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The synthesis and the study of the antitumor activity of 1,4-diaryl-5,6,7,8-tetrahydro-2,2a,8a triazacyclopenta[*cd*]azulene derivatives

Aim. To synthesize, prove the structural framework and study the antitumor activity of 1,4-diaryl-5,6,7,8-tetrahydro-2,2a,8a-triazacyclopenta [*cd*]azulene derivatives.

Results and discussion. To determine the antineoplastic activity of 1-phenyl-4-aryl-5,6,7,8-tetrahydro-2,2a,8a-triazacyclopenta[*cd*]azulenes **7a-g** and 1-(4[1]-bromophenyl)-4-aryl-5,6,7,8-tetra-hydro-2,2a,8a-triazacyclopenta [*cd*]azulenes **7h-k** the study *in vitro* was carried out on 60 lines of cancer cells (leukemia, non-small cell lung cancer, colon cancer, CNS cancer, melanoma, ovarian cancer, renal cancer, prostate cancer and breast cancer) under the effect of the substance in the concentration of 10^{-5} mol/l according to the standard procedure of the mitotic activity assessment of the new potential bioactive compounds by the fluorescent coloring method (sulphorhodamine B as a dye) performed in the US National Institute of cancer within the Development Therapeutic Program.

Experimental part. 2-Methoxy-3,4,5,6-tetrahydro-*7H*-azepine was obtained by alkylation of caprolactam with dimethyl sulfate. 3-Phenyl or (4[1]-bromophenyl)-(6,7,8,9-tetrahydro-5H-[1,2,4]triazolo[4,3-a]azepine 4 a,b was obtained by condensation of 2-methoxy-3,4,5,6-tetrahydro-*7H*-azepine 1 with 4-bromobenzoic acid hydrazide and subsequent cyclization of the intermediate product. The ^{1}H-NMR spectra were recorded on a Bruker VXR-300 spectrometer (Germany) with the working frequency of 299.945 MHz, in DMSO-d_6 using tetramethylsilane (TMS) as an internal standard. The purity of the compounds synthesized was controlled by TLC on the Silufol UV-254 plates in the system of chloroform – methanol (9 : 1).

Conclusions. New chemical compounds – derivatives of 1-phenyl(4[1]-bromphenyl)-4-aryl-5,6,7,8-tetrahydro-2,2a,8a-triaza-cyclopenta[*cd*]azulene have been synthesized. The anticancer activity of the compounds obtained on 60 lines of tumor cells in the US National Cancer Institute has been studied. The high-active compounds that exhibit high levels of the antitumor activity have been identified.

***Key words*:** 1,4-diaryl-5,6,7,8-tetrahydro-2,2a,8a-triazacyclopenta[*cd*]azulenes; antitumor activity

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Синтез та вивчення протипухлинної активності похідних 1,4-діарил-5,6,7,8-тетрагідро-2,2а,8а-триазациклопента[*cd*]азуленів

Мета роботи – синтезувати, довести структурну будову та провести вивчення протипухлинної активності похідних 1,4-діарил-5,6,7,8-тетрагідро-2,2а,8а-триазациклопента[*cd*]азуленів.

Результати та їх обговорення. Для визначення протипухлинної активності 1-феніл-4-арил-5,6,7,8-тетрагідро-2,2а,8а-триазациклопента[*cd*]азулену **7a-g** та 1-(4[1]-бромфеніл)-4-арил-5,6,7,8-тетрагідро-2,2а,8а-триазациклопента[*cd*]азулену **7h-k** дослідження проведено *in vitro* на 60 лініях ракових клітин (лейкемії, легень, товстого кишківника, ЦНС, меланоми, яєчників, нирок, простати, молочної залози) при дії речовини в концентрації 10^{-5} моль/л за стандартною процедурою оцінки мітотичної активності нових потенційних біологічно активних сполук методом флуоресцентного зафарбування (барвник – сульфородамін Б), виконаних у Національному інституті раку США (National Cancer Institute of Health, USA) в рамках Development Therapeutic Program.

Експериментальна частина. 2-Метокси-3,4,5,6-тетрагідро-*7H*-азепін одержано алкілуванням капролактаму диметилсульфатом. 3-(4[1]-Бромфеніл)-6,7,8,9-тетрагідро-*5H*-[1,2,4]триазоло[4,3-а]азепін одержано конденсацією 2-метокси-3,4,5,6-тетрагідро-*7H*-азепіну з гідразидом пара-бромбензойної кислоти та подальшою циклізацією проміжного продукту. Спектри ПМР були зареєстровані на спектрометрі Bruker VXR-300, робоча частота – 299,945 МГц, внутрішній стандарт ТМС. Контроль за чистотою синтезованих сполук здійснювався за допомогою ТШХ на пластинках Silufol UV-254 в системі хлороформ – метанол 9 : 1.

Висновки. Синтезовані нові хімічні речовини – похідні 1,4-діарил-5,6,7,8-тетрагідро-2,2а,8а-триазациклопента [*cd*]азулену. Вивчена протиракова активність одержаних сполук на 60 лініях пухлинних клітин в Національному інституті раку США. Ідентифіковані високоактивні сполуки, які проявили високий рівень протипухлинної активності.

***Ключові слова*:** 1,4-діарил-5,6,7,8-тетрагідро-2,2а,8а-триазациклопента[*cd*]азулени; протипухлинна активність

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Синтез и изучение противоопухолевой активности производных 1,4-диарил-5,6,7,8-тетрагидро-2,2а,8а-триазациклопента[*cd*]азуленов

Цель работы – синтезировать, доказать структурное строение и провести изучение противоопухолевой активности производных 1,4-диарил-5,6,7,8-тетрагидро-2,2А, 8а-триазациклопента[*cd*]азулена.

Результаты и их обсуждение. Для определения противоопухолевой активности 1-фенил-4-арил-5,6,7,8-тетрагидро-2,2а, 8а-триазациклопента [*cd*] азулена **7a-g** и 1-(4[1]-бромфенил)-4-арил-5,6,7,8-тетрагидро-2,2а,8а-триазациклопента[cd]азулена **7h-k** было проведено исследование *in vitro* на 60 линиях раковых клеток (лейкемии, легких, толстого кишечника, ЦНС, меланомы, яичников, почек, простаты, молочной железы) при воздействии вещества в концентрации 10^{-5} моль/л по стандартной процедуре оценки митотической активности новых потенциальных биологически активных соединений методом флуоресцентной окраски (краситель – сульфородамин Б), выполненных в Национальном институте рака США (National Cancer Institute of Health, USA) в рамках Development Therapeutic Program.

Экспериментальная часть. 2-метокси-3,4,5,6-тетрагидро-*7H*-азепин получено алкилированием капролактама диметилсульфатом. 3-(4[1]-бромфенил)-6,7,8,9-тетрагидро-*5H*-[1,2,4]триазоло[4,3-а]азепин получено конденсацией 2-метокси-3,4,5,6-тетрагидро-*7H*-азепин с гидразидом парабромбензойной кислоты и последующей циклизацией промежуточного продукта. Спектры ПМР были зарегистрированы на спектрометре Bruker VXR-300, рабочая частота – 299,945 МГц, внутренний стандарт ТМС. Контроль за чистотой синтезированных соединений осуществлялся с помощью ТСХ на пластинках Silufol UV-254 в системе хлороформ – метанол 9 : 1.

