, **9e** Ar **=** 3-Me–C_6H_4, **9f** Ar **=** 4-Me–C_6H_4, **9g** Ar **=** 2-Cl–C_6H_4, 9**h** Ar **=** 3-Cl–C_6H_4, **9i** Ar **=** 4-Cl–C_6H_4, **9j** Ar **=** 3,4-di-Cl–C_6H_3, **10k** Ar = Ph, **10l** Ar **=** 4-Me–C_6H_4, **10m** Ar = 4-Cl–C_6H_4

Scheme. The synthesis of 1-(4[1]-chlorophenyl)-4-(*para*-tolyl)-5,6,7,8-tetrahydro-2*a*,4*a*-diazacyclopenta[*cd*]azulene-2-carboxylic acid derivatives **9a–j**, **10k–m**

Table

The antiviral activity of 1-(4-chlorophenyl)-4-(*para*-tolyl)-5,6,7,8-tetrahydro-2*a*,4*a*-diazacyclopenta[*cd*]azulene-2-carboxylic acid (4-methoxyphenyl)amide **9d** against Flu A H1N1 California/07/2009 virus strain

Compound	Structure	Type of virus	EC_{50}, μg/mL	IC_{50}, μg/mL	SI
9d		Flu A H1N1 California/07/2009	3.4	>100	>29
Ribavirin		Flu A H1N1 California/07/2009	8.7	>320	>37
Amizone		Flu A H1N1 California/07/2009	47	>100	>2.1

Notes: EC_{50} — 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;
IC_{50} — 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 IC_{50} to EC_{50} 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 EC_{50}, IC_{50} 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-2*a*,4*a*-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 Amizon substance. The selectivity index of the compound under research appeared to be more than 29 and IC_{50} > 100 μg/mL. At the same time, the selectivity index of Ribavirin was more than 37 and IC_{50} > 320 μg/mL. It should be noted that if IC_{50} 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-7*H*-azepine **1** was obtained by alkylating 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-*a*]azepine **3** was obtained by the method described in [20].

^{1}H 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-d_6 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*-tolyl)-6,7,8,9-tetrahydro-5*H*-imidazo[1,2-*a*]azepin-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. Calcd. for $C_{23}H_{24}BrClN_2O$, %: N 6.09. Found, %: N 6.16.

The synthesis of 1-(4-chlorophenyl)-4-(*para*-tolyl)-5,6,7,8-tetrahydro-2*a*,4*a*-diazacyclopenta-[*cd*]azulene 6. To the suspension of 1-[2-(4-chlorophenyl)-2-oxoethyl]-3-(*para*-tolyl)-6,7,8,9-tetrahydro-*5H*-imidazo[1,2-*a*]azepin-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. Calcd. for $C_{23}H_{21}ClN_2$, %: 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-2*a*,4*a*-diazacyclopenta[*cd*]azulene-2-carboxylic acid arylamides 9a–j. Reflux the mixture of 1-(4-chlorophenyl)-4-(*para*-tolyl)-5,6,7,8-tetrahydro-2a,4a-diazacyclopenta[*cd*] 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-2*a*,4*a*-diazacyclopenta[*cd*]azulene-2-carboxylic acid phenylamide 9a. Yield – 1.90 g (79 %). M. p. 212–213°C (from benzene). Anal. Calcd. for $C_{30}H_{26}ClN_3O$, %: Cl 7.40, N 8.75. Found, %: Cl 7.56, N 8.53. ^{1}H NMR (300 MHz, DMSO-d_6), δ, ppm: 1.88–2.01 (2H, m, CH_2), 2.03–2.11 (2H, m, CH_2), 2.42 (3H, s, CH_3), 2.39–2.70 (2H, m, CH_2), 3.80–4.08 (2H, m, CH_2), 6.97 (1H, s, NH), 6.89–7.24 (5H, m, C_6H_5), 7.31 (2H, d, *J* = 8.3 Hz, C_6H_4), 7.43 (2H, d, *J* = 8.3 Hz, C_6H_4,), 7.47 (2H, d, *J* = 8.8 Hz, C_6H_4), 7.56 (2H, d, *J* = 8.8 Hz, C_6H_4), 7.84 (1H, s, 3-CH).

