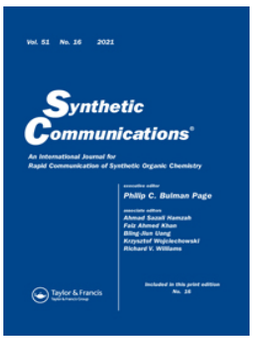

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Synthesis and anticancer activity of novel 2-alkylthio-4-amino-5-(thiazol-2-YL)pyrimidines

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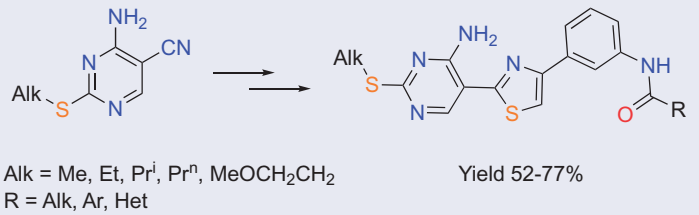
[a]Medicinal Chemistry Center, Togliatti State University, Togliatti, Russian Federation; [b]Laboratory of Biomarkers and Mechanisms of Tumor Angiogenesis, N. N. Blokhin National Medical Research Center of Oncology, Moscow, Russian Federation

ABSTRACT

A series of new fist-time synthesized of thiazolyl-substituted 4-amino-pyrimidine was obtained on the basis of a two-stage process including thioamidation of 4-amino-5-cyanopyrimide followed by one-pot acylation and Hantzsch synthesis in good yield (52–77%). All synthesized compounds showed a good anticancer effect in antiproliferative assay (end point) on three tumor lines A431, A549 и HT-1080

GRAPHICAL ABSTRACT



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Cancer cell lines; cytotoxic activity; Hantzsch synthesis; heterocyclization; nitriles; pyrimidines; thiazoles; thioamides

Introduction

The production of new target-type antitumor compounds remains one of the most important tasks of modern medicinal chemistry. The design of this kind of compounds is mainly based on the synthetic modification of various heterocyclic compounds.[1–5]

Recently, pyrimidine-based compounds such as cediranib, pazopanib, tandutinib, dasatinib, and vandetanib have been identified as promising agents to treat cancer and have already advanced to clinical trials.[6] Furthermore, pyrimidine-based compounds can be found in many commercially available anticancer drugs, which are used to treat breast, ovarian, pancreatic, bladder, colon, esophageal, stomach, cervical, kidney, gastric, lung, chronic lymphocytic leukemia, and colorectal cancer.[7–9] Hence, witnessing the recent advancement of pyrimidine compounds in cancer treatment and their versatility

CONTACT Alexander S. Bunev a.s.bunev@gmail.com; a.bunev@tltsu.ru Medicinal Chemistry Center, Togliatti State University, Togliatti, Russian Federation.

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Table 1. Cytotoxicity of the synthesized compounds against human cancer cell line.