Выводы. Синтезированы новые химические соединения – производные 1,4-диарил-5,6,7,8-тетрагидро-2,2а,8а-триазациклопента[*cd]*азулена. Изучена противораковая активность полученных соединений на 60 линиях опухолевых клеток в Национальном институте рака США. Идентифицированы высокоактивные соединения, которые проявили высокий уровень противоопухолевой активности.

***Ключевые слова*:** 1,4-диарил-5,6,7,8-тетрагидро-2,2а,8а-триазациклопента[*cd*]азулены; противоопухолевая активность

For today more than 50 antitumor medicines active at different forms of malignant formations are applied for the treatment of a tumoral disease and achievement of the palliative effect, which leads to tumor reduction and consequently to clinical remission. Antineoplastic drugs with different mechanisms of action which are used in the treatment regimens are known. At the same time, the pronounced clinical effect is from 20 % to 80 %, in some cases remission is up to 2 years, and more than 10 % of patients have remission more than 3 years. Cyclophosphamide, methotrexate, vincristine, adriablastin have had a wide application [1-3]. Methotrexate inhibits the cellular mitosis, slows down the growth of malignant formations and is more active in relation to cells, which rapidly grow. Adriamycin is the only cytostatic agent exhibiting an insignificant activity in relation to hepatocellular carcinomas (the curative effect is 3-70 %, mostly 36.5 %). The mechanism of drug multiresistance impedes the use of cytostatic medicines.

The medicines mentioned have the necessary medicinal properties, but show considerable side effects of blood formation (leukopenia, anemia, thrombocytopenia), CNS (feeling of tiredness, dizziness, headache, aphasia, drowsiness, convulsions), reproductive system (osteogenesis and spermatogenesis disorders, oligospermatism, menstrual disorders, decreased libido, impotence), urinary system (hematuria, cystitis, severe renal dysfunction), allergic and dermatological reactions and other side effects.

Some triazole derivatives demonstrate the antioplastic action – these are Letrozole, Anastrozole and Vorozole [4].

The medicine Letrozole (Femara) – 4,4 '-((*1H*-1,2,4-triazol-1-yl)-methylene) dibenzonitrile used as an antineoplastic hormonal drug and antagonist of hormones in malignant formations of a mammary gland is known [5-6].

Anastrozole shows the activity against estrogen-dependent breast tumors in women [7, 8]. It is a selective non-steroid inhibitor of the enzyme aromatase, which leads to a decrease in the estradiol levels in peripheral tissues. It is known that breast tumor diseases in the world are 22.9 % of the total amount of oncological diseases (Fig. 1) [9].

When taking Anastrozole and Letrozole anemia, thrombophlebitis and leukopenia can progress, and these indications are the reason for drug withdrawal.

Results and discussion

Increase in efficiency of chemotherapy of a tumoral disease, first of all, is connected with creation of new, effective antineoplastic medicines.

The derivatives of 1-phenyl-4-aryl-5,6,7,8-tetrahydro-2,2a,8a-triazacyclopenta[*cd*]azulenes **7a-g** and 1-(4[1]-bromophenyl)-4-aryl-5,6,7,8-tetrahydro-2,2a,8a-triazacyclopenta[*cd*]azulenes **7h-k** showing the antineoplastic activity were synthesized.

The derivatives of 1-phenyl-4-aryl-5,6,7, 8-tetrahydro-2,2a,8a-triazacyclopenta[*cd*]azulenes **7a-g** and 1-(4[1]-bromophenyl)-4-aryl-5, 6,7,8-tetrahydro-2,2a,8a-triazacyclopenta[*cd*] azulenes **7h-k** were obtained with high yields when using the known synthetic approaches in several stages by the following Scheme (Fig. 2).

To determine the antineoplastic activity of 1-phenyl-4-aryl-5,6,7,8-tetrahydro-2,2a,8a-triaza-

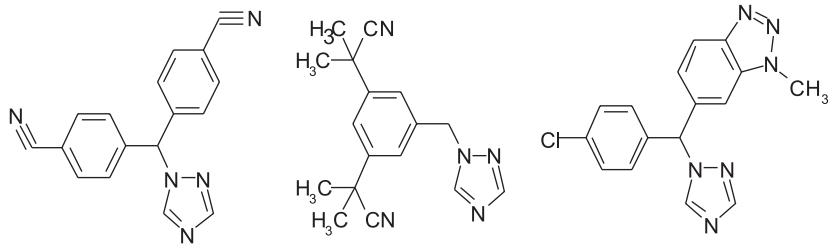
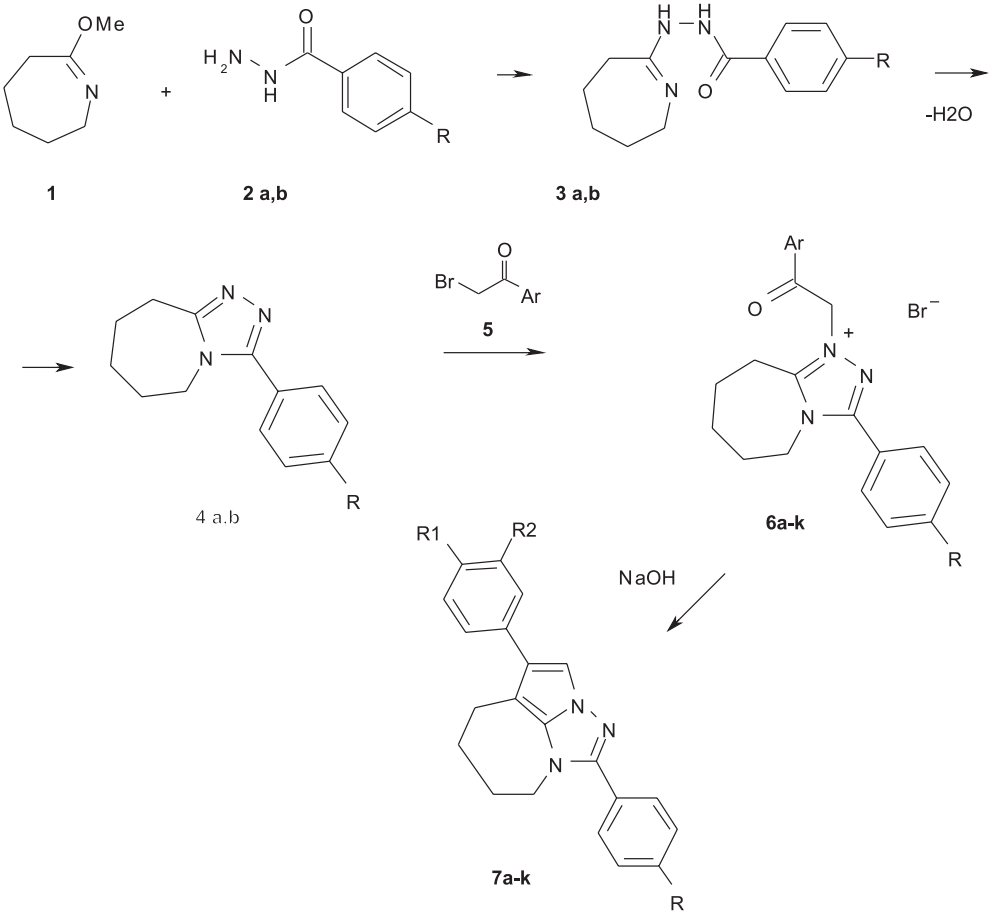


Fig. 1. The structural formula for Letrozole, Anastrozole and Vorozole

cyclopenta[*cd*]azulenes **7a-g** and 1-(4[1]-bromophenyl)-4-aryl-5,6,7,8-tetra-hydro-2,2a,8a-triazacyclopenta[*cd*]azulenes **7h-k** the study *in vitro* was carried out on 60 lines of cancer cells (leukemia, non-small cell lung cancer, colon cancer, CNS cancer, melanoma, ovarian cancer, renal cancer, prostate cancer and breast cancer) under the effect of the substance in the concentration of 10-5 mol/l according to the standard procedure of the mitotic activity assessment of the new potential bioactive compounds by the fluorescent coloring method (sulphorhodamine B as a dye) performed in the US National Institute of cancer within the Development Therapeutic Program [10]. The result of the studies conducted was expressed as a percentage of the cancer cell growth compared to the control – 5-fluorouracil. Tab. 1 shows the efficiency of compounds in inhibition of the cancer cell growth compared to the control.