1-(4-Chlorophenyl)-4-(*para*-tolyl)-5,6,7,8-tetrahydro-2*a*,4*a*-diazacyclopenta[*cd*]azulene-2-carboxylic acid (2-methoxyphenyl)amide 9b. Yield – 1.76 g (69 %). M. p. 230–231°C (from benzene). Anal. Calcd. for $C_{31}H_{28}ClN_3O_2$, %: Cl 6.96, N 8.24. Found, %: Cl 6.81, N 8.39. ^{1}H NMR (300 MHz, DMSO-d_6), δ, ppm: 1.87–1.98 (2H, m, CH_2), 2.03–2,15 (2H, m, CH_2), 2.43 (3H, s, CH_3), 2.35–2.64 (2H, m, CH_2), 3.50 (3H, s, OCH_3), 3.85–4.05 (2H, m, CH_2), 7.45 (1H, s, NH), 6.75–8.43 (4H, m, C_6H_4,), 7.31 (2H, d, *J* = 8.3 Hz, C_6H_4), 7.56 (2H, d, *J* = 8.3 Hz, C_6H_4), 7.48 (2H, d, *J* = 8.8 Hz, C_6H_4), 7.56 (2H, d, *J* = 8.8 Hz, C_6H_4), 7.91 (1H, s, 3-CH).

1-(4-Chlorophenyl)-4-(*para*-tolyl)-5,6,7,8-tetrahydro-2*a*,4*a*-diazacyclopenta[*cd*]azulene-2-carboxylic acid (3-methoxyphenyl)amide 9c. Yield – 1.86 g (73 %). M. p. 203–204°C (from benzene). Anal. Calcd. for $C_{31}H_{28}ClN_3O_2$, %: Cl 6.96, N 8.24. Found, %: Cl 7.08, N 8.41. ^{1}H NMR (300 MHz, DMSO-d_6), δ (ppm): 1.89–1.99 (2H, m, CH_2), 2.04–2.14 (2H, m, CH_2), 2.43 (3H, s, CH_3), 2.40–2.70 (2H, m, CH_2), 3.72 (3H, s, OCH_3), 3.82–4.12 (2H, m, CH_2), 6.43–7.06 (4H, m, C_6H_4), 7.01 (1H, s, NH), 7.31 (2H, d, *J* = 7.8 Hz, C_6H_4), 7.45 (2H, d, *J* = 7.8 Hz, C_6H_4), 7.48 (2H, d, *J* = 8.3 Hz, C_6H_4), 7.59 (2H, d, *J* = 8.3 Hz, C_6H_4), 7.86 (1H, s, 3-CH).

1-(4-Chlorophenyl)-4-(*para*-tolyl)-5,6,7,8-tetrahydro-2a,4a-diazacyclopenta[*cd*]azulene-2-carboxylic acid (4-methoxyphenyl)amide 9d. Yield – 1.94 g (76 %). M. p. 202–204°C (from benzene). Anal. Calcd. for $C_{31}H_{28}ClN_3O_2$, %: Cl 6.96, N 8.24. Found, %: Cl 6.85, N 8.33. ^{1}H NMR (300 MHz, DMSO-d_6), δ, ppm: 1.85–1.95 (2H, m, CH_2), 2.02–2.13 (2H, m, CH_2), 2.43 (3H, s, CH_3), 2.41–2.74 (2H, m, CH_2), 3.71 (3H, s, OCH_3), 3.81–4.18 (2H, m, CH_2), 6.97 (1H, s, NH), 6.74 (2H, d, *J* = 9.3 Hz, C_6H_4), 7.06 (2H, d, *J* = 9.3 Hz, C_6H_4), 7.30 (2H, d, *J* = 8.3 Hz, C_6H_4), 7.44 (2H, d, *J* = 8.3 Hz, C_6H_4), 7.48 (2H, d, *J* = 8.8 Hz, C_6H_4), 7.56 (2H, d, *J* = 8.8 Hz, C_6H_4), 7.84 (1H, s, 3-CH).

