SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF 3-(2-N-(ARYL,ACYL)AMINO-5-METHYL-1,3-ThIAZOL-4-YL)-2H-CHROMEN-2-ONES

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The aim of this work is to study methods of 3-(2-N-(aryl, acyl)amino-5-methyl-1,3-thiazol-4-yl)-2H-chromen-2-ones preparation and their antimicrobial activity.

Materials and methods. 1H NMR spectra were recorded on Varian Mercury-200 (200 MHz), 13C NMR spectra were acquired on Bruker Avance 500 (500 MHz) and 13C NMR (125 MHz) in DMSO-d₆ and CDCl₃, LC-MS analysis of compounds was performed on an Agilent 1100 HPLC instrument with chemical ionization at atmospheric pressure (APCI). The study of antimicrobial activity of compounds was performed by agar well diffusion method. The docking studies were performed using Autodock Vina.

Results and discussion. The interaction of 3-(2-bromopropanoyl)-2H-chromen-2-ones with N-substituted thioureas produced novel derivatives of 3-(2-N-(aryl, acyl)amino-5-methyl-1,3-thiazol-4-yl)chromen-2-ones. The study of antimicrobial activity of the obtained compounds allowed to identify active samples against E. coli and P. aeruginosa strains. Among the tested compounds, 8-methoxy-3-{2-[(2-methoxyphenyl)amino]-5-methyl-1,3-thiazol-4-yl]-2H-chromen-2-one showed higher activity than the reference drug Streptomycin against E. coli strain. Some compounds showed high activity against P. aeruginosa. Docking studies of the synthesized compounds indicated that they can bind in the active site to bacterial tRNA (guanine37-N1)-methyltransferase.

Conclusions. Novel derivatives of 2H-chromen-2-ones with 2-N-(aryl, acyl)amino-5-methyl-1,3-thiazol moiety at the position 3 were obtained by the Hantzsch thiazole synthesis starting from 3-(2-bromopropanoyl)-2H-chromen-2-ones. Studies of antimicrobial activity allowed to identify new 2H-chromen-2-one derivatives as equipotent antimicrobial agents to the reference drug Streptomycin or even more potent. The docking studies revealed that the synthesized compounds may be inhibitors of tRNA (guanine37-N1)-methyltransferase, which is a crucial enzyme for survival of different bacteria, e.g. P. aeruginosa during stress conditions.

Keywords: coumarin, thiazole, antimicrobials, alkyl-group, synthesis

1. Introduction
Coumarin (2H-chromen-2-one) is the part of many compounds with antimicrobial and antifungal activity [1–4]. The recent studies show that 2H-chromen-2-ones can reduce the bacterial biofilm formation for some strains of bacteria as the result making them less antibiotic resistant [5–8]. The results of drug design research also show promising antimicrobial effect of 3-(2-N-R-amino-1,3-thiazol-4-yl)-2H-chromen-2-ones [9–11].

These compounds in most cases are prepared by the Hantzsch thiazole synthesis method using the reaction of thiocarboxamides [10–12] with the widely known 3-(2-bromobenzooyl)-2H-chromen-2-ones [13–15]. It is interesting that 3-propanoyl-2H-chromen-2-ones [16, 17] were already reported, but the data about their keto-fragment α-bromination, their application as intermediates for synthesis of 3-(2-N-R-amino-5-alkyl-1,3-thiazol-4-yl)-2H-chromen-2-ones as well as the data about their biological activity have not been published.

The aim of this work is to study methods of 3-(2-N-(aryl, acyl)amino-5-methyl-1,3-thiazol-4-yl)-2H-chromen-2-ones preparation and investigate their antimicrobial activity.

2. Planning (methodology) of the research
In order to obtain the target 3-(2-N-(aryl, acyl)amino-5-methyl-1,3-thiazol-4-yl)-2H-chromen-2-ones as the objects for further antimicrobial studies, the possibility of application of 3-(α-bromoacetyl)2H-chromen-2-ones bromination procedure for preparation of 3-(2-bromopropanoyl)-2H-chromen-2-ones form 3-propanoyl derivatives should have been studied. The scope and limitations of the Hantzsch thiazole synthesis using 3-(2-bromopropanoyl)-2H-chromen-2-ones and substituted thioureas should be experimentally investigated, the procedure improvement should be suggested if needed. The further antimicrobial activity screening was planned as well as its results' analysis with computational chemistry methods.

