A study of antimicrobial and antifungal activity of 2-((5-(2-bromophenyl)-4-substituted-4H,1,2,4-triazol-3-yl)thio)acetates

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A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation; D – writing the article; E – critical revision of the article; F – final approval of the article

Bacteria and fungi are among the most ancient creatures found on Earth. Since the advent of medicine, humankind has always sought new means and ways to combat these microorganisms. In modern scientific society, the tendency to seek new antimicrobial and antifungal agents is only increasing. 1,2,4-triazole derivatives, among which effective drugs and new molecules have already been found, make quite an interesting platform for the creation of new antifungal and antimicrobial agents. A promising direction for the search for antimicrobial and antifungal agents are 2-((5-(2-bromophenyl)-4-substituted-4H,1,2,4-triazol-3-yl)thio)acetates.

The aim of work was the investigation of antimicrobial and antifungal activity among new 2-((5-(2-bromophenyl)-4-substituted-4H,1,2,4-triazol-3-yl)thio)acetates.

Materials and methods. The substances were synthesized at the Department of Natural Sciences for International Students and Toxicological Chemistry. The antimicrobial and antifungal activity of the newly synthesized 2-((5-(2-bromophenyl)-4-substituted-4H,1,2,4-triazol-3-yl)thio)acetates was studied with the method of serial dilutions. *Staphylococcus aureus* ATCC 25923, *Escherichia coli* ATCC 25922, *Pseudomonas aeruginosa* ATCC 27853, and *Candida albicans* ATCC 885–653 were used as a set of standard test strains.

Results. As a result, the antimicrobial and antifungal activity of 14 new compounds was investigated. The most active compounds with antifungal effect are IIf–IIh. Substances IIf–IIh and IIj, IIk have moderate antimicrobial effect to *P. aeruginosae*. 

Conclusions. Some results are obtained regarding “structure – antimicrobial and antifungal effect” dependence: the replacement of the ethyl radical with phenyl or methyl in the fourth position of the 1,2,4-triazole cycle in the 2-((5-(2-bromophenyl)-4-R-4H,1,2,4-triazol-3-yl)thio)acetate acid molecule results in reduction of the antimicrobial effect; conversion to 2-((5-(2-bromophenyl)-4-substituted-4H,1,2,4-triazol-3-yl)thio)acetate salts and the choice of dimethylammonium as cation leads to an increase in the antimicrobial and antifungal effect.

Key words: antimicrobial activity, antifungal activity, triazoles, acids, salts, heterocyclic compounds.

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Исследование противомикробной и противогрибковой активности 2-((5-(2-бромфенил)-4-замещенных-4H-1,2,4-триазол-3-ил)тио)ацетатов

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Цель работы – исследование противомикробной и противогрибковой активности среди синтезированных ранее 2-((5-(2-бромфенил)-4-замещенных-4H-1,2,4-триазол-3-ил)тио)ацетатов.

Материалы и методы. Исследуемые вещества синтезированы на кафедре естественных дисциплин для иностранных студентов. Противомикробную и противогрибковую активность новых синтезированных 2-((5-(2-бромфенил)-4-замещенных-4H-1,2,4-триазол-3-ил)тио)ацетатов исследовали методом серийных разведений. Использован набор стандартных тестовых штаммов Staphylococcus aureus ATCC 25923, Pseudomonas aeruginosa ATCC 27853, Escherichia coli ATCC 25922, Candida albicans ATCC 885-653.

Результаты. Исследовано противомикробное и противогрибковое действие 14 новых соединений. Самые активные соединения с противомикробным эффектом – IIIf–IIlh. Вещества IIIf–IIlh и IIj, IIk имеют умеренное противомикробное действие на Staphylococcus aureus ATCC 25923.

Выводы. Сделаны выводы о зависимости «структура – противомикробный и противогрибковый эффект»: замена этилового радикала метиловым или фениловым в четвертом положении 1,2,4-триазольного цикла в молекуле 2-((5-(2-бромофенил)-4-R-4H-1,2,4-триазол-3-ил)тио)ацетатных кислот приводит к уменьшению противомикробного эффекта; переход к солям 2-((5-(2-бромфенил)-4-замещенных-4H-1,2,4-триазол-3-ил)тио)ацетатных кислот и выбор диметиламина как катиона ведет к увеличению противомикробного и противогрибкового эффекта.