The determination is performed by a highly sensitive fluorometric method, assessing quantitatively the intensity of fluorescent radiation color (sulphorhodamine B as a dye) in 48 hours of cell radiation with the compound tested. The result of the studies conducted was expressed as a percentage of the cancer cell growth compared to the control. The system of selection and study of compounds with the potential



where **2-4 a**) R=H, **b**) R=Br. **5-7 a)**: R, R_1, R_2 =H, **b)** R, R_2 =H, R_1 =CH_3; **c)** R, R_2 =H, R_1 =OCH_3; **d)** R, R_2 = H, R_1= OC_2H_5; **e)** R = H, R_1R_2 = -OCH_2CH_2O-; **f)** R, R_2 = H, R_1 = Cl; **g)** R, R_2 = H, R_1 = Br; **h)** R=Br, R_2 = H, R_1 = CH_3; **i)** R=Br, R_2 = H, R_1= $OCHF_2$; **j)** R=Br, R_1, R_2 =OCH_3; **k)** R=Br, R_1R_2 = -OCH_2CH_2O-.

Fig. 2. The synthesis of 1,4-diaryl-5,6,7,8-tetrahydro-2,2a,8a-triazacyclopenta[*cd*]azulenes **7 a-k**

antineoplastic activity *in vitro* is based on the determination of percentage of the cancer cell growth (PG) under the effect of the compound tested. In the experimental conditions, the compounds studied in the concentration of 10-5 mol/l found the ability to inhibit the growth of cancer cells covering almost the entire spectrum of human cancer (Tab. 1).

According to Tab. 1 compounds **7 b-e** with electron-donor substitutes in position 4 of the heterocyclic system in relation to cells of leukemia, non-small cell lung cancer, colon cancer, CNS cancer, melanoma, ovarian cancer, renal cancer, prostate cancer and breast cancer revealed the highest antineoplastic activity than the reference drug – 5-fluorouracil.

Compounds with electron-withdrawing substitutes **7f, g** showed the activity at the level of the reference drug.

Thus, all compounds **7a-g** inhibited the growth of cancer cells of CCRF-CEM, HL-60 (TB), K-562, MOLT-4, RPMI-8226 and SR leukemia more than the reference by 11.09-94.60 %. In relation to CCRF-CEM cells the data of compounds **7c** and **7d** were -0.35 % and -6.01 %, respectively, i.e. these compounds not only stopped the growth and division of cells, but also destroyed them.

Compounds **7c** and **7d** stopped the growth and division of COLO 205 cells of colon cancer, and destroyed them by -47.03 % and -85.81 %, respectively. It should be noted that the same compounds were especially active in relation to cancer cells of MCF7, HS 578T, VT-549 and MDA-MB-468 breast cancer with the values of -12.82 %, -15.55 %, -0.58 % and -9.61 %, respectively.

Compound **7h** exceeded the reference drug on 19 lines of cancer cells, **7i** – on 18 lines, **7j** – on 52 lines and **7k** – on 47 lines among 60 lines studied.

Compound **7h** was effective against HL-60 (TB) leukemia cells (exceeding the action of 5-fluorouracil by 15.58 %), UACC-257 melanoma (exceeding the action of 5-fluorouracil by 18.23 %), PC-3 prostate cancer (exceeding the action of 5-fluorouracil by 11.71 %).

Compound **7i** was effective against RPMI-8226 leukemia cells (exceeding the action of 5-fluorouracil by 23.32 %), EKVX non-small cell lung cancer (exceeding the action of 5-fluorouracil by 11.96 %), NT-29 colon cancer (exceeding the action of 5-fluorouracil by 25.59 %), TK-10 renal cancer (exceeding the action of 5-fluorouracil by 41.94 %).

Compound **7j** was effective against CCRF-CEM, HL60 (TB) leukemia cells, MOLT-4 indicators were -24.52 %; -13.14 %; -5.16 %, respectively, i.e. this compound not only stopped the growth and division of cells, but also destroyed them. The compound destroyed HOP-92 non-small cell lung cancer – 25.68 %; OVCAR-3 ovarian cancer – 13.80 % and UO-31 renal cancer – 29.09 %. This compound showed the activity in relation to K-562 leukemia cells (exceeding the action of 5-fluorouracil by 93.25 %), HCT-116 colon cancer (exceeding the action of 5-fluorouracil by 96.20 %), PC-3 prostate cancer (exceeding the action of 5-fluorouracil by 93.14 %), VT-549, T-47D breast cancer (exceeding the action of 5-fluorouracil by 79.97 % and 81.62 %, respectively).

Compound **7k** was effective against CCRF-CEM, RPMI-8226 leukemia cells (exceeding the action of 5-fluorouracil by 95.82 % and 83.51 %, respectively), HOP-92 non-small cell lung cancer (exceeding the action of 5-fluorouracil by 40.88 %), HCT-116 colon cancer (exceeding the action of 5-fluorouracil by 16.04 %), SF-539 CNS cancer (exceeding the action of 5-fluorouracil by 17.93 %), LOX IMVI, M14, SK-MEL-2 melanoma (exceeding the action of 5-fluorouracil by 14.28 %; 13.27 %; and 20.68 %, respectively), OVCAR-5, OVCAR-8 ovarian cancer (exceeding the action of 5-fluorouracil by 17.73 % and 18.05 %), PC-3 prostate cancer (exceeding the action of 5-fluorouracil by 81.12 %).

At the second stage of our studies, or the in-depth screening *in vitro*, the compounds were tested in five concentrations in 10-fold dilution (100 μm, 10 μm, 1 μm, 0.1 μm and 0.01 μm) on the lines of human cancer cells listed. As a result of the experiment three dose-dependent parameters, namely GI50 – the concentration of the compound causing inhibition of 50 % cell line growth; TGI – the concentration creating complete inhibition of the cell growth; LC_{50} – the concentration causing death of 50 % of tumor cells, were calculated. GI_{50} is interpreted as the effective level of inhibition, TGI is the cytostatic effect, while LC_{50} is the lethal concentration causing the cytotoxic action. If logarithmic values of the parameters studied ($lgGI_{50}$, lgTGI and $lgLC_{50}$) are less than – 4.00, then the compound is considered to be active [11-13].

According to the results of the screening (Tab. 2), the compounds tested revealed the considerable level of the anticarcinogenic activity. Compound **7b** showed the significant level of the anticarcinogenic activity in relation to HOP-62 (lgGI50 = -5.76; lgTGI = -5.42; lgLC50 = -5.08) non-small cell lung cancer; SNB-75 CNS cancer ($lgGI_{50}$ = -5.68; lgTGI = -5.32; $lgLC_{50}$ = -4.79) and U251 ($lgGI_{50}$ = -5.57; lgTGI = -5.07; $lgLC_{50}$ = -4.16); OVCAR-3 ovarian cancer ($lgGI_{50}$ =-5.61; lgTGI = -5.27; $lgLC_{50}$ = -4.10) and SK-OV-3 ($lgGI_{50}$ = -5.67; lgTGI = -5.28; $lgLC_{50}$ = -4.27).

