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Synthesis of novel fused thiopyrano[2,3-d]thiazole derivatives as potential anticancer agents

Synteza nowych pochodnych tiopirano[2,3-d]tiazolu jako potencjalnych leków przeciwnowotworowych

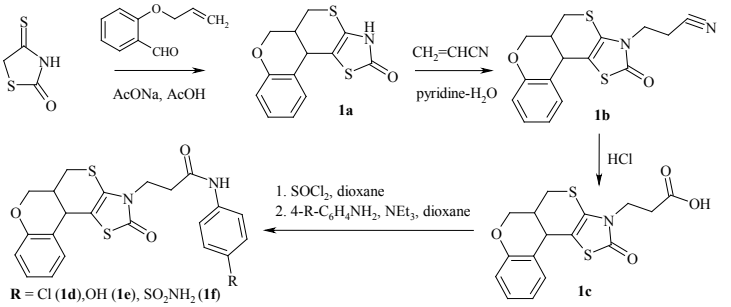
INTRODUCTION

Biological studies of thiopyrano[2,3-*d*]thiazole derivatives, which mimic some biophore fragments of 5-ylidene-4-thiazolidinones [2, 4, 5, 7], allowed us to confirm our previous hypothesis about the development of pharmacological activity of the mentioned heterocyclic systems, and this served as a basis for the synthesis of compounds rows with high biological potential [1, 8]. The fact of presented biological activity gives us reasons for proceeding in synthesis of new fused heterocycles based on 4-thiazolidinone derivatives, exactly chromeno[4',3':4,5]thiopyrano[2,3-*d*] thiazole derivatives as potential anticancer agents.

MATERIAL AND METHODS

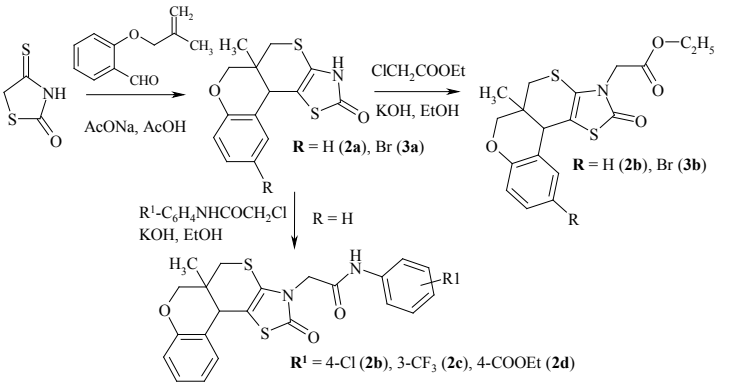
Starting 3-unsubstituted chromeno[4',3':4,5]thiopyrano[2,3-*d*]thiazole derivatives (**1a**, **2a, 3a**) were synthesized using 4-thioxo-2-thiazolidinone and allyloxo- or (2-methylallyloxy)-benzaldehydes according to domino-Knoevenagel-*hetero*-Diels-Alder reaction [6, 9]. For introducing carboxylic group functionality into 3-(chromeno[4',3':4,5]thiopyrano[2,3-*d*]thiazole)-propionitrile (**1b**) cyanoethylation reaction of compound **1a** and acrylonitrile was carried out. This derivative was transformed into respective carboxylic acid **1c** by treatment of hydrochloric and acetic acids mixture. Compounds (**1d-1f**) were synthesized via forming of corresponding acid chloride which was used in the acylation reactions of primary amines (Scheme 1).

Scheme 1



Following alkylation reaction of fused heterocycles (**2a, 3a**) with ethylchloroacetate, and various chloroacetamides, via intermediate *N*-potassium salts, novel 3-substituted chromeno[4',3':4,5] thiopyrano[2,3-*d*]thiazole derivatives (**2b-2d, 3b**) were synthesized (Scheme 2).

Scheme 2



The structures of all newly synthesized compounds were confirmed by elemental analyses, ^{1}H and ^{13}C NMR spectroscopy.

Anticancer activity evaluation of synthesized compounds was carried out in the National Cancer Institute (NCI, Bethesda, Maryland, USA) [3, 10]. Results were observed on 60 tumor cell lines representing all forms of cancer (such as, non-small cell lung cancer, colon cancer, breast cancer, ovarian cancer, leukemia, renal cancer, melanoma, prostate cancer) at single concentration of 10^{-5} M.

RESULTS AND DISCUSSION

Among 10 tested compounds six active or moderate active ones (**1a**, **1b**, **1d**, **2b**, **2d**, **3b**) were found and for two others (**1e, 1f**) primary anticancer assays are in progress.