Ключевые слова: противомикробная и противогрибковая активность, 1,2,4-триазол, кислоты, соли, гетероциклические соединения.

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Modern people probably cannot imagine their lives without vitamins, painkillers, antimicrobials, antivirals, antifungals, etc. As a result, bacteria that used to be eliminated by conventional penicillin in the 20th century, at present have become resistant even to more sophisticated antibiotics.

The thirst for existence and the constant transformation of bacteria encourages scientists around the world to create new and new antimicrobials. Certainly, it is much easier to create an active molecule on an already known platform, which has proven itself as a biologically active nucleus [1–4].

Aim
That’s why the aim of this work is to investigate antimicrobial and antifungal activity of new 2-((5-(2-bromophenyl)-4-substituted-4H-1,2,4-triazol-3-yl)thio)acetates.

Materials and methods
Antimicrobial and antifungal activity of the newly synthesized 2-((5-(2-bromophenyl)-4-substituted-4H-1,2,4-triazol-3-yl)thio)acetates was investigated with the method of serial dilutions according to guidelines [14]. The synthesized compounds were prepared by double serial dilutions, with the initial concentration of 1 mg/ml in Mueller–Hinton broth, in the volume of 1 ml. Then 0.1 ml of microbial curtain (106 µl) was added. Minimum inhibitory concentration (MIC) was determined without visible growth in a test tube with a minimum concentration of the drug; the minimum bactericidal/fungicidal concentration (MBC/MFC) was determined without growth on agar after inoculation from transparent tubes. The synthesized compounds were dissolved in dimethylsulfoxide.

A set of standard test strains of Staphylococcus aureus ATCC 25923, Pseudomonas aeruginosa ATCC 27853, Escherichia coli ATCC 25922, Candida albicans ATCC
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885-653 was used. CHLORHEXIDINE-ZDOROV’E® (Ukraine) and FLUCONAZOLE-DARNYTSYA® (Ukraine) were used as comparative drugs.

**Results**

As a result, the antimicrobial and antifungal activity of 14 new compounds was investigated.

The most active compounds with antifungal effect are IIf–IIh. Substances IIf–IIh and IIj, IIk have moderate antimicrobial effect to *P. aeruginosae*.

Some conclusions have been made regarding “structure – biological activity” dependence.

**Discussion**

The antimicrobial and antifungal activity of 2-((5-(2-bromophenyl)-4-substituted-4H-1,2,4-triazol-3-yl)thio)acetate acids is moderate. The most active compound is Ib (2-((5-(2-bromophenyl)-4-ethyl-4H-1,2,4-triazol-3-yl)thio)acetate acid) (Table 1, 2).

The replacement of the ethyl radical with phenyl or methyl in the fourth position of the 1,2,4-triazole cycle in the 2-((5-(2-bromophenyl)-4-R-4H-1,2,4-triazol-3-yl)thio)acetate acid molecule results in antimicrobial effect reduction (Fig. 1).

Considering the antifungal activity of 2-((5-(2-bromophenyl)-4-substituted-4H-1,2,4-triazol-3-yl)thio)acetate salts, the compounds IIf, IIg, IIh demonstrate antifungal effect, respectively, MIC 31.25 μg/ml, MFcC 32.25 μg/ml. Replacement of the potassium cation either with sodium or dimethylammonium or 2-aminoethanol reduces antifungal activity (Table 3).

A study of the antimicrobial activity of 2-((5-(2-bromophenyl)-4-substituted-4H-1,2,4-triazol-3-yl)thio)acetate salts showed that the most active compounds to *P. aeruginosae* are substances IIf – IIh and IIj, IIk. Thus, the introduction of dimethylammonium cation to the molecule of 2-((5-(2-bromophenyl)-4-substituted-4H-1,2,4-triazol-3-yl)thio)acetate acid leads to an increase in the antimicrobial effect. Also, the introduction of ethyl and phenyl radical in position 4 to the 2-((5-(2-bromophenyl)-4-substituted-4H-1,2,4-triazol-3-yl)thio)acetate acid molecule leads to a positive antimicrobial effect (Fig. 2).