Compound **7c** had the anticarcinogenic activity in relation to MOLT-4 ($lgGI_{50}$ = -5.75; lgTGI = -5.39; $lgLC_{50}$ = -5.03) leukemia; HOP-92 non-small cell lung cancer ($lgGI_{50}$ = -5.91; lgTGI = -5.38; $lgLC_{50}$ = -4.27) and NCI-H522 ($lgGI_{50}$ = -5.72; lgTGI = -5.26; $lgLC_{50}$ = -4.45); COLO 205 colon cancer ($lgGI_{50}$ = -5.65; lgTGI = -5.30; $lgLC_{50}$ = -4.87), HCC2998 ($lgGI_{50}$ = -5.42; lgTGI = -4.83; $lgLC_{50}$ = -4.19) та HCT-116 ($lgGI_{50}$ = -5.60; lgTGI = -4.93; $lgLC_{50}$ = -4.07); SF-539 CNS cancer ($lgGI_{50}$ = -5.43; lgTGI = -4.80; $lgLC_{50}$ = -4.20) and U251 ($lgGI_{50}$ = -5.56; lgTGI = -4.86; $lgLC_{50}$ = -4.00); LOX IMVI melanoma

Table 1

The anti-tumor activity of 1,4-diaryl-5,6,7,8-tetrahydro-2,2a,8a-triazacyclopenta[*cd*]azulenes **7 h-k** *in vitro* on the lines of cancer cells under the action of substances in the concentration of 10^{-5} mol/L

The lines of cancer cells		**7a**	**7b**	**7c**	**7d**	**7e**	**7f**	**7g**	**7h**	**7i**	**7j**	**7k**
1	2	3	4	5	6	7	8	9	10	11	12	13
Leukemia	CCRF-CEM	36.45	11.08	-0.36	-6.01	13.38	79.98	42.33	88.79	117.33	-24.52	4.18
	HL-60(TB)	48.12	-1.56	-20.72	45.27	56.24	93.93	88.18	84.32	99.56	-13.14	96.87
	K-562	32.89	10.27	7.22	19.60	21.60	82.05	79.43	105.17	91.79	6.75	88.90
	MOLT-4	51.99	21.17	3.47	33.73	15.08	76.61	62.86	93.08	100.52	-5.16	87.09
	RPMI-8226	30.83	17.18	15.20	25.07	21.68	94.56	78.04	101.07	76.68	7.36	16.49
	SR	65.69	26.07	5.40	52.47	47.70	78.96	88.91	93.43	108.10	9.36	90.33
Non-Small Cell Lung Cancer	A549/ATCC	71.48	35.01	13.14	90.39	25.00	88.58	82.41	88.39	90.95	46.49	90.80
	EKVX	52.57	14.35	–	–	43.06	–	–	104.42	88.04	–	–
	HOP-62	70.51	40.83	7.40	103.6	39.85	108.7	99.80	119.31	107.70	63.91	96.19
	HOP-92	–	–	-4.13	43.08	20.16	95.15	79.42	78.16	–	-25.68	59.12
	NCI-H226	88.55	34.02	21.07	100.3	43.91	102.5	85.72	95.58	103.72	78.87	96.71
	NCI-H23	86.79	42.46	8.91	90.65	72.96	96.66	98.87	107.42	108.50	100.59	86.15
	NCI-H322M	122.5	78.19	15.20	94.91	60.15	95.51	117.7	110.08	99.09	25.38	115.44
	NCI-H460	–	27.87	–	–	30.64	105.4	94.93	103.17	102.09	–	–
	NCI-H522	–	–	35.98	83.37	69.18	83.64	97.50	93.01	–	47.47	75.34
Colon Cancer	COLO 205	56.98	-47.03	-85.81	98.44	26.94	104.1	103.3	118.12	121.10	50.47	101.44
	HCC2998	88.70	–	21.37	98.45	46.25	106.1	110.4	106.79	112.04	103.34	88.64
	HCT-116	35.69	1.59	-1.47	53.96	11.09	89.81	77.69	113.29	95.52	3.80	83.96
	HCT-15	101.5	77.51	39.17	104.0	84.59	94.09	97.42	110.44	111.93	54.63	91.42
	HT-29	43.88	11.54	6.95	110.4	30.18	98.02	104.1	109.14	74.41	31.50	92.39
	KM12	57.61	20.71	14.73	69.85	35.11	99.02	74.82	111.46	103.74	19.79	93.21
	SW-620	–	21.23	–	–	34.70	111.3	105.8	106.31	104.66	–	–
CNS Cancer	SF-268	87.21	47.78	23.10	85.34	50.78	86.45	98.63	103.48	103.02	38.18	96.98
	SF-295	–	30.01	–	–	35.47	–	–	105.47	137.23	–	–
	SF-539	88.32	63.68	11.63	96.28	56.30	95.87	108.2	116.41	111.67	71.95	82.07
	SNB-19	73.33	38.36	–	–	52.79	–	–	100.11	98.61	–	–
	SNB-75	–	–	28.71	88.33	54.03	87.87	90.65	106.95	–	71.63	94.01
	U251	41.17	26.17	10.26	92.75	8.45	89.97	84.64	86.94	93.79	23.48	88.11
Melanoma	LOX IMVI	77.74	22.83	9.87	84.26	33.49	99.45	90.61	105.67	100.15	96.36	85.72
	MALME-3M	86.46	0.27	-11.78	86.23	16.44	–	–	98.55	85.42	36.07	87.00
	M14	73.57	30.97	13.72	91.75	37.57	105.4	90.55	106.55	103.36	35.21	86.73
	MDA-MB-435	80.37	22.74	10.95	96.74	30.82	101.1	108.3	112.99	113.54	16.28	104.79
	SK-MEL-2	–	–	0.56	98.76	–	101.2	112.2	–	–	69.14	79.32
	SK-MEL-28	74.73	28.90	43.24	102.2	63.74	102.3	108.1	113.92	114.18	97.33	105.65
	SK-MEL-5	81.81	6.10	1.44	98.92	26.83	97.28	88.50	97.05	97.53	52.00	96.06
	UACC-257	87.91	24.36	18.97	103.6	0.71	99.48	105.1	81.77	101.25	58.15	96.22
	UACC-62	81.36	52.61	35.89	93.40	49.53	93.01	93.38	106.04	94.77	74.07	87.87
Ovarian cancer	IGROV1	74.21	15.84	25.81	98.63	56.48	94.87	99.39	114.56	101.51	31.00	95.23
	OVCAR-3	59.96	-23.00	-17.59	53.10	33.80	103.8	92.40	117.55	109.40	-13.80	95.53
	OVCAR-4	–	–	31.60	97.84	65.81	99.75	92.22	97.88	108.87	83.18	99.63
	OVCAR-5	90.97	74.56	36.28	86.23	99.34	88.23	87.89	99.05	106.59	39.08	82.27
	OVCAR-8	54.57	29.22	14.31	78.65	9.22	82.38	78.95	91.69	109.86	44.38	81.95
	NCI/ADR-RES	100.9	92.18	78.66	101.2	92.59	106.4	102.84	107.55	104.57	103.61	96.83
	SK-OV-3	–	–	27.80	99.22	82.59	96.63	102.75	120.71	106.93	83.57	91.88