	Survival,[a] %				Survival, %		
Compounds	A431	A549	HT-1080	Compounds	A431	A549	HT-1080
8a	13.5 ± 9.3	67.7 ± 9.3	40.1 ± 4.7	**8m**	23.9 ± 8.5	73.3 ± 7.2	71.4 ± 5.2
8b	22.9 ± 3.2	66.6 ± 3.2	54.5 ± 8.8	**8n**	36.6 ± 3.7	83.9 ± 1.3	63.5 ± 2.7
8c	23.2 ± 7.0	60.3 ± 7.0	62.6 ± 7.6	**8o**	32.0 ± 1.2	74.0 ± 8.5	95.7 ± 10.1
8d	10.2 ± 5.1	77.0 ± 5.1	55.5 ± 1.1	**8p**	25.9 ± 3.5	53.1 ± 6.0	79.7 ± 4.7
8e	15.7 ± 8.2	88.7 ± 8.2	63.3 ± 7.2	**8q**	28.4 ± 6.8	88.2 ± 3.7	50.2 ± 3.7
8f	21.7 ± 4.1	54.0 ± 4.1	43.9 ± 1.3	**8r**	62.5 ± 1.9	75.8 ± 6.6	77.1 ± 2.2
8g	23.2 ± 8.2	79.1 ± 8.2	54.0 ± 8.5	**8s**	71.1 ± 7.5	27.4 ± 0.5	53.9 ± 8.4
8h	21.2 ± 4.7	75.9 ± 4.2	53.1 ± 6.0	**8t**	74.0 ± 7.3	75.8 ± 6.6	107.1 ± 2.2
8i	44.5 ± 8.8	70.1 ± 4.7	84.6 ± 7.5	**8u**	62.9 ± 5.0	63.4 ± 2.9	98.5 ± 4.6
8j	17.3 ± 1.1	74.5 ± 8.8	41.8 ± 7.3	**8v**	61.1 ± 6.2	64.0 ± 2.0	105.6 ± 3.7
8k	30.9 ± 7.2	52.6 ± 7.6	75.8 ± 5.0	**8w**	32.1 ± 5.2	83.9 ± 5.2	100.9 ± 9.3
8l	47.7 ± 1.3	75.5 ± 1.1	73.3 ± 6.2	**8x**	41.2 ± 2.7	83.3 ± 4.5	107.3 ± 12.9
Gefitinib	1.8 ± 2.7	6.1 ± 3.2	3.9 ± 1.3	Gefitinib	1.8 ± 2.7	6.1 ± 3.2	3.9 ± 1.3

[a]Add 50 μM test compound, incubation 72 h.

as anticancer drugs promoted us to use pyrimidine as the core structural unit of our target bioactive compounds.

Among various heterocycles that have been explored for developing pharmaceutically important molecules, thiazoles, fused thiazoles, and thiazoles linked to various heterocyclic rings through different linkages have recently attracted great attention. They were found to be associated with a wide range of chemotherapeutic activities including antimicrobial,[10–14] antifungal,[15] antiparasitic,[16] and antiviral[17] activities. On the other hand, thiazole-containing compounds were reported to contribute to a variety of anticancer potentials including antitumor,[18,19] cytotoxic,[20,21] antiproliferative,[22] DNA-cleaving,[23] and angiogenesis inhibiting[24] activities. Interest in the chemotherapeutic activity of thiazoles was potentiated after the discovery of the natural antineoplastic antibiotics tiazofurin[25,26] bleomycin, netropsin, and thiazole netropsin.

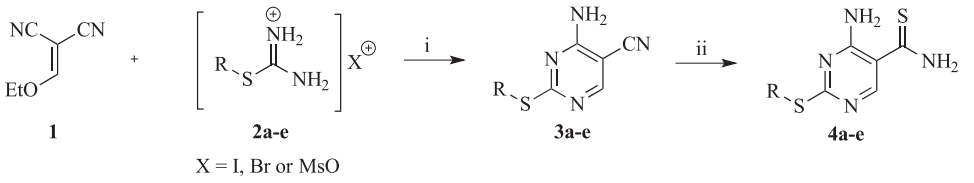
Consequently, to exploit the potentialities of thiazoles toward cancer treatment and also considering the remarkable anticancer properties of pyrimidines, we intended to conjugate these subunits in one structural frame.

Results and discussion

The presented work demonstrates a synthetic strategy for combining two pharmacologically active scaffolds, which consists in the transformation of 4-amino-5-cyanopyrimidine derivatives into the corresponding thioamides, followed by the Hantzsch reaction.

