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S. V. Vlasov, I. O. Zhuravel', V. P. Chernykh

National University of Pharmacy

ANTICANCER ACTIVITY STUDY OF 6-HETARYLTHIENO[2,3-*d*]PYRIMIDINE DERIVATIVES

The synthesis of 6-hetarylthieno[2,3-d]pyrmidine derivatives modified with 1,2,4-oxadiazole, 1,3,4-oxadiazole and 1,3-thiazole units has been performed and their anticancer activity was studied by the National cancer institute (USA, Maryland, Bethesda) using in vitro assay with the 60 human cancer cell lines. It was found that 1-benzyl-5-methyl-3-phenyl-6-(3-phenyl-1,2,4-oxadiazol-5-yl)thieno[2,3-d]pyrimidine-2,4(1H,3H)-dione appeared to be the most active compound among all of the used in the experiment; it has selectively inhibited the growth of the HOP-92 lung cancer cell line. The compound 6-{2-[(4-fluorophenyl)amino]-1,3-thiazol-4-yl}-5-methyl-3-phenylthieno[2,3-d] pyrimidine-2,4(1H,3H)-dione displayed antitumor activity against prostate cancer cell lines and also inhibited the growth of some leukemia and lung cancer cell lines.

Key words: thiophene; pyrimidine; heterocycles; anticancer agents

INTRODUCTION

The derivatives of thieno[2,3-*d*]pyrimidine in the last years are extensively studied as anticancer agents by the scientific groups in the whole world. Among the compounds with similar structure the derivatives active against adenocarcinoma of cervix uteri, some types of liver and breast cancer [4, 19, 24] were reported. Some of them inhibit the growth of colon cancer [16, 17, 27] or have the wide range of anticancer activity [5, 6, 15, 18]. The compounds containing thieno[2,3-*d*]pyrimidine fragment were reported as inhibitors of tyrosine kinases, which can be considered as possible anticancer drugs [7, 10, 22, 27]. The study of anticancer activity of 5-methyl-4-oxo-3,4-dihydrothieno[2,3-*d*]pyrimidine-6-carboxylic acid esters and amides also showed the prosperity for anticancer drugs search in this class of thieno[2,3-*d*]pyrimidines [11, 12, 14]. However, the anticancer activity of thieno[2,3-*d*]pyrimidine derivatives modified at position 6 with heterocyclic substituent has not been reported before. Considering the facts mentioned above, we studied the anticancer activity of the of 6-hetarylthieno[2,3-d] pyrimidine obtained by us [1, 2, 3, 26].