Continuation of Table 1

1	2	3	4	5	6	7	8	9	10	11	12	13
Renal Cancer	786-0	82.60	28.40	13.82	94.03	68.63	96.04	92.30	101.16	98.95	50.80	96.52
	A498	–	50.13	28.35	78.77	73.45	108.0	84.39	105.70	106.36	59.60	116.27
	ACHN	77.06	16.73	5.60	80.57	55.50	94.97	88.04	113.11	109.62	25.54	87.88
	CAKI-1	112.7	66.55	70.01	92.04	81.67	97.62	95.19	99.32	107.78	66.24	97.72
	RXF 393	96.22	45.79	23.74	110.2	58.55	114.8	103.6	101.24	116.50	82.46	101.82
	SN12C	75.20	48.84	15.18	91.08	24.67	90.33	86.18	101.54	100.44	59.84	83.41
	TK-10	38.10	11.66	30.75	98.02	73.20	100.2	105.6	104.17	58.06	73.04	98.29
	UO-31	81.52	50.95	11.34	82.47	77.64	79.40	86.72	96.54	84.67	-29.09	90.06
Prostate cancer	PC-3	86.35	22.90	9.47	19.28	9.61	83.39	72.38	88.29	–	6.86	18.88
	DU-145	81.38	33.92	19.78	74.58	41.00	108.6	93.58	111.97	101.46	30.73	101.07
Breast cancer	MCF7	21.85	-12.82	13.28	94.86	37.09	86.98	80.80	96.23	95.68	67.25	94.64
	MDA-MB-231/ATCC	79.64	52.47	15.46	95.53	68.38	105.3	88.40	106.44	109.93	89.28	97.81
	HS 578T	–	-15.55	27.76	86.95	27.36	92.79	82.80	113.12	110.88	49.98	103.38
	BT-549	–	–	-0.58	73.95	51.29	99.51	88.66	–	–	20.03	73.76
	T47D	–	–	1.97	66.14	58.32	82.51	73.93	114.50	88.12	18.38	76.04
	MDA-MB-468	45.83	3.71	-9.61	89.38	18.61	113.4	83.85	102.12	108.74	49.43	92.91

($lgGI_{50}$ = -5.60; lgTGI = -5.12; $lgLC_{50}$ = -4.54), MALME-3M ($lgGI_{50}$ = -5.73; lgTGI = -5.38; $lgLC_{50}$ = -5.03), SK-MEL-2 ($lgGI_{50}$ = -5.61; lgTGI = -5.27; $lgLC_{50}$ = -4.57), SK-MEL-28 ($lgGI_{50}$ = -5.48; lgTGI = -4.84; $lgLC_{50}$ = -4.22), SK-MEL-5 ($lgGI_{50}$ = -5.77; lgTGI = -5.48; $lgLC_{50}$ = -5.19), UACC-62 ($lgGI_{50}$ = -5.76; lgTGI = -5.40; $lgLC_{50}$ = -5.04); RXF 393 renal cancer ($lgGI_{50}$ = -5.65; lgTGI = -5.13; $lgLC_{50}$ = -4.44) and UO-31 ($lgGI_{50}$ = -5.55; lgTGI = -4.95; $lgLC_{50}$ = -4.14); MDA-MB-231/ATCC breast cancer ($lgGI_{50}$ = -5.68; lgTGI = -5.30; $lgLC_{50}$ = -4.39).

Compound **7e** had the anticarcinogenic activity in relation to MOLT-4 ($lgGI_{50}$ = -5.75; lgTGI = -5.32; $lgLC_{50}$ = -4.26) leukemia; HOP-62 non-small cell lung cancer ($lgGI_{50}$ = -5.55; lgTGI = -4.92; $lgLC_{50}$ = -4.19), NCI-H460 ($lgGI_{50}$ = -5.56; lgTGI = -4.97; $lgLC_{50}$ = -4.25) and NCI-H522 ($lgGI_{50}$ = -5.54; lgTGI = -4.91; $lgLC_{50}$ = -4.19); COLO 205 colon cancer ($lgGI_{50}$ = -5.70; lgTGI = -5.33; $lgLC_{50}$ = -4.81), HCC2998 ($lgGI_{50}$ = -5.47; lgTGI = -4.79; $lgLC_{50}$ = -4.15), HCT-116 ($lgGI_{50}$ = -5.61; lgTGI = -4.98; $lgLC_{50}$ = -4.36), KM12 ($lgGI_{50}$ = -5.49; lgTGI = -4.91; $lgLC_{50}$ = -4.39), SW-620 ($lgGI_{50}$ = -5.48; lgTGI = -4.84; $lgLC_{50}$ = -4.38); SF-295 CNS cancer ($lgGI_{50}$ = -5.65; lgTGI = -5.16; $lgLC_{50}$ = -4.40), SF-539 ($lgGI_{50}$ = -5.43; lgTGI = -4.93; $lgLC_{50}$ = -4.35) and U251 ($lgGI_{50}$ = -5.70; lgTGI = -4.86; $lgLC_{50}$ = -4.18); LOX IMVI melanoma ($lgGI_{50}$ = -5.64; lgTGI= -4.94; $lgLC_{50}$ = -4.36), MALME-3M ($lgGI_{50}$ = -5.71; lgTGI = -5.25; $lgLC_{50}$ = -4.47), M14 ($lgGI_{50}$ = -5.48; lgTGI = -4.89; $lgLC_{50}$ = -4.13), SK-MEL-28 ($lgGI_{50}$ = -5.31; lgTGI = -4.68; $lgLC_{50}$ = -4.10), SK-MEL-5 ($lgGI_{50}$ = -5.86; lgTGI = -5.56; $lgLC_{50}$ = -5.26), UACC-62 ($lgGI_{50}$ = -5.75; lgTGI = -5.27; $lgLC_{50}$ = -4.62); OVCAR-3 ovarian cancer ($lgGI_{50}$ = -5.58; lgTGI = -5.01; $lgLC_{50}$ = -4.50); 786-0 renal cancer ($lgGI_{50}$ = -5.41; lgTGI = -4.80; $lgLC_{50}$ = -4.20) and RXF 393 ($lgGI_{50}$ = -5.63; lgTGI = -5.02; $lgLC_{50}$ = -4.37); MDA-MB-231/ATCC breast cancer ($lgGI_{50}$ = -5.64; lgTGI = -5.13; $lgLC_{50}$ = -4.17); BT-549 ($lgGI_{50}$ = -5.44; lgTGI = -5.02; $lgLC_{50}$ = -4.42) and MDA-MB-468 ($lgGI_{50}$ = -5.94; lgTGI = -5.07; $lgLC_{50}$ = -4.12).

Compound **7 j** was active in relation to COLO 205 cells of colon cancer (the $lgGI_{50}$ value = -5.32, lgTGI = -4.76 and $lgLC_{50}$ =-4.27) SK-MEL-5 melanoma ($lgGI_{50}$ =-5.37, lgTGI =-4.76 and $lgLC_{50}$ =-4.25) and RXF 393 renal cancer (the $lgGI_{50}$ value = -5.62, lgTGI = -5.08, and $lgLC_{50}$ =-4.21).

Thus, the derivatives of 1-phenyl-4-aryl-5,6,7,8-tetrahydro-2,2a,8a-triazacyclopenta [*cd*]azulenes and 1-(4^1-bromophenyl)-4-aryl-5,6,7,8-tetrahydro-2,2a,8a-triazacyclopenta [*cd*]azulene exhibit the antineoplastic activity in relation to a wide range of cancer cells and can become the basis for creating new effective anticancer agents.