1-(4-Chlorophenyl)-4-(*para*-tolyl)-5,6,7,8-tetrahydro-2*a*,4*a*-diazacyclopenta[*cd*]azulene-2-carboxylic acid (3-methylphenyl)amide 9e. Yield – 1.70 g (69 %). M. p. 218–219°C (from benzene). Anal. Calcd. for $C_{31}H_{28}ClN_3O$, %: Cl 7.19, N 8.50. Found, %: Cl 7.28, N 8.64. ^{1}H NMR (300 MHz, DMSO-d_6), δ, ppm: 1.88–1.97 (2H, m, CH_2), 2.02–2.13 (2H, m, CH_2), 2.26 (3H, s, CH_3), 2.43 (3H, s, CH_3), 2.42–2.72 (2H, m, CH_2), 3.81–4.12 (2H, m, CH_2), 6.71–7.05 (4H, m, C_6H_4), 6.97 (1H, s, NH), 7.31 (2H, d, *J* = 8.3 Hz, C_6H_4), 7.45 (2H, d, *J* = 8.3 Hz, C_6H_4), 7.48 (2H, d, *J* = 8.8 Hz, C_6H_4), 7.58 (2H, d, *J* = 8.8 Hz, C_6H_4), 7.85 (1H, s, 3-CH).

1-(4-Chlorophenyl)-4-(*para*-tolyl)-5,6,7,8-tetrahydro-2*a*,4*a*-diazacyclopenta[*cd*]azulene-2-carboxylic acid (4-methylphenyl)amide 9f. Yield – 1.65 g (67 %). M. p. 221–223°C (from benzene). Anal. Calcd. for $C_{31}H_{28}ClN_3O$, %: Cl 7.19, N 8.50. Found, %: Cl 7.28, N 8.64. ^{1}H NMR (300 MHz, DMSO-d_6), δ, ppm: 1.87–1.98 (2H, m, CH_2), 2.01–2.12 (2H, m, CH_2), 2.25 (3H, s, CH_3), 2.42 (3H, s, CH_3), 2.39–2.68 (2H, m, CH_2), 3.80–4.10 (2H, m, CH_2), 6.97 (2H, d, *J* = 8.3 Hz, C_6H_4), 7.01 (2H, d, *J* = 8.3 Hz, C_6H_4), 6.98 (1H, s, NH), 7.30 (2H, d, *J* = 8.3 Hz, C_6H_4), 7.44 (2H, d, *J* = 8.3 Hz, C_6H_4), 7.47 (2H, d, *J* = 8.3 Hz, C_6H_4), 7.56 (2H, d, *J* = 8.3 Hz, C_6H_4), 7.85 (1H, s, 3-CH).

1-(4-Chlorophenyl)-4-(*para*-tolyl)-5,6,7,8-tetrahydro-2*a*,4*a*-diazacyclopenta[*cd*]azulene-2-carboxylic acid (2-chlorophenyl)amide 9g. Yield – 1.88 g (73 %). M. p. 202–203°C (from propanol-2). Anal. Calcd. for $C_{30}H_{25}Cl_2N_3O$, %: Cl 13.80, N 8.16. Found, %: Cl 13.50, N 8.24. ^{1}H NMR (300 MHz, DMSO-d_6), δ, ppm: 1.85–1.95 (2H, m, CH_2), 2.03–2.13 (2H, m, CH_2), 2.43 (3H, s, CH_3), 2.35–2.63 (2H, m, CH_2), 3.82–4.12 (2H, m, CH_2), 6.87–8.51 (4H, m, C_6H_4), 7.39 (1H, s, NH), 7.31 (2H, d, *J* = 7.8 Hz, C_6H_4), 7.45 (2H, d, *J* = 8.8 Hz, C_6H_4), 7.46 (2H, d, *J* = 8.3 Hz, C_6H_4), 7.53 (2H, d, *J* = 8.3 Hz, C_6H_4), 7.90 (1H, s, 3-CH).