MATERIALS AND METHODS

Chemical part

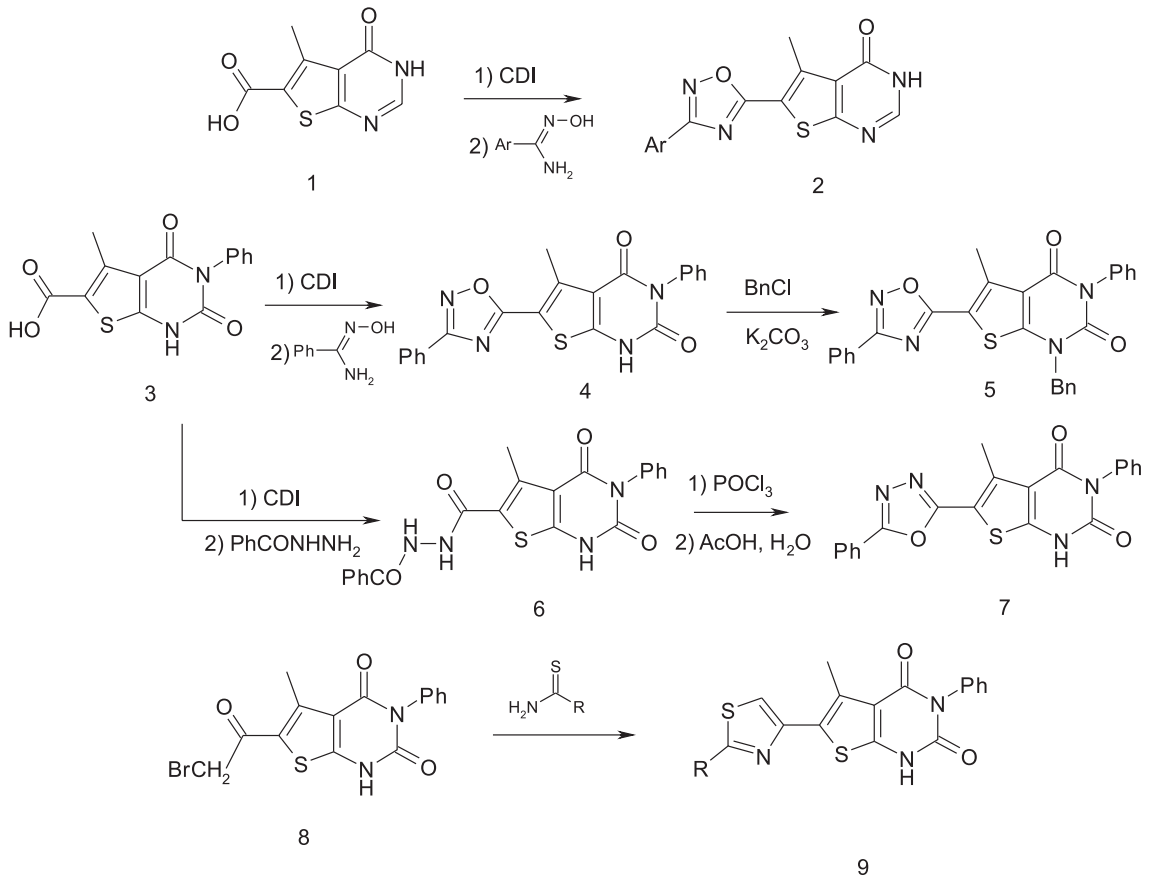
All of the solvents and reagents were obtained from the commercial sources. All the melting points were measured with the Kofler bench (°C) and were not corrected. ^{1}H NMR spectra were recorded with Varian Mercury (200 MHz) spectrometer in DMSO-d_6, using TMS as the standard (δ scale, shifts reported in ppm). Chromato-mass analysis was performed with PE SCIEX API 150EX chromatograph equipped with mass spectrometer. Elemental analysis was performed by Kjeldahl method.

General method for synthesis of 5-methyl-6-(3-aryl-1,2,4-oxadiazol-5-yl)thieno[2,3-*d*]pyrimidin-4(3*H*)-ones (2a,2b) and 5-methyl-3-phenyl-6-(3-phenyl-1,2,4-oxadiazol-5-yl)thieno[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (4). To 4 mmol of the corresponding acid **1** or **3** 4.2 mmol of 1,1'-carbonyldiimidazole was added and the mixture was heated at 100 °C in anhydrous DMF (7 ml) for 20 minutes. Then to the clear solution of imidazolide 4.2 mmol of the corresponding arylamidoxime was added and the mixture was additionally heated at 130 °C for 6 hours. Then the precipitate formed was filtered off from the reaction mixture and crystallized from pure DMF.

5-Methyl-6-(3-phenyl-1,2,4-oxadiazol-5-yl)thieno[2,3-*d*]pyrimidin-4(3*H*)-one (2a). M.p. > 300 °C. Yield – 68 %. ^{1}H NMR (200 MHz, DMSO-d_6): 2,89 (3H, s, CH_3); 7,5 (3H, m, 3H+4H+5H); 8,02 (2H, m, 2H+6H); 8,18 (1H, s, CH); 12,52 (1H, br.s, NH). LC/MS: m/z (MH^+) 311. Found, %: N 18.15. $C_{15}H_{10}N_4O_2S$. Calculated, %: N 18.05. M.w. 310,34.

6-[3-(4-Methoxyphenyl)-1,2,4-oxadiazol-5-yl]-5-methylthieno[2,3-*d*]pyrimidin-4(3*H*)-one (2b). M.p. > 300 °C. Yield – 85 %. ^{1}H NMR (200 MHz, DMSO-d_6): 2,89 (3H, s, CH_3), 3,81 (3H, s, OCH_3); 7,09 (2H, d, 3H+5H); 7,92 (2H, d, 2H+6H); 8,21 (1H, s, CH); 12.67 (1H, br.s, NH). LC/MS: m/z (MH^+) 341. Found, %: N 16,43. $C_{16}H_{12}N_4O_3S$. Calculated, %: N 16,46. M.w. 340,36.

