Mendeleev Communications

Mendeleev Commun., 2025, **35**, 66–68

Synthesis and biological activity of thiazole–carbohydrate conjugates based on thiacarpine, an analogue of the cytotoxic alkaloid from the ascidian *Polycarpa aurata*

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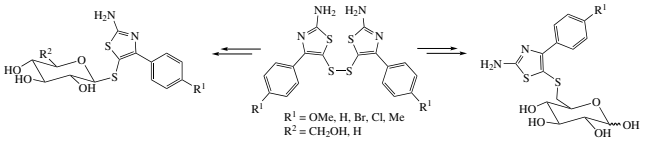
DOI: 10.71267/mencom.7522

Based on bis(2-amino-4-phenyl-5-thiazolyl) disulfides, thiazole analogues of polycarpine, a cytotoxic alkaloid from the ascidian *Polycarpa aurata*, a wide range of thiazole–carbohydrate conjugates based on D-glucose and D-xylose has been obtained. Antitumor and antimicrobial activity for the synthesized compounds has been studied.



Keywords: polycarpine, thiacarpine, bis(2-amino-4-phenyl-5-thiazolyl) disulfide, thioglycosides, *Polycarpa aurata*.

The ascidian *Polycarpa aurata* is a source of imidazole alkaloids, in particular polycarpine and a number of others which exhibit cytotoxic activity against various tumor cell lines (Figure 1).[1–4] However, *in vivo* experiments have shown that polycarpine and its derivatives have high acute toxicity. At the same time, synthetic analogue of polycarpine, thiacarpine, showed less acute toxicity and had a greater therapeutic index,[5] which makes its derivatives promising for further drug development.

Having a wide pharmacological spectrum, 2-aminothiazole derivatives are important substances in medicinal chemistry and drug development.[6–8] Thus, 2-aminothiazole derivatives exhibit antitumor,[9–11] antiviral,[12] antimicrobial,[13–15] anticonvulsant,[16] antidiabetic,[17] antiprion[18] and other properties.[19] For example, *in vitro* studies of the antitumor activity of various 2-aminothiazole derivatives have demonstrated their potent and selective inhibitory activity against a wide range of human cancer cell lines, such as breast, leukemia, lung, colon, CNS, melanoma, ovarian, kidney, and prostate.[20–22]