1-(4-Chlorophenyl)-4-(*para*-tolyl)-5,6,7,8-tetrahydro-2*a*,4*a*-diazacyclopenta[*cd*]azulene-2-carboxylic acid (3-chlorophenyl)amide 9h. Yield – 1.98 g (77 %). M. p. 205–206 °C (from propanol-2). Anal. Calcd. for $C_{30}H_{25}Cl_2N_3O$, %: Cl 13.80, N 8.16. Found, %: Cl 13.50, N 8.24. ^{1}H NMR (300 MHz, DMSO-d_6), δ, ppm: 1.82–1.98 (2H, m, CH_2), 2.01–2.13 (2H, m, CH_2), 2.39 (3H, s, CH_3), 2.37–2.67 (2H, m, CH_2), 3.78–4.08 (2H, m, CH_2), 7.47 (1H, s, NH), 6.86–7.60 (12H, m, 3×C_6H_4), 7.82 (1H, s, 3-CH).

1-(4-Chlorophenyl)-4-(*para*-tolyl)-5,6,7,8-tetrahydro-2*a*,4*a*-diazacyclopenta[*cd*]azulene-2-carboxylic acid (4-chlorophenyl)amide 9i. Yield – 2.08 g (81 %). M. p. 245–246 °C (from propanol-2). Anal. Calcd. for $C_{30}H_{25}Cl_2N_3O$, %: Cl 13.80, N 8.16. Found, %: Cl 13.50, N 8.24. ^{1}H NMR (300 MHz, DMSO-d_6), δ, 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_2), 3.80–4.10 (2H, m, CH_2), 7.37 (1H, s, NH), 7.32 (2H, d, *J* = 7.8 Hz, C_6H_4), 7.46 (2H, d, *J* = 7.8 Hz, C_6H_4), 7.45 (2H, d, *J* = 8.3 Hz, C_6H_4), 7.53 (2H, d, *J* = 8.3 Hz, C_6H_4), 7.51 (2H, d, *J* = 8.6 Hz, C_6H_4), 7.61 (2H, d, *J* = 8.6 Hz, C_6H_4), 7.89 (1H, s, 3-CH).

1-(4-Chlorophenyl)-4-(*para*-tolyl)-5,6,7,8-tetrahydro-2*a*,4*a*-diazacyclopenta[*cd*]azulene-2-carboxylic acid (3,4-dichlorophenyl)amide 9j. Yield – 2.08 g (87 %). M. p.250–251 °C (from propanol-2). Anal. Calcd. for $C_{30}H_{25}Cl_2N_3O$, %: Cl 13.8, N 8.16. Found, %: Cl 13.5, N 8.24. ^{1}H NMR (300 MHz, DMSO-d_6), δ, ppm: 1.81–1.93 (2H, m, CH_2), 1.98–2.12 (2H, m, CH_2), 2.39 (3H, s, CH_3), 2.36–2.64 (2H, m, CH_2), 3.78–4.06 (2H, m, CH_2), 7.48 (1H, s, NH), 7.34 (2H, d, *J* = 7.8 Hz, C_6H_4), 7.56 (2H, d, *J* = 7.8 Hz, C_6H_4), 6.97–7.79 (7H, m, C_6H_4+C_6H_3), 7.81 (1H, s, 3-CH).