5-Methyl-3-phenyl-6-(3-phenyl-1,2,4-oxadiazol-5-yl)thieno[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (4). M.p. > 300 °C. Yield – 87 %. ^{1}H NMR (200 MHz, DMSO-d_6): 2,86 (3H, s, CH_3), 7,22 (2H, d, 2H+6H); 7,44 (3H, t, 3H+4H+5H);



Scheme

2a*: Ar = C_6H_5;* **2b***: Ar = 4-$OCH_3C_6H_5$;* **9a***: R = CH_3;* **9b***: R = NH_2;* **9c***: R = $NHCH_2C_6H_5$;* **9d***: R = NH(4-FC_6H_5).*

7,58 (3H, t, 3'H+4'H+5'H); 8,08 (2H, d, 2'H+6'H). LC/MS: m/z (MH^+) 403. Found, %: N 14,04. $C_{21}H_{14}N_4O_3S$. Calculated, %: N 13,92. M.w. 402,43.

Method for synthesis of 1-benzyl-5-methyl-3-phenyl-6-(3-phenyl-1,2,4-oxadiazol-5-yl)thieno[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (5). To 1 mmol of the compound **4** in 1.5 ml of DMF 1.5 mmol of K_2CO_3 and 1.2 mmol of benzyl chloride was added The mixture was heated at 100 °C and stirred overnight. After the cool reaction mixture was diluted with water and the precipitate formed was washed with 2-propanol-water mixture. M.p. – 244-246 °C. Yield – 75 %. ^{1}H NMR (200 MHz, DMSO-d_6): 2,83 (3H, s, CH_3); 5,26 (3H, s, NCH_2Ph); 7,45 (13H, m, ArH); 8,02 (2H, d, ArH). LC/MS: m/z (MH^+) 493. Found, %: N 11,33. $C_{28}H_{20}N_4O_3S$. Calculated, %: N 11,37. M.w. 492,56.

Method for synthesis of 5-метил-3-phenyl-6-(5-phenyl-1,3,4-oxadiazol-2-yl)thieno[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (7). To the mixture of the acid **3** (0.0165 Mol) 1,1'-carbonyldiimidazole (0.017 Mol) was added and the reaction was heated at 80 °C in anhydrous DMF till the end of carbon dioxide release and then additional for 25 minutes. Then to the clear solution of imidazolide benzohydrazide (0.0165 Mol) was added and the reaction mixture was heated at 130 °C for 3-4 hours. Then the cool reaction mixture was quenched with water and the precipitate of the compound **6** was filtered off and dried at 70 °C. Dry derivative **6** was dissolved in 45 ml of phosphorous oxychloride and boiled for 5 hours. Then the cool reaction mixture was poured onto the crashed ice and the precipitate formed was filtered off and dissolved in 70 % acetic acid. The reaction mixture was stirred and boiled for 12 hours. Then the mixture was diluted with water and the precipitate formed was filtered off and washed with plenty of cold water. M.p. >300 °C. Yield – 63 %. ^{1}H NMR (200 MHz, DMSO-d_6): 2,79 (3H, s); 7,30 (2H, d); 7,39-7,67 (6H, m); 8,03 (2H, m); 12,64 (1H, br.s). LC/MS: m/z (M^+) 402. Found, %: N 14,15. $C_{21}H_{14}N_4O_3S$. Calculated, %: N 13,92. M.w. 402,43.

General method for synthesis of 5-methyl-6-(2-R-1,3-thiazol-4-yl)-3-phenylthieno[2,3-*d*]pyrimidin-2,4(1*H*,3*H*)-diones (9a-d). To 0.001 Mol of the corresponding thioamide in glacial acetic acid 0.4 g of the compound **8** was added and the mixture was boiled for 2-3 hours. After the reaction mixture was diluted with water and the precipitate formed was filtered off and suspended in water, then 1 ml of concentrated ammonia solution was added to the mixture and it was boiled for 1 hour. The precipitate from the reaction mixture was filtered off, washed with plenty of water and dried.