Experimental part

2-Methoxy-3,4,5,6-tetrahydro-7H-azepine **1** was obtained by alkylation of caprolactam with dimethyl sulfate using the method [14]. 3-Phenyl or (4^1-bromophenyl)-(6,7,8,9-tetrahydro-5H-[1,2,4]triazolo[4,3-a]azepine 4 a,b was obtained by condensation of 2-methoxy-3,4,5,6-tetrahydro-*7H*-azepine 1 with 4-bromobenzoic acid hydrazide and subsequent cyclization of the intermediate product **3** by the method [15].

The ^{1}H-NMR-spectra were recorded on a Bruker VXR-300 spectrometer (Germany) with the working frequency of 299,945 MHz, in DMSO-d_6 using tetramethylsilane (TMS) as an internal standard. The purity of the compounds synthesized was controlled by TLC on the Silufol UV-254 plates in the system of chloroform - methanol (9 : 1).

Table 2

The results of the in-depth *in vitro* screening of compounds **7 b, c, e, j** in the concentration gradient of 10^{-4}-10^{-8} M

The lines of cancer cells		**7b** $lgGI_{50}$	**7b** lgTGI	**7b** $lgLC_{50}$	**7c** $lgGI_{50}$	**7c** lgTGI	**7c** $lgLC_{50}$	**7e** $lgGI_{50}$	**7e** lgTGI	**7e** $lgLC_{50}$	**7j** $lgGI_{50}$	**7j** lgTGI	**7j** $lgLC_{50}$
1	2	3	4	5	6	7	8	9	10	11	12	13	14
Leukemia	CCRF-CEM	-5.55	-4.00	-4.00	-6.07	-5.50	-4.00	-5.88	-5.26	-4.00	-5.62	-5.16	-4.00
	HL-60(TB)	–	–	–	-5.72	-5.31	-4.00	-5.62	-4.63	-4.00	-5.47	-4.88	-4.00
	K-562	–	-4.00	-4.00	-5.94	-5.07	-4.00	-6.03	-4.99	-4.00	-5.43	-4.00	-4.00
	MOLT-4	–	- 4.00	-4.00	-5.75	-5.39	-5.03	-5.75	-5.32	-4.26	-5.54	-5.08	-4.00
	RPMI-8226	-5.58	-4.00	-4.00	-5.87	-5.30	-4.00	-5.80	-5.14	-4.00	-5.53	-5.00	-4.00
	SR	-4.00	-4.00	-4.00	-5.85	-5.17	-4.00	-5.82	-5.20	-4.00	-5.48	-4.09	-4.00
Non-Small Cell Lung Cancer	A549/ATCC	-5.56	–	-4.00	-5.55	-4.00	-4.00	-5.62	-4.00	-4.00	-5.07	-4.00	-4.00
	EKVX	-5.42	-4.00	-4.00	–	–	–	-5.63	-4.00	-4.00	–	–	–
	HOP-62	-5.76	-5.42	-5.08	-5.48	-4.71	-4.00	-5.55	-4.92	-4.19	-4.92	-4.00	-4.00
	HOP-92	-5.79	-5.25	-4.00	-5.91	-5.38	-4.27	-5.63	-5.17	-4.00	-5.75	-5.22	-4.00
	NCI-H226	-5.50	-4.13	-4.00	-5.47	-4.74	-4.00	-5.68	-5.00	-4.00	-5.12	-4.00	-4.00
	NCI-H23	-5.30	-4.00	-4.00	-5.59	-5.04	-4.00	-5.47	-4.00	-4.00	-5.10	-4.00	-4.00
	NCI-H322M	-5.42	-4.00	-4.00	-5.58	-5.11	-4.00	-5.45	-4.49	-4.00	-4.82	-4.00	-4.00
	NCI-H460	-5.64	-	-4.00	-5.50	-4.95	-4.00	-5.56	-4.97	-4.25	-5.05	-4.00	-4.00
	NCI-H522	-5.48	-4.99	-4.00	-5.72	-5.26	-4.45	-5.54	-4.91	-4.19	-5.48	-4.49	-4.00
Colon cancer	COLO 205	-5.29	-4.00	-4.00	-5.65	-5.30	-4.87	-5.70	-5.33	-4.81	-5.32	-4.76	-4.27
	HCC2998	-4.00	-4.00	-4.00	-5.42	-4.83	-4.19	-5.47	-4.79	-4.15	-5.00	-4.00	-4.00
	HCT-116	-5.55	-5.16	-4.00	-5.60	-4.93	-4.07	-5.61	-4.98	-4.36	-5.43	-4.00	-4.00
	HCT-15	-4.00	-4.00	-4.00	-5.51	-4.51	-4.00	-5.14	-4.00	-4.00	-4.90	-4.00	-4.00
	HT-29	-4.00	-4.00	-4.00	-5.54	-4.69	-4.00	-5.49	-4.85	-4.00	-5.39	-4.00	-4.00
	KM12	-5.29	-4.00	-4.00	-5.47	-4.72	-4.00	-5.49	-4.91	-4.39	-5.22	-4.00	-4.00
	SW-620	-5.41	-4.00	-4.00	-5.48	-4.38	-4.00	-5.48	-4.84	-4.38	-5.36	-4.00	-4.00
CNS cancer	SF-268	-5.11	-4.00	-4.00	-5.31	-4.00	-4.00	-5.39	-4.69	-4.00	-5.18	-4.00	-4.00
	SF-295	-5.41	-4.59	-4.00	-5.63	-5.19	-4.00	-5.65	-5.16	-4.40	-5.17	-4.19	-4.00
	SF-539	-5.58	–	-4.00	-5.43	-4.80	-4.20	-5.43	-4.93	-4.35	-4.91	-4.00	-4.00
	SNB-19	-5.08	-4.00	-4.00	-5.39	-4.00	-4.00	-5.45	-4.00	-4.00	-5.25	-4.00	-4.00
	SNB-75	-5.68	-5.32	-4.79	-5.48	-4.30	-4.00	-5.52	-4.77	-4.00	-5.20	-4.00	-4.00
	U251	-5.57	-5.07	-4.16	-5.56	-4.86	-4.00	-5.70	-4.86	-4.18	-5.44	-4.00	-4.00
Melanoma	LOX IMVI	-5.43	-4.00	-4.00	-5.60	-5.12	-4.54	-5.64	-4.94	-4.36	-5.36	-4.32	-4.00
	MALME-3M	–	–	–	-5.73	-5.38	-5.03	-5.71	-5.25	-4.47	-5.39	-4.37	-4.00
	M14	-5.16	-4.00	-4.00	-5.43	-4.00	-4.00	-5.48	-4.89	-4.13	-5.20	-4.00	-4.00
	MDA-MB-435	-5.31	-4.00	-4.00	-5.53	-4.91	-4.00	-5.49	-4.59	-4.00	-5.39	-4.00	-4.00
	SK-MEL-2	-5.47	-4.00	-4.00	-5.61	-5.27	-4.57	-5.51	-5.06	-4.00	-5.07	-4.28	-4.00
	SK-MEL-28	–	-4.00	-4.00	-5.48	-4.84	-4.22	-5.31	-4.68	-4.10	-5.09	-4.00	-4.00
	SK-MEL-5	-5.62	-5.09	-4.00	-5.77	-5.48	-5.19	-5.86	-5.56	-5.26	-5.37	-4.76	-4.25
	UACC-257	–	-4.00	-4.00	-5.52	-5.01	-4.00	-5.55	-4.97	-4.00	-5.09	-4.00	-4.00
	UACC-62	-5.50	-4.00	-4.00	-5.76	-5.40	-5.04	-5.75	-5.27	-4.62	-5.18	-4.07	-4.00
Ovarian cancer	IGROV1	-5.36	-4.63	-4.00	-5.48	-4.58	-4.00	-5.46	-4.00	-4.00	-4.95	-4.00	-4.00
	OVCAR-3	-5.61	-5.27	-4.10	-5.53	-4.67	-4.00	-5.58	-5.01	-4.50	-5.41	-4.00	-4.00
	OVCAR-4	-5.55	-5.14	-4.00	-5.52	-4.00	-4.00	-5.47	-4.00	-4.00	-5.07	-4.00	-4.00
	OVCAR-5	-	-4.00	-4.00	-5.47	-4.00	-4.00	-	-	-	-4.63	-4.00	-4.00
	OVCAR-8	-5.53	-4.89	-4.00	-5.64	-4.00	-4.00	-5.65	-4.63	-4.00	-5.37	-4.00	-4.00
	NCI/ADR-RES	-5.38	-4.00	-4.00	-5.23	-4.00	-4.00	-4.24	-4.00	-4.00	-4.28	-4.00	-4.00
	SK-OV-3	-5.67	-5.28	-4.27	-5.43	-4.75	-4.00	-5.50	-4.36	-4.00	-4.59	-4.00	-4.00