The general procedure for the synthesis of 1-(4-chlorophenyl)-4-(*para*-tolyl)-5,6,7,8-tetrahydro-2*a*,4*a*-diazacyclopenta[*cd*]azulene-2-carbothioic acid arylamides 10k–m. Reflux the mixture of 1-(4-chlorophenyl)-4-(*para*-tolyl)-5,6,7,8-tetrahydro-2*a*,4*a*-diazacyclopenta[*cd*]azulene **6** (0.005 mole) and the appropriate arylisothiocyanate **8k–m** (0.005 mole) in 50 mL of dry benzene for 2 hours. After cooling filter the solid precipitates **10k–m**, 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-2*a*,4*a*-diazacyclopenta[*cd*]azulene-2-carbothioic acid phenylamide 9k. Yield – 2.03 g (82 %). M. p. 196–197 °C (from propanol-2). Anal. Calcd. for $C_{30}H_{26}ClN_3O$, %: N 8.47. Found, %: N 8.65. ^{1}H NMR (500 MHz, DMSO-d_6), δ, ppm: 1.80–1.92 (2H, m, CH_2), 1.98–2.06 (2H, m, CH_2), 2.24 (3H, s, CH_3), 2.44–2.66 (2H, m, CH_2), 3.94–4.14 (2H, m, CH_2), 7.22–7.91 (13H, m, C_6H_4+ C_6H_4+C_6H_5), 8.58 (1H, s, 3-CH), 8.99 (1H, s, NH).

1-(4-Chlorophenyl)-4-(*para*-tolyl)-5,6,7,8-tetrahydro-2*a*,4*a*-diazacyclopenta[*cd*]azulene-2-carbothioic acid (4-methylphenyl)amide 9l. Yield – 1.96 g (77 %). M. p. 219–220 °C (from benzene). Anal. Calcd. for $C_{31}H_{28}ClN_3S$, %: N 8.24. Found, %: N 8.06. ^{1}H NMR (500 MHz, DMSO-d_6), δ, ppm: 1.82–1.94 (2H, m, CH_2), 2.01–2.11 (2H, m, CH_2), 2.21 (3H, s, CH_3), 2.43 (3H, s, CH_3), 2.36–2.64 (2H, m, CH_2), 3.81–4.17 (2H, m, CH_2), 6.97 (1H, s, NH), 6.96 (2H, d, *J* = 7.8 Hz, C_6H_4), 7.11 (2H, d, *J* = 8.1 Hz, C_6H_4), 7.32 (2H, d, *J* = 7,8 Hz, C_6H_4), 7.44 (2H, d, *J* = 8,1 Hz, C_6H_4), 7.36 (2H, d, *J* = 8.4 Hz, C_6H_4), 7.48 (2H, d, *J* = 8.4 Hz, C_6H_4), 8.52 (1H, s, 3-CH), 8.75 (1H, s, NH).

1-(4-Chlorophenyl)-4-(*para*-tolyl)-5,6,7,8-tetrahydro-2*a*,4*a*-diazacyclopenta[*cd*]azulene-2-carbothioic acid (4-chlorophenyl)amide 9m. Yield – 2.12 g (80 %). M. p. 216–217 °C (from propanol-2). Anal. Calcd. for $C_{31}H_{25}Cl_2N_3S$, %: N 7.92. Found, %: N 8.08. ^{1}H NMR (500 MHz, DMSO-d_6), δ, ppm: 1.88–1.96 (2H, m, CH_2), 2.01–2.13 (2H, m, CH_2), 2.19 (3H, s, CH_3), 2.38–2.68 (2H, m, CH_2), 3.84–3.14 (2H, m, CH_2), 7.21 (4H, s, C_6H_4), 7.29 (2H, d, *J* = 7.9 Hz, C_6H_4), 7.41 (2H, d, *J* = 7.9 Hz, C_6H_4), 7.36 (2H, d, *J* = 8.1 Hz, C_6H_4), 7.51 (2H, d, *J* = 8.1 Hz, C_6H_4), 7.36 (2H, d, *J* = 8.4 Hz, C_6H_4), 7.48 (2H, d, *J* = 8.4 Hz, C_6H_4), 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-2*a*,4*a*-diazacyclopenta[*cd*]-azulene-2-carboxylic acid arylamides and 1-(4-chlorophenyl)-4-(*para*-tolyl)-5,6,7,8-tetrahydro-2*a*,4*a*-diazacyclopenta[*cd*]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-2*a*,4*a*-diazacyclopenta[*cd*]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.

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