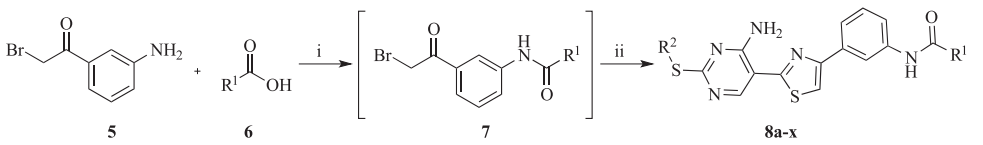
The target 4-amino-5-cyanopyrimidines **3a–e** were obtained on the basis of (1-ethoxyethylidene)malonitrile **1** and *S*-alkylisothiourea salt **2** (hydroiodide, hydrobromide or mesylates). Thioamides of pyrimidine series **4a–e**, previously not described in the literature, were obtained in the course of the thioamidation of nitriles **3** under the action of hydrogen sulfide in pyridine (Scheme 1).[27–29]

Target compounds **8a–x** were obtained by the Hantzsch reaction between thioamides **4a–e** and the corresponding *N*-acylated 3-aminophenacyl bromide **7**. It is noteworthy that the acylation of 3-aminophenacyl bromide and the Hantzsch reaction were successfully carried out in the one pot format. Activated CDI carboxylic acid **6** was introduced



a R = Me, **b** R = Et, **c** R = Pr^n, **d** R = Pr^i, **e** R = $MeOCH_2CH_2$

Scheme 1. Reagents and conditions: (i) Pr^i_2EtN, EtOH, reflux, 8 h; (ii) H_2S, Et_3N, Py, r.t.,12 h.



8a $R^1 = R^2$ = Me 74%
8b R^1 = Me, R^2 = Et 76%
8c R^1 = Me, $R^2 = Pr^n$ 68%
8d R^1 = Me, $R^2 = Pr^i$ 76%
8e R^1 = Me, $R^2 = MeOCH_2CH_2$ 51%
8f R^1 = Et, R^2 = Me 58%
8g R^1 = c-C_3H_5, R^2 = Me 62%
8h R^1 = c-C_4H_7, R^2 = Me 71%
8i R^1 = c-C_5H_9, R^2 = Me 75%
8j R^1 = tetrahydro-2*H*-pyran-4-yl, R^2 = Me 77%
8k R^1 = Ph, R^2 = Me 76%
8l R^1 = 2-FC_6H_4, R^2 =Me 52%
8m R^1 = 3-FC_6H_4, R^2 =Me 77%
8n R^1 = 4-FC_6H_4, R^2 =Me 76%
8o R^1 = 4-$F_3CC_6H_4$, R^2 = Me 71%
8p R^1 = pyridin-3-yl, R^2 = Me 69%
8q R^1 = pyridin-4-yl, R^2 = Me 57%
8r R^1 = Ph, R^2 = Et 74%
8s R^1 = 2-FC_6H_4, R^2 = Et 62%
8t R^1 = 2-FC_6H_4, $R^2 = Pr^n$ 55%
8u R^1 = Ph, $R^2 = Pr^i$ 74%
8v R^1 3-FC_6H_4, $R^2 = Pr^i$ 63%
8w R^1 = Ph, $R^2 = MeOCH_2CH_2$ 76%
8x R^1 = 3-FC_6H_4, $R^2 = MeOCH_2CH_2$ 72%

Scheme 2. Reagents and conditions: (i) CDI (1.2 equiv.), MeCN, r.t., 1 h, then **5** (1.0 equiv.), r.t., 5 h; (ii) **4** (1 equiv.), reflux, 12 h, then solution $NaHCO_3$.

into the acylation reaction of amine **5**, followed by prolonged reflux (12 h) with thioamide **4** (Scheme 2).

The structure of all the synthesized compounds **3a–e**, **4a–e**, and **8a–x** were confirmed by nuclear magnetic resonance (NMR) analysis. All the final compounds showed a characteristic chemical shift to a proton substitute and carbon on the pyrimidine ring. Spectral analysis data are provided as Supplementary Information.

The synthesized 4-amino-5-cyanopyrimidine derivatives were evaluated for cytotoxic activities by MTT assay against human lung adenocarcinoma cell line A549, human epidermoid carcinoma cell line A431, and human sarcoma cell line HT-1080 (Table 1).