Continuation of Table 2

1	2	3	4	5	6	7	8	9	10	11	12	13	14
Renal Cancer	786-0	-5.69	-5.37	-	-5.43	-4.73	-4.00	-5.41	-4.80	-4.20	-5.27	-4.13	-4.00
	A498	-5.52	-4.00	-4.00	-5.78	-5.23	-4.00	-5.53	-5.03	-4.00	-5.70	-4.65	-4.00
	ACHN	-5.72	-5.38	-5.04	-5.50	-4.00	-4.00	-	-	-	-5.37	-4.00	-4.00
	CAKI-1	-5.44	-4.00	-4.00	-5.48	-4.00	-4.00	-5.38	-4.59	-4.00	-4.82	-4.00	-4.00
	RXF 393	-5.67	-5.22	-4.21	-5.65	-5.13	-4.44	-5.63	-5.02	-4.37	-5.62	-5.08	-4.21
	SN12C	-5.30	-4.00	-4.00	-5.52	-4.60	-4.00	-5.65	-4.86	-4.00	-5.36	-4.00	-4.00
	TK-10	-5.55	-5.18	-4.00	-5.50	-4.00	-4.00	-5.40	-4.37	-4.00	-5.15	-4.13	-4.00
	UO-31	-5.70	-5.38	-	-5.55	-4.95	-4.14	-5.44	-4.74	-4.00	-5.42	-4.66	-4.00
Prostate cancer	PC-3	-5.38	-4.00	-4.00	-5.74	-5.07	-4.00	-5.60	-4.00	-4.00	-5.52	-4.00	-4.00
	DU-145	-5.08	-4.00	-4.00	-5.47	-4.00	-4.00	-5.55	-4.82	-4.00	-5.01	-4.00	-4.00
Breast cancer	MCF7	-5.33	-4.00	-4.00	-5.51	-4.00	-4.00	-5.53	-4.00	-4.00	-5.39	-4.00	-4.00
	MDA-MB-231/ATCC	-5.62	-5.15	-4.00	-5.68	-5.30	-4.39	-5.64	-5.13	-4.17	-5.35	-4.40	-4.00
	HS 578T	-5.37	-4.00	-4.00	-5.59	-4.54	-4.00	-5.38	-4.08	-4.00	-5.36	-4.00	-4.00
	BT-549	-4.50	-4.00	-4.00	-5.42	-4.51	-4.00	-5.44	-5.02	-4.42	-5.25	-4.00	-4.00
	T47D	-5.43	-4.00	-4.00	-5.54	-4.00	-4.00	-5.64	-4.00	-4.00	-5.41	-4.00	-4.00
	MDA-MB-468	-5.57	-5.05	-4.00	-5.85	-5.26	-4.00	-5.94	-5.07	-4.12	-5.57	-4.73	-4.00

The melting points were measured on a small-sized heating table with a RNMK 05 observation device (VEB Analytik, Dresden).

The general procedure for the synthesis of 1-phenyl-4-aryl-5,6,7,8-tetrahydro-2,2a,8a-triazacyclopenta[*cd*] azulenes 7 a-k. Boil the mixture of 0.01 Mole of the appropriate 3-aryl-6,7,8,9-tetrahydro-5H-[1,2,4]triazole [4,3-a]azepine **4 a,b** and 0.01 Mole of the substituted phenacyl bromide **5** in 80 ml of ethyl acetate for 1 hour. After cooling decant the solvent, wash the residue – quarternary salt **6 a-k** – with the ester, add 40 ml of 5 % NaOH solution and boil the reaction mixture for 3 hours. After cooling filter the precipitate, wash with water, then dry in air and recrystallize from benzene.

1,4-diphenyl-5,6,7,8-tetrahydro-2,2a,8a-triazacyclopenta[*cd*]azulene 7a. Yield – 1.19 g (38 %). M. p. – 189-191 °C (from benzene). Anal. Calcd. for $C_{21}H_{19}N_3$. %: N 13.4. Found, %: N 13.2. ^{1}H NMR (300 MHz, DMSO-d_6), δ (ppm): 2.01 (m, 4H, 6,7-CH_2CH_2), 2.80 (m, 2H, 5-CH_2), 4.08 (m, 2H, 8-CH_2), 7.24 (s, 1H, 3-H), 7.49-7.81 (m, 10H, 2Ph).

1-Phenyl-4-(para-tolyl)-5,6,7,8-tetrahydro-2,2a,8a-triazacyclopenta[*cd*]azulene 7b. Yield – 1.41 g (43 %). M. p. – 190-192 °C (from benzene). Anal. Calcd. for $C_{22}H_{21}N_3$. %: N 12.8. Found, %: N 13.1, ^{1}H NMR (300 MHz, DMSO-d_6), δ (ppm): 2.00 (m, 4H, 6,7-CH_2CH_2), 2.31 (c, 3H, CH_3), 2.81 (м, 2H, 5-CH_2), 4.08 (m, 2H, 8-CH_2), 7.17 and 7.37 (d-d, 4H, C_6H_4), 7.22 (s, 1H, 3-H), 7.57-7.80 (m, 5H, Ph).

1-Phenyl-4-(4^1-methoxyphenyl)-5,6,7,8-tetrahydro-2,2a,8a-triazacyclopenta[*cd*]azulene 7c. Yield – 1.75 g (51 %). M. p. – 181-182 °C (from benzene). Anal. Calcd. for $C_{22}H_{21}N_3O$. %: N 12.2. Found, %: N 12.5. ^{1}H NMR (300 MHz, DMSO-d_6), δ (ppm): 2.01 (m, 4H, 6,7-CH_2CH_2), 2.78 (m, 2H, 5-CH_2), 3.77 (s, 3H, OCH_3), 4.08 (m, 2H, 8-CH_2), 6.94 and 7.41 (d-d, 4H, C_6H_4, J = 8.7 Hz), 7.21 (s, 1H, 3-H), 7.56-7.81 (m, 5H, Ph).