Table 1. Prescreening results of antitumor activity for synthesized compounds

Comp.	Mean growth inhibition percent/ activity range ,%	The most sensitive lines (growth, %)
2a	96.05 / 30.63 ÷147.33	**RC:** TK-10 (30.63). UO-31 (30.88)
3b	49.23 / 7.34 ÷ 101.18	***L***: CCRF-CEM (7.34). SR (10.12). K-562 (10.55); ***BC***: MDA-MB-435 (7.52); ***CC***: HT-29 (9.91)
2b	78.77 / 46.95 ÷ 116.20	***L***: RPMI-8226 (46.95); ***BC***: T-47D (52.40)
2d	87.03 / 0.43 ÷ 156.66	***L***: CCRF-CEM (0.43). RPMI-8226 (35.25); ***NsCLC:*** HOP-92 (46.11); ***BC***: T-47D (49.33)
1b	101.04 / 8.59 ÷ 304.74	***BC***: HS 578T (8.59); ***NsCLC:*** EKVX (39.22); ***CNSC:*** SF-268 (58.00)
1d	91.69 / 60.09 ÷ 126.78	***CNSC:*** SNB-75 (60.09)

NsCLC – non-small sell lung cancer; *BC* – breast cancer, *OC* – ovarian cancer, *L* – leukemia, *RC* –renal cancer, *M* – melanoma, *CNSC* – CNS cancer

It is worth to mention that the highest growth inhibition was observed for compounds **1b**, **2d** and **3b**. Compound **1b** is rather active towards breast cancer cell line HS 578T: GI=8.59%; compound **2d** is active towards leukemia cell line CCRF-CEM: GI=0.43%; and compound **3b** shows anticancer activity relatively leukemia cell lines: CCRF-CEM: GI=7.34%, SR GI=10.12%, K-562 GI=10.55%; breast cancer cell line: MDA-MB-435: GI=7.52%; and colon cancer: HT-29: GI=9.91%. Compound **3b** was revealed to be the most active antitumor agent. The structure of this substance differs from the other tested compounds by the presence of bromine atom in the core heterocycle and by the presence of aliphatic ester substituent in the position 3. It allows us to consider the character of substituent in the 3 position of basic condensed system as the crucial factor in revealing anticancer activity by chromeno[4',3':4,5]thiopyrano[2,3-*d*]thiazole derivatives.

CONCLUSIONS

Preparative synthesis method of novel 3-substituted (5aRS,11bSR)-3,5a,6,11b-tetrahydro-2*H*,5*H*-chromeno[4´,3´:4,5]thiopyrano[2,3-*d*][1,3]thiazol-2-one and 5a-methyl–(5aRS,11bSR)-3,5a,6,11b-tetrahydro-2*H*,5*H*-chromeno[4´,3´:4,5]thiopyrano[2,3-*d*][1,3]thiazol-2-one derivatives has been worked out. Anticancer activity studies of synthesized substances revealed that the highest antitumor activity was shown by compounds **1b**, **2d** and **3b**. These compounds possess a distinctive pattern of selective action against breast cancer, colon cancer and leukemia cell lines. Results of this study prompt us to in-depth anticancer studies of fused thiazole derivatives as possible "drug-like" molecules.

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SUMMARY

The paper presents a synthetic strategy for chromeno[4',3':4,5]thiopyrano[2,3-*d*]thiazole derivatives search and a study of their probable anticancer activity. To verify the chemical structures of synthesized substances, we performed ^{1}H and ^{13}C NMR analysis on the chemical samples. Anticancer cytotoxicity of these heterocyclic compounds was studied according to NCI protocol. Among others, compounds **1b**, **2d** and **3b** showed the highest antitumor activity in the 60 cell line assay. These compounds possess a distinctive pattern of selective action against breast cancer, colon cancer and leukemia cell lines.

Keywords: synthesis, novel anticancer agent, thiopyrano[2,3-d]thiazole derivatives

STRESZCZENIE

W pracy przedstawiono strategię syntezy pochodnych chromeno[4',3':4,5]tiopirano[2,3-*d*] thiazolu i wyniki badań nad ich prawdopodobnym działaniem przeciwnowotworowym. W celu zweryfikowania struktury chemicznej zsyntetyzowanych substancji przeprowadzono analizę z zastosowaniem ^{1}H i ^{13}C NMR. Cytotoksyczność przeciwnowotworowa tych substancji

heterocyklicznych była badana zgodnie z protokołem NCI. Spośród wszystkich substancji 1b, 2d i 3b wykazały najwyższą aktywność przeciwnowotworową w 60 oznaczeniach linii komórkowych. Te substancje wykazywały wyraźne działanie na linie komórkowe komórek raka piersi, jelita grubego i białaczki.

Słowa kluczowe: synteza, nowe środki przeciwnowotworowe, pochodne tiopirano[2,3-d]tiazolu