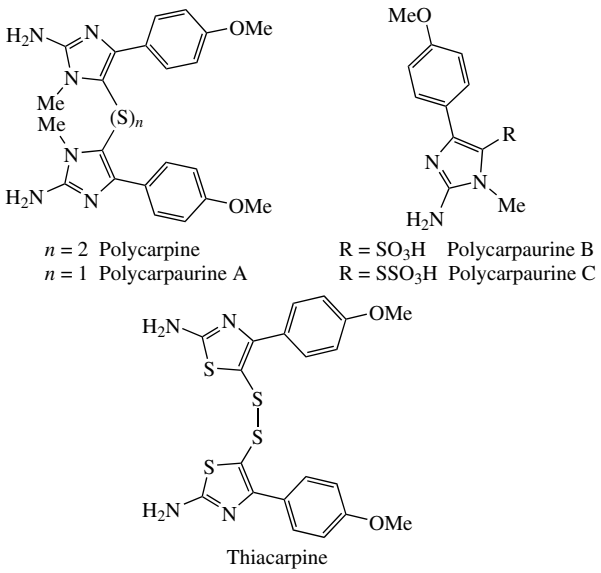
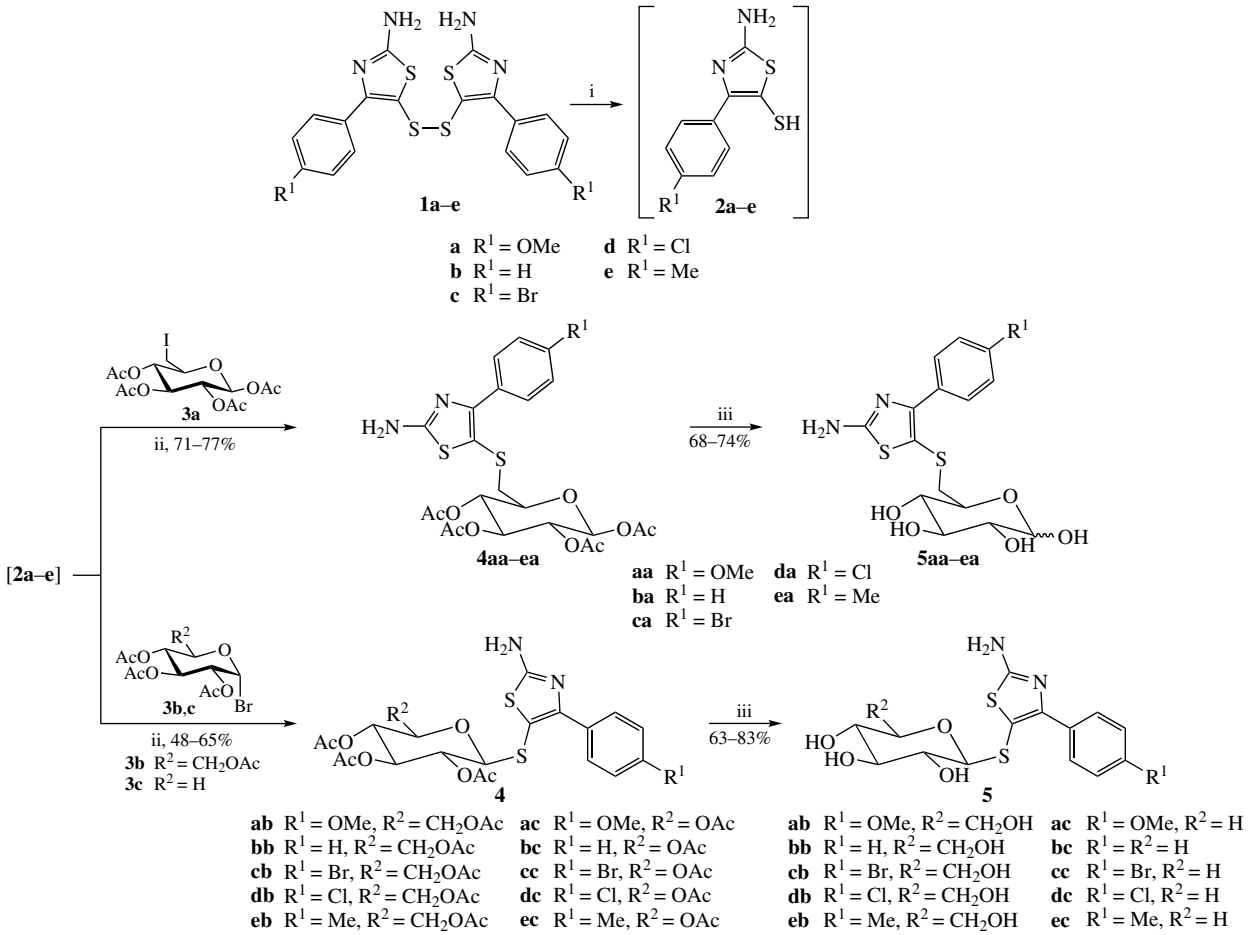


Figure 1 Structures of thiacarpine and alkaloids from ascidian *Polycarpa aurata*.

The combination of different fragments in one hybrid molecule leads to a significant change in biological properties. Thus, the introduction of non-polar fragments enhances lipophilicity and, as a rule, increases cytotoxicity by facilitating diffusion through cell membranes. The introduction of polar fragments can increase water solubility and, consequently, bioavailability. We have previously shown that the introduction of a glucose fragment into the molecule of a cytotoxic substance can often reduce its toxicity and enhance the selectivity of action on tumor cells due to the so-called Warburg effect, increased consumption of glucose by tumor cells compared to normal ones.[23,24] To this end, in this work we obtained thiazole–carbohydrate conjugates based on thiacarpine and its derivatives, in which the thiazole and carbohydrate fragments are connected through one sulfur atom.