5-Methyl-6-(2-methyl-1,3-thiazol-4-yl)-3-phenylthieno[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (9a). M.p. > 300 °C. Yield – 75 %. ^{1}H NMR (200 MHz, DMSO-d_6):

Table

ANTICANCER ACTIVITY *IN VITRO* SCREENING OF THE DERIVATIVES OF 6-HETARYLTHIENO[2,3-*d*]PYRIMIDINE SYNTHESIZED TOWARDS 60 HUMAN CELL LINES

Cpd.	Mean growth, %	Range of growth, %	Most sensitive cell line growth, % (cancer line/type)
1	2	3	4
2a	104.78	82.89-123.24	82.89 (MCF7/BC) 86.47 (CCRF-CEM/L) 90.10 (HOP-92/ NSCLC) 90.89 (RPMI-8226/L)
2b	102.64	82.87-126.41	82.87 (SR/L) 87.24 (SN12C/ RC) 89.18 (BT-549/ BC) 90.81 (RPMI-8226/L)
4	97.78	70.29-120.01	70.29 (UO-31/RC) 78.15 (SNB-75/CNSC) 82.96 (RPMI-8226/L) 82.75 (SN12C/RC) 84.67 (T-47D/BC) 87.85 (BT-549/BC) 87.80 (UACC-62/M) 88.90 (U251/CNSC) 88.96 (NCI-H226/ NSCLC) 90.22 (MALME-3M/M)
5	100.66	17.44-132.19	17.44 (HOP-92/ NSCLC) 68.62 (RPMI-8226/L) 72.30 (PC-3/PC) 79.18 (CCRF-CEM/L) 81.49 (SNB-75/CNSC) 86.90 (SF-268/CNSC) 87.16 (IGROV1/ OV)
7	99.67	58.11-127.46	58.11 (HOP-92/NSCLC) 68.18 (PC-3/ PC) 73.23 (RPMI-8226/L) 77.66 (CCRF-CEM/L) 81.55 (A498/ RC) 89.41 (SN12C/RC) 89.46 (MCF7/BC) 90.31 (CAKI-1/RC) 90.83 (MDA-MB-231/ATCC/BC)
9a	100.17	76.22-123.95	76.22 (HOP-92/ NSCLC) 77.89 (A498/RC) 82.26 (CAKI-1/RC) 84.44 (786-0/RC) 87.91 (HCT-15/ColC) 89.41 (BT-549/BC) 89.85 (OVCAR-5/OV)
9b	99.66	77.84-126.54	77.84 (CAKI-1/RC) 78.43 (786-0/ RC) 80.08 (SR/L) 80.87 (A498/RC) 83.45 (HOP-92/NSCLC) 84.35 (PC-3/ PC) 90.20 (MDA-MB-435/M) 90.74 (CCRF-CEM/L)
9c	94.60	53.32-123.15	53.32 (HOP-92/NSCLC) 57.34 (A498/RC) 78.14 (UO-31/RC) 78.15 (T-47D/BC) 80.94 (786-0/RC) 83.27 (PC-3/PC) 85.47 (NCI-H23/NSCLC) 85.87 (HCT-15/ ColC) 86.86 (HCT-116/ ColC) 87.26 (ACHN/RC) 88.51 (NCI-H226/NSCLC) 88.71 (CAKI-1/RC) 89.22 (UACC-62/M) 89.25 (BT-549/BC) 89.51 (SK-MEL-5/M) 90.70 (RPMI-8226/L) 90.79 (HS 578T/BC)
9d	90.55	39.25-127.52	30.38 (PC-3/PC) 38.36 (CCRF-CEM/L) 39.25 (RPMI-8226/L) 40.85 (HOP-92/NSCLC) 49.30 (K-562/L) 72.20 (A549/ATCC/NSCLC) 73.25 (KM12/ColC) 73.80 (T-47D/BC) 75.02 (MOLT-4/L) 76.69 (SNB-75/CNSC) 76.94 (CAKI-1/RC) 77.97 (A498/RC) 78.38 (HCT-15/ColC) 79.01 (HCT-116/ColC) 80.98 (HL-60(TB)/L) 81.97 (BT-549/BC) 82.69 (SR/L) 83.24 (OVCAR-3/OV) 84.18 (UO-31/RC) 85.92 (U251/CNSC) 86.44 (ACHN/RC) 87.11 (IGROV1/OV) 90.66 (MCF7/BC)

Table continued

ColC…colon cancer; M…melanoma; NSCLC…non-small cell lung cancer; RC…renal cancer; CNSC…CNS cancer; L…leukemia; BC…breast cancer; PC…prostate cancer; OV…ovarian cancer

2,57 (3H, s, CH_3); 2,67 (3H, s, CH_3); 7,27 (2H, m, Ar-H); 7,42 (3H, m, Ar-H); 7,57 (1H, s, CH thiazole); 12,36 (1H, br.s, NH). LC/MS: m/z (MH^+) 356. Found, %: N 11,99. $C_{17}H_{13}N_3O_2S_2$. Calculated, %: N 11,82. M.w. 355,44.