The synthesized compounds exhibited cytotoxicity activities against A431 cell lines. Based on cell viability data we selected compounds **8d** and **8e** for further study. The low activity of compounds **8t–x** is partly due to the poor solubility of these compounds.

Conclusion

In conclusion, a straightforward and efficient protocol for the first-time synthesis of novel functionalized pyrimidines derivatives has been developed. Mild reaction

conditions, good yields, operational simplicity and the absence of tedious separation procedures, clean reaction profiles, high atom economy, inexpensive starting materials are the key advantages of the present protocol. Most of the compounds possessed cytotoxicity effects on all the tested cell lines.

Experimental

General

All reagents and solvents were purchased from commercial sources and used without further purification.[1] H and ^{13}C NMR spectra were acquired on a Bruker Avance spectrometer (600 and 150 MHz, respectively) in DMSO-d_6, internal standard was TMS. ^{19}F NMR spectra were recorded on the Bruker Avance III 500 spectrometer, operating at 471 MHz. ^{19}F chemical shifts was measured relative to $CFCl_3$ as an external standard. Elemental analysis was performed on a vario EL cube analyzer. Melting points were determined on a Boetius hot stage and were not corrected. All compounds reported in this communication are at least 95+% pure judged by HPLC UV detection (Agilent Technologies 1220 Infinity LC) and optionally NMR.

Synthesis of 4-amino-2-alkylthiopyrimidine-5-carbonitriles (typical procedure)

A mixture (1-ethoxyethylidene)malonitrile **1** (50 mmol), *S*-alkylisothiourea salt **2** (hydroiodide, hydrobromide or mesylates) (50 mmol), Pr^i_2EtN (60 mmol) and ethanol (250 mL) was reacted under reflux conditions for approximately 8 h. When the reaction was complete (TLC monitoring, hexane/EtOAc 7:3), the reaction mixture was poured into water (400 mL), then washed thoroughly with water. The product was isolated by filtration, dried, and recrystallized from 95% ethanol.

Synthesis of 4-amino-2-alkylthiopyrimidine-5-carbothiamide (typical procedure)

A mixture of compound **3** (10 mmol) and $E_{t3}N$ (20 mmol) in 50 ml of pyridine is saturated with H_2S for 2 h while cooling on ice. Then the mixture is left for 12 h. After the product is precipitated with water, filtered off, dried and recrystallized from DMF.

Synthesis of pyrimidines 8a–x (typical procedure)

CDI (2.2 mmol) was added to a solution of the corresponding carboxylic acid **6** (2.1 mmol) in 20 mL of anhydrous MeCN, and the mixture was stirred for an hour at room temperature. Next, phenacyl bromide **5** (2 mmol) is added to the resulting imidazolide and stirring is continued for **5** h. Then the corresponding thioamide **4** (2 mmol) in 25 mL of MeCN is added to the resulting solution. The resulting mixture was refluxed for 12 h, neutralized with 20% $NaHCO_3$ solution, and the reaction mixture was diluted with water. The precipitated product was filtered off, dried in air, and recrystallized from DMF.

N-(3-(2-(4-Amino-2-(methylthio)pyrimidin-5-yl)thiazol-4-yl)phenyl)acetamide (8a)

Yield 74%, mp 213–214 °C. Found, %: C 54.01; H 4.63; N 19.66. $C_{16}H_{15}N_5OS_2$. Calculated, %: C 53.76; H 4.23; N 19.59. ^{1}H NMR (500 MHz, DMSO-d_6): 10.12 (s, 1H), 8.65 (s, 1H), 8.43 (s, 2H), 8.19 (s, 1H), 8.04 (s, 1H), 7.68–7.58 (m, 2H), 7.40 (t, $J = 7.9$ Hz, 1H), 2.51 (s, 2H), 2.08 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6): 171.8, 169.0, 164.8, 158.8, 155.3, 154.3, 140.4, 134.3, 129.8, 121.2, 119.5, 117.1, 113.3, 106.0, 24.5, 13.9.

ORCID

Alexander S. Bunev http://orcid.org/0000-0001-6408-8329

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