**Table 1.** “Structure – effect” dependence between 2-((5-(2-bromophenyl)-4-substituted-4H-1,2,4-triazol-3-yl)thio)acetate acids

| Substance | R            | Antimicrobial effect | Antifungal effect |
|-----------|--------------|----------------------|-------------------|
| Ia        | CH₃          | ↔                    | ↔                 |
| Ib        | C₂H₅         | ↔                    | ↔                 |
| Ic        | C₆H₅         | ↔                    | ↔                 |

**Table 2.** Antimicrobial and antifungal activity of 2-((5-(2-bromophenyl)-4-substituted-4H-1,2,4-triazol-3-yl)thio)acetate acids and salts

| Substance | Antimicrobial activity | Antifungal activity |
|-----------|------------------------|---------------------|
|           | *E. coli* ATCC 25922   | *S. aureus* ATCC 25923 | *P. aeruginosae* ATCC 27853 | *C. albicans* |
|           | MIC, μg/ml             | MBcC, μg/ml         | MIC, μg/ml             | MBcC, μg/ml | MIC, μg/ml | MFcC, μg/ml |
| Chlorhexidine | -                      | 25.0                | -                      | 18.8         | -            | -          |
| Flucanazole    | 15.6                   | -                    | -                      | 200          | -            | -          |
| Ia           | 125                    | 125                  | 62.5                   | 125          | 62.5         | 125        |
| Ib           | 62.5                   | 125                  | 62.5                   | 125          | 62.5         | 125        |
| Ic           | 125                    | 125                  | 62.5                   | 125          | 62.5         | 125        |
| Ila          | 62.5                   | 125                  | 62.5                   | 125          | 62.5         | 125        |
| Ilb          | 62.5                   | 125                  | 62.5                   | 125          | 62.5         | 125        |
| Ilc          | 62.5                   | 125                  | 62.5                   | 125          | 62.5         | 125        |
| Ilid         | 62.5                   | 125                  | 62.5                   | 125          | 62.5         | 125        |
| Ill          | 62.5                   | 125                  | 62.5                   | 125          | 62.5         | 125        |
| Ilg          | 62.5                   | 125                  | 62.5                   | 125          | 62.5         | 125        |
| Ilh          | 62.5                   | 125                  | 62.5                   | 125          | 62.5         | 125        |
| Ill          | 62.5                   | 125                  | 62.5                   | 125          | 62.5         | 125        |
| Ilj          | 62.5                   | 125                  | 62.5                   | 125          | 62.5         | 125        |
| Ilk          | 62.5                   | 125                  | 62.5                   | 125          | 62.5         | 125        |
It should be noted that the compound IIf (dimethylammonium 2-((5-(2-bromophenyl)-4-ethyl-1,2,4-triazol-3-yl)thio)acetate), while investigating the antimicrobial activity of 2-((5-(2-bromophenyl)-4-substituted-1,2,4-triazol-3-yl)thio)acetate salts against *E. coli*, has a slightly stronger bactericidal effect comparing to other compounds.

The antimicrobial activity to *S. aureus* is moderate and similar to all 2-((5-(2-bromophenyl)-4-substituted-1,2,4-triazol-3-yl)thio)acetate salts.

As a result of the research it should be noted that the conversion to 2-((5-(2-bromophenyl)-4-substituted-1,2,4-triazol-3-yl)thio)acetate salts and the choice of dimethylammonium as cation leads to an increase in the antimicrobial and antifungal effects.

**Conclusions**

As a result, the antimicrobial and antifungal activity of 14 new 2-((5-(2-bromophenyl)-4-substituted-1,2,4-triazol-3-yl)thio)acetates has been investigated.

Compounds with antifungal effect are IIf–IIh. Substances IIf–IIj and IIk have moderate antimicrobial effect to *P. aeruginosa*. But none of the compounds surpasses the comparison drug.

Some conclusions are drawn regarding the “structure – antimicrobial and antifungal effect” dependence:
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Fig. 2. Antimicrobial and antifungal activity of 2-((5-(2-bromophenyl)-4-substituted-4H-1,2,4-triazol-3-yl)thio)acetate salts.

250 μg/ml – 0, 125 μg/ml – 1, 62.5 μg/ml – 2, 31.25 μg/ml – 3.
the replacement of the ethyl radical with methyl or phenyl in the fourth position of the 1,2,4-triazole cycle in the 2-((5-(2-bromophenyl)-4-R-4H-1,2,4-triazol-3-yl)thio)acetate acid molecule results in the antimicrobial effect reduction;

— conversion to 2-((5-(2-bromophenyl)-4-substituted-4H-1,2,4-triazol-3-yl)thio)acetate salts and the choice of dimethylammonium as a cation leads to an increase in the antimicrobial and antifungal effect.

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