6-(2-Amino-1,3-thiazol-4-yl)-5-methyl-3-phenylthieno[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (9b). M.p. > 300 °C. Yield – 63 %. ^{1}H NMR (200 MHz, DMSO-d_6): 2,55 (3H, s, CH_3); 6,63 (1H, s, CH thiazole); 7,18 (2H, s, NH_2); 7,22 (2H, d, 2H+6H); 7,44 (3H, m, 3H+4H+5H). LC/MS: m/z (MH^+) 357. Found, %: N 15,88. $C_{16}H_{12}N_4O_2S_2$. Calculated, %: N 15.72. M.w. 356,43.

6-[2-(Benzylamino)-1,3-thiazol-4-yl]-5-methyl-3-phenylthieno[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (9c). M.p. >300 °C. Yield – 92 %. ^{1}H NMR (200 MHz, DMSO-d_6): 2,55 (3H, s, CH_3); 4,43 (2H, d, CH_2); 6,69 (1H, s, CH thiazole); 7,35 (10H, m, Ar-H); 8,29 (1H, t, NH). LC/MS: m/z (MH^+) 447. Found, %: N 12,58. $C_{23}H_{18}N_4O_2S_2$. Calculated, %: N 12,55. M. 446,55.

6-{2-[(4-Fluorophenyl)amino]-1,3-thiazol-4-yl}-5-methyl-3-phenylthieno[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (9d). M.p. >300 °C. Yield – 82 %. ^{1}H NMR (200 MHz, DMSO-d_6): 2,55 (3H, s, CH_3); 6,93 (1H, s, CH

thiazole); 7,35 (9H, m, Ar-H); 10,37 (1H, br.s, NH); 12,23 (1H, br.s, NH). Found, %: N 12,40. $C_{22}H_{15}FN_4O_2S_2$. Calculated, %: N 12,44. M. 450,52.

Anticancer activity study

The screening of anticancer activity has been performed by the National cancer institute (USA, Maryland, Bethesda) as the part of the international program "Developmental Therapeutic Program" of the National institute of health using *in vitro* assay towards the 60 human cancer cell lines [8, 9, 20, 23], which were inoculated and pre-incubated on a microtiter plate. The compounds were added to the cell cultures in 10^{-5} Mol/L concentration and further incubated at controlled temperature for 48 hours. The percentage of the cell line growth was determined with a protein binding dye, sulforhodamine B (SRB). Results for each tested compound were reported as the percent growth of the treated cells when compared to the control cells. The authors declare no conflict of interests.

RESULTS AND DISCUSSION

Synthesis of the compound for screening was performed using heterocyclizations starting from the acids **1** and **3** [1, 13] using their interaction with areneamidoximes for preparation of 1,2,4-oxadiazol-3-yl derivatives **2a,b** and **4**, or using the similar procedure for benzohydrazide as we already have reported [25]. The derivative 5 was prepared by alkylation of 5-methyl-3-phenyl-6-(3-phenyl-1,2,4-oxadiazol-5-yl)thieno[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione **4** with benzyl chloride. The derivatives of 5-methyl-6-(2-1,3-thiazol-4-yl)-3-phenylthieno[2,3-*d*]pyrimidin-2,4(1*H*,3*H*)-dione **9** were obtained from 3-phenyl-6-(α-bromoacetyl)-5-methylthieno[2,3-*d*]pyrimidin-2,4(1*H*,3*H*)-dione **8** [3] (Scheme).

For all of the obtained compounds the screening of their anticancer activity has been performed by The National cancer institute (USA) under the frame of Developmental Therapeutic Program (www.dtp.nci.nih.gov), using the standard [8, 9, 20, 23] 60 cell line assay protocol (concentration of the compounds 10^{-5} Mol/L). The human tumor cell lines were derived from the different cancer types: leukemia, melanoma, lung, breast, ovarian, colon, renal, prostate and CNS cancers. The results of anticancer screening are listed in the table.

The results of the anticancer activity screening showed that most of the compounds have moderate anticancer activity. The most active compound is the derivative **5**, which displayed selective activity against the HOP-92 lung cancer cell line growth. The compound **7** also appeared to be active against the HOP-92 cell line but it is less active than the compound **5**.