1-Phenyl-4-(4^1-ethoxyphenyl)-5,6,7,8-tetrahydro-2,2a,8a-triazacyclopenta[*cd*]azulene 7d. Yield – 1.32 g (37 %). M. p. – 197-198 °C (from benzene). Anal. Calcd. for $C_{23}H_{23}N_3O$. %: N 11.8. Found, %: N 12.1. ^{1}H NMR (300 MHz, DMSO-d_6), δ (ppm): 1.35 (t, 3H, CH_3), 2.05 (m, 4H, 6,7-CH_2CH_2), 2.80 (m, 2H, 5-CH_2), 4.05 (q, 2H, CH_2), 4.08 (m, 2H, 8-CH_2), 6.89 and 7.31 (d-d, 4H, C_6H_4, J = 8.4 Hz), 7.09 (s, 1H, 3-H), 7.53-7.78 (m, 5H, Ph).

1-Phenyl-4-(2,3-dehydrobenzene[1,4]dioxane-6-yl)-5,6,7,8-tetrahydro-2,2a,8a-triazacyclopenta[*cd*]azulene 7e. Yield – 1.30 g (35 %). M. p. – 152-153 °C (from benzene). Anal. Calcd. for $C_{23}H_{21}N_3O_2$. %: N 11.3. Found, %: N 11.5. ^{1}H NMR (300 MHz, DMSO-d_6), δ (ppm): 1.86-2.00 (m, 4H, 6,7-CH_2CH_2), 2.75 (m, 2H, 5-CH_2), 3.70 (m, 2H, 8-CH_2), 4.24 (m, 4H, -OCH_2CH_2O-), 6.80-6.87 (m, 3H, C_6H_3), 7.28 (s, 1H, 3-H), 7.40-7.51 (m, 5H, Ph).

1-Phenyl-4-(4^1-chlorophenyl)-5,6,7,8-tetrahydro-2,2a,8a-triazacyclopenta[*cd*]azulene 7f. Yield – 1.43 g (43 %). M. p. – 208-209 °C (from benzene). Anal. Calcd. for $C_{21}H_{18}ClN_3$. %: N 12.1. Found, %: N 12.2. ^{1}H NMR (300 MHz, DMSO-d_6), δ (ppm): 2.01 (m, 4H, 6,7-CH_2CH_2), 2.80 (m, 2H, 5-CH_2), 4.08 (m, 2H, 8-CH_2), 7.36 (s, 1H, 3-H), 7.38-7.80 (m, 9H, C_6H_4+Ph).

1-Phenyl-4-(4^1-bromophenyl)-5,6,7,8-tetrahydro-2,2a,8a-triazacyclopenta[*cd*]azulene 7g. Yield – 2.31 g (59 %). M. p. – 214-216 °C (from benzene). Anal. Calcd. for $C_{21}H_{18}BrN_3$. %: N 10.7. Found, %:

N 10.9. ^{1}H NMR (300 MHz, DMSO-d_6), δ (ppm): 2.00 (m, 4H, 6,7-CH_2CH_2), 2.80 (m, 2H, 5-CH_2), 4.07 (m, 2H, 8-CH_2), 7.35 (s, 1H, 3-H), 7.46 and 7.51 (d-d, 4H, C_6H_4, J = 8.4 Hz), 7.56-7.80 (m, 5H, Ph).

1-(4^1-bromphenyl)-4-(para-tolyl)-5,6,7,8-tetrahydro-2,2a,8a-triazacyclopenta[*cd*]azulene 7h. Yield – 1.91 g (47 %). M. p. – 197-198 °C. Anal. Calcd. for $C_{22}H_{20}BrN_3$. %: Br 19.7, N 10.3. Found, %: Br 19.4, N 10.2. ^{1}H NMR (300 MHz, DMSO-d_6), δ (ppm): 2.01 (m, 4H, 6,7-CH_2CH_2), 2.30 (s, 3H, CH_3), 2.80 (m, 2H, 5-CH_2), 4.08 (m, 2H, 8-CH_2), 7.24 (s, 1H, 3-H), 7.16 and 7.37 (d-d, 4H, C_6H_4, J = 8.1 Hz), 7.74 and 7.78 (d-d, 4H, C_6H_4, J = 8.7 Hz).

1-(4^1-bromophenyl)-4-(4^2-difluoromethoxyphenyl)-5,6,7,8-tetrahydro-2,2a,8a-triazacyclopenta[cd]azulene 7i. Yield – 2.38 g (52 %). M. p. – 203-204 °C (from pyridine). Anal. Calcd. for $C_{22}H_{18}BrF_2N_3O$. %: N 9.16. Found, %: N 9.28. ^{1}H NMR (300 MHz, DMSO-d_6), δ (ppm): 2.05 (m, 4H, 6,7-CH_2CH_2), 2.82 (m, 2H, 5-CH_2), 4.08 (m, 2H, 8-CH_2), 7.08 (t, 1H, $OCHF_2$, J = 73 Hz), 7.23 (s, 1H, 3-H), 7.72 (s, 4H, C_6H_4).

1-(4^1-bromophenyl)-4-(3^2,4^2-dimethoxyphenyl)-5,6,7,8-tetrahydro-2,2a,8a-triazacyclopenta[*cd*]azulene 7j. Yield – 1.76 g (39 %). M. p. – 191-192 °C (from toluene). Anal. Calcd. for $C_{23}H_{22}BrN_3O_2$. Calcd., %: Br 17.7, N 9.28. Found, %: Br 17.4, N 9.35. ^{1}H NMR (300 MHz, DMSO-d_6), δ (ppm): 2.02 (m, 4H, 6,7-CH_2CH_2), 2.80 (m, 2H, 5-CH_2), 3.76 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 4.08 (m, 2H, 8-CH_2), 6.93-7.05 (m, 3H, C_6H_3), 7.24 (s, 1H, 3-H), 7.73 and 7.78 (d-d, 4H, C_6H_4, J = 9.3 Hz).

1-(4^1-bromphenyl)-4-(2,3-de-hydrobenzene [1,4]dioxane-6-yl)-5,6,7,8-tetrahydro-2,2a,8a-triazacyclopenta[*cd*]azulene 7k. Yield – 1.76 g (39 %). M. p. – 212-213 °C (from toluene). Anal. Calcd. for $C_{23}H_{20}BrN_3O_2$. %: Br 17.7, N 9.33. Found, %: Br 17.9, N 9.52. ^{1}H NMR (300 MHz, DMSO-d_6), δ (ppm): 2.01 (m, 4H, 6,7-CH_2CH_2), 2.77 (m, 2H, 5-CH_2), 4.09 (m, 2H, 8-CH_2), 4.24 (m, 4H, OCH_2CH_2O-), 6.81-6.92 (m, 3H, C_6H_3), 7.18 (s, 1H, 3-H), 7.72 and 7.79 (d-d, 4H, C_6H_4, J = 9.3 Hz).

Conclusions

1. New chemical compounds – derivatives of 1 1-phenyl-4-aryl-5,6,7,8-tetrahydro-2,2a,8a-triazacyclopenta[*cd*]azulenes **7a-g** and 1-(4^1-bromphenyl)-4-aryl-5,6,7,8-tetrahydro-2,2a,8a-triazacyclopenta[*cd*]azulenes **7h-k** showing the antineoplastic activity have been synthesized.

2. The compounds, which are characterized by the high level of effective inhibition of leukemia, non-small cell lung cancer, colon cancer, CNS cancer, melanoma, ovarian cancer, renal cancer, prostate cancer and breast cancer, have been identified for the in-depth preclinical studies.

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