The acetylated conjugates (Scheme 1) were obtained by the reaction of halogen derivatives of carbohydrates **3a–c** and 5-mercapto derivatives of thiazoles **2a–e** formed by reduction of bis(2-amino-4-phenyl-5-thiazolyl) disulfides **1a–e**. The reduction of disulfides **1a–e** was carried out with sodium dithionite in a water–acetone solution. Halogen derivatives of carbohydrates **3a–c** were added to the resulting 5-mercapto derivatives **2a–e** without isolation, which led to the target acetylated conjugates **4**. The acetylated derivatives **4** were deprotected into conjugates **5** with sodium methoxide in methanol solution (see Scheme 1).



Scheme 1 *Reagents and conditions*: i, $Na_2S_2O_4$, acetone–H_2O (1 : 1 v/v), room temperature, 1 h; ii, acetone–H_2O (1 : 1 v/v), room temperature, 12 h; iii, MeONa/MeOH, room temperature, 30 min.

Studies of cytotoxic and cytostatic activity on three human tumor cell lines (Hela cervical adenocarcinoma, Mda-mb-231 triple negative breast cancer, PC-3 prostate adenocarcinoma), as well as normal human embryonic kidney cells HEK-293 showed that most of the studied compounds did not have a cytotoxic effect on cells within 24 h, and also did not exhibit a cytostatic effect after 48 h of incubation (Table 1). The starting compounds **1a–e** were found to exhibit cytotoxicity and inhibit the growth of *Staphylococcus aureus* and yeast-like fungi *Candida albicans*. Compounds **4aa–bc** and **4cc–ec**, **5aa–ec** were not cytotoxic to human tumor cells at concentrations up to 100 μM, while most of them inhibited the growth of microorganisms (*S. aureus* and *C. albicans*). Compound **4bc** inhibited the growth of gram-positive bacteria by approximately 50% and yeast-like fungi by 35%. Compounds **4db** and **5ca** did not exhibit cytotoxic effect on cells and did not inhibit the growth of microorganisms at concentrations up to 100 μM. Thus, the modification of compounds **1a–e** led to the loss of cytotoxic properties against tumor cells, while maintaining antimicrobial activity. Also, the studied compounds did not reveal hemolytic activity in the concentration range up to 100 μM. It was found that the original disulfides **1a–e** and acetylated conjugates **4ca**, **4cb** affected cell viability when incubated for 48 h (see Table 1). No selective effect was found. For the conjugates **4ca** and **4cb** that showed the greatest activity, the effect on the processes of apoptosis, migration and colony formation of PC-3 prostate tumor cells was studied.

Table 1 Cytotoxic (EC_{50}) activity of acetylated conjugates **4ca** and **4cb** on cancer and normal cell lines.

Compound	Tested cell lines (48 h), EC_{50}/μM			
	PC-3	Hela	Mda-mb-231	HEK-293
4ca	76.26	77.15	>100	68.32
4cb	42.12	71.12	77.91	88.39
4cc	>100	>100	>100	>100

Incubation of PC-3 cells with selected substances leads to a significant decrease in the number of living cells (Table 2). It was found that the inversion of phosphotidylserine on the outer monolayer of the plasma membrane of tumor cells of the PC-3 line occurs under the influence of the studied compounds for 48 h. Thus, the maximum effect was observed at a concentration of 50 μM, both when exposed to compound **4ca** and **4cb**. The percentage of cells in early apoptosis significantly increased to 23.55 ± 4.53 and 35.44 ± 1.06%, respectively. In control cells this value was 6.61 ± 0.12%. When exposed to a concentration of 25 μM of compound **4cb**, the number of apoptotic cells also significantly increased, up to 15.46 ± 0.92%. There was also an

Table 2 Apoptosis profile for the PC-3 cell line after 48 h: control, **4ca** and **4cb** (25 and 50 μM).[a]

Compound (concentration)	Live	Early apop.	Late apop./ Dead	Dead
Control	85.69 ± 0.94	6.61 ± 0.12	6.39 ± 0.92	1.31 ± 0.15
4ca (25 μM)	77.61 ± 2.41	8.37 ± 1.06	9.43 ± 1.55	4.59 ± 0.19[b]
4ca (50 μM)	61.39 ± 5.55	23.55 ± 4.53[b]	13.56 ± 1.53[b]	1.49 ± 0.50
4cb (25 μM)	80.69 ± 2.51	15.46 ± 0.92[b]	6.01 ± 0.42	1.87 ± 0.17
4cb (50 μM)	59.49 ± 1.04	35.44 ± 1.06[b]	4.67 ± 0.35	0.81 ± 0.11

[a]Data are presented as means ± SEM. [b]P value ⩽0.05 is considered significant.