Among the compounds of 5-methyl-6-(2-1,3-thiazol-4-yl)-3-phenylthieno[2,3-*d*]pyrimidin-2,4(1*H*,3*H*)-dione series **9**, the derivative **9d**, substituted with fluorine atom in the aromatic ring at aminothiazole, was determined as the most active towards prostate cancer and some lines of leukemia together with the lung cancer.

CONCLUSIONS

The anticancer activity study for the derivatives of 6-(1,2,4-oxadiazol-5-yl)thieno[2,3-*d*]pyrimidine, 6-(5-phenyl-1,3,4-oxadiazol-2-yl)thieno[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione and 6-(thiazol-4-yl)thieno[2,3-*d*]pyrimidin-2,4(1*H*,3*H*)-dione derivatives performed by the National cancer institute (USA, Maryland, Bethesda) showed that the most of these compounds displayed moderate anticancer activity. It was found that 1-benzyl-5-methyl-3-phenyl-6-(3-phenyl-1,2,4-oxadiazol-5-yl)thieno[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione appeared to be the most active compound among all of the used in the experiment; it has selectively inhibited the growth of the HOP-92 lung cancer cell line. The compound 6-{2-[(4-fluorophenyl) amino]-1,3-thiazol-4-yl}-5-methyl-3-phenylthieno [2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione displayed antitumor activity against prostate cancer cell lines and also inhibited the growth of some leukemia and lung cancer cell lines.

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С. В. Власов, И. А. Журавель, В. П. Черных

ИЗУЧЕНИЕ ПРОТИВОРАКОВОЙ АКТИВНОСТИ ПРОИЗВОДНЫХ 6-ГЕТАРИЛТИЕНО[2,3-*d*]ПИРИМИДИНА

Осуществлен синтез производных 6-гетарилтиено[2,3-*d*]пиримидина, замещенных ядрами 1,2,4-оксадиазола, 1,3,4-оксадиазола и 1,3-тиазола, которые были тестированы на противораковую активность в Национальном институте рака (США, Мериленд, Бетесда) методом *in vitro* на клетках 60 линий злокачественных опухолей человека. Установлено, что наиболее активным среди тестированных соединений является 1-бензил-5-метил-3-фенил-6-(3-фенил-1,2,4-оксадиазол-5-ил)тиено[2,3-*d*]пиримидин-2,4(1*H*,3*H*)-дион, который селективно угнетает рост клеток линий рака легких НОР-92. Вещество 6-{2-[(4-фторфенил)амино]-1,3-тиазол-4-ил}-5-метил-3-фенилтиено[2,3-*d*]пиримидин-2,4(1*H*,3*H*)-дион показал активность по отношению к линии рака простаты, а также отдельных линий лейкемии и рака легких.

Ключевые слова: тиофен; пиримидин; гетероциклы; противораковые средства

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С. В. Власов, І. О. Журавель, В. П. Черних

ВИВЧЕННЯ ПРОТИРАКОВОЇ АКТИВНОСТІ ПОХІДНИХ 6-ГЕТАРИЛТІЄНО[2,3-*D*]ПІРИМІДИНУ

Здійснено синтез похідних 6-гетарилтієно[2,3-*d*]піримідину, заміщених ядрами 1,2,4-оксадіазолу, 1,3,4-оксадіазолу та 1,3-тіазолу, які були тестовані на протиракову активність у Національному інституті раку (США, Мериленд, Бетезда) методом *in vitro* на клітинах 60 ліній злоякісних пухлин людини. Встановлено, що найбільш активною серед тестованих сполук є 1-бензил-5-метил-3-феніл-6-(3-феніл-1,2,4-оксадіазол-5-іл)тієно[2,3-*d*]піримідин-2,4(1*H*,3*H*)-діон, яка селективно пригнічує ріст клітин лінії раку легень НОР-92. Речовина 6-{2-[(4-флуорофеніл)аміно]-1,3-тіазол-4-іл}-5-метил-3-фенілтієно[2,3-*d*]піримідин-2,4(1*H*,3*H*)-діон виявила активність по відношенню до лінії раку простати, а також окремих ліній лейкемії та раку легень.

Ключові слова: тіофен; піримідин; гетероцикли; протиракові засоби

Адреса для листування:
61168, м. Харків, вул. Блюхера, 4.
Національний фармацевтичний університет

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