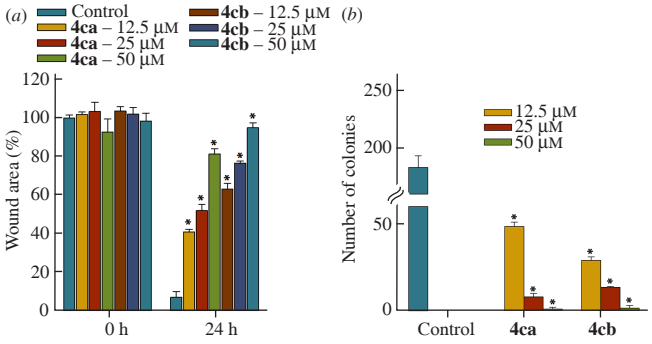


Figure 2 (*a*) Cell migration analysis (ImageJ 1.52 software was used). (*b*) Effect of conjugates **4ca** and **4cb** on the formation of colonies of PC-3 tumor cells. Data are presented as means ± SEM. *P value ⩽0.05 is considered significant.

increase in the number of cells in the stage of late apoptosis/necrosis, which was statistically different from the control (see Table 2).

In this work, the scratch-wound assay was used to analyze the possibility of suppressing the migration ability of PC-3 malignant cells. Substances that reduce the ability of malignant cells to invade may be useful as antimetastatic agents. It was found that conjugates **4ca** and **4cb** reliably inhibited the migration of PC-3 cells over the entire studied concentration range up to 12.5 μM [Figure 2(*a*)]. The effect of **4ca** and **4cb** conjugates on survival, division, and the ability to form colonies of PC-3 cells was studied. The study showed that both compounds at all concentrations reliably blocked the growth and formation of tumor cell colonies [Figure 2(*b*)]. A dose-dependent migration inhibition effect was observed for **4ca** and **4cb**. Compound **4cb** showed the maximum blocking of migration by 94.54 ± 2.54% relative to control at a concentration of 50 μM. After 24-hour incubation at a concentration of 25 μM, **4ca** reduced migration by 51.65 ± 3.35%, and **4cb** by 76.14 ± 1.14%, respectively. At the minimum tested concentration of 12.5 μM of compounds, **4ca** blocks tumor cell migration by 40.79 ± 1.21%, and **4cb** by 62.14 ± 2.86% compared to the control.

For the synthesized compounds, antimicrobial activity was studied on the yeast-like fungi *Candida albicans*, gram-positive *Staphylococcus aureus* and gram-negative bacteria *Escherichia coli*, as well as radical-binding activity and inhibition of the urease enzyme. Thiazole–carbohydrate conjugates showed less activity compared to the parent disulfides (see Online Supplementary Materials, Table S2).

In summary, a wide range of thiazole–carbohydrate conjugates have been synthesized. Preliminary screening of obtained compounds for biological activity has shown that the introduction of a carbohydrate fragment into the molecule leads to a decrease in activity compared to the starting disulfides. Based on the data obtained, it can be assumed that the disulfide bond, for which thiol–disulfide equilibrium is possible in biological systems, is responsible for the higher activity of the parent compounds.

We thank Dr. R. S. Popov for MS measurements and Dr. V. P. Glazunov for recording IR spectra. The study was carried out on the equipment of the Collective Facilities Center 'The Far Eastern Center for Structural Molecular Research (NMR/MS) PIBOC FEB RAS'. This research was funded by Russian Science Foundation (grant no. 23-23-00357).

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.71267/mencom.7522.

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Received: 5th June 2024; Com. 24/7522