3. Materials and methods
Chemical experiments. 1H NMR spectra were recorded on Varian Mercury-200 (200 MHz), 13C NMR spectra were acquired on Bruker Avance 500 (500 MHz) and 13C NMR (125 MHz) in DMSO-d₆ and CDCl₃. TMS was used as internal standard. LC-MS analysis of compounds was performed on an Agilent
3. Materials and methods

Chemical experiments. ¹H NMR spectra were recorded on Varian Mercury-200 (200 MHz), ¹³C NMR spectra were acquired on Bruker Avance 500 ¹H NMR (500 MHz) and ¹³C NMR (125 MHz) in DMSO-d₆ and CDCl₃. TMS was used as internal standard. LC-MS analysis of compounds was performed on an Agilent 1100 HPLC instrument with diode array and mass-selective detectors (Agilent LC-MSD SL), Zorbax SB-C18 column (4.6×15 mm) with chemical ionization at atmospheric pressure (APCI). Elemental analysis was performed on a EuroVector EA-3000 instrument. Melting points were determined on a Kofler bench. All solvents and reagents were commercially available. A study of antimicrobial activity of compounds 4 was performed by agar well diffusion method [18, 19]. The concentration of microbial cells was determined by McFarland standard [20]; the value was 10⁷ cells in 1 ml of the media. The 18-24 hours culture of microorganisms was used for tests. For the bacteria cultivation, Müller-Hinton agar was used and Sabouraud agar was applied for C. albicans cultivation. The compounds were tested as the DMSO solution (concentration 100 µg per mL); the volume of the solution was 0.3 mL (the same as Streptomyces). Each experiment was repeated thrice. The antibacterial activity was estimated by the growth inhibition zone diameter for each microorganism [18].

The docking studies were performed using AutoDock Vina [21]. Docking studies were performed for flexible ligands and rigid models of proteins. Crystallographic data for tRNA (guanine-37-N1)-methyltransferase (EC2.1.1.228; TrmD) (5ZH[7]) and its active sites was obtained from the Protein Data Bank [22].

3-Propanoyl-2H-chromen-2-ones were prepared according to the known methods [16, 17].

3-(2-Bromopropanoyl)-2H-chromen-2-ones (general method).

3-Propanoyl-2H-chromen-2-one 1 (0.1 mole) was dissolved in 160 ml of chloroform. The bromine solution (0.1 mole, 5.2 ml in 16 ml of chloroform) was added dropwise to the solution of 1 stirring at room temperature. The reaction mixture was stirred and slightly heated (to 40–50 °C) until hydrogen bromide evolution was complete and absorbed by 10 % water solution of NaOH. Then, 70 % of the solvent volume was evaporated and allowed to cool. Crystals, which were formed were collected by filtration and gently washed with small portions of chloroform and ethanol.

3-(2-Bromopropanoyl)-2H-chromen-2-one (2a).

The compound was obtained in 85 % yield as a yellow powder; ¹H NMR (500 MHz, CDCl₃): δ 1.88 (d, 3H, J=6.5 Hz, CH₃), 5.91 (q, 1H, J=6.5 Hz, CH), 7.33 – 7.45 (m, 2H, H Ar), 7.64 – 7.74 (m, 2H, H Ar), 8.59 (s, 1H, H-4); ¹³C NMR (125 MHz, CDCl₃): δ 19.3, 45.9, 116.8, 118.2, 122.8, 125.1, 130.0, 143.6, 149.0, 155.2, 158.5, 191.7. LC-MS, m/z: 281 [M+H]⁺. Mp 153 – 155 °C. Anal. Caled for C₁₁H₁₂BrO₃: C, 51.43; H, 3.35.

3-(2-Bromopropanoyl)-8-methoxy-2H-chromen-2-one (2b).

The compound was obtained in 76 % yield as a yellow powder; ¹H NMR (500 MHz, CDCl₃): δ 1.85 (d, 3H, J=6.5 Hz, CH₃), 5.95 (q, 1H, J=6.5 Hz, CH), 7.17 – 7.31 (m, 3H, H Ar), 8.55 (s, 1H, H-4); ¹³C NMR (125 MHz, CDCl₃): δ 19.3, 45.9, 56.3, 116.1, 118.8, 121.1, 123.0, 125.0, 144.8, 147.1, 149.1, 158.0, 191.8. LC-MS, m/z: 312 [M+H]⁺. Mp 110 – 112 °C. Anal. Caled for C₁₃H₁₂BrO₃: C, 50.19; H, 3.56. Found: C, 50.37; H, 3.60.

3-(2-N-Amino-5-alkyl-1,3-thiazol-4-yl)-2H-chromen-2-ones (4 general method). To the solution of 3-(2-bromopropanoyl)-2H-chromen-2-one 2 (1 mmole) in the minimal amount of 2-propanol, the solution of thiourea 3 (1 mmole) was added. Almost immediately after addition, the formation of clear solution was observed and after 4-10 minutes, the product precipitated. The mixture was additionally stirred at reflux for 1 hour and then cooled down to room temperature. The reaction mixture was neutralized with ammonium hydroxide solution. The precipitate was collected by filtration and dried.

3-(2-Amino-5-methyl-1,3-thiazol-4-yl)-2H-chromen-2-one (4a). The compound was obtained in 75 % yield as a yellow powder; ¹H NMR (200 MHz, DMSO-d₆): δ 2.15 (s, 3H, CH₃), 6.85 (br. s, 2H, NH₃), 7.36 (t, 1H, J=7.5 Hz, H-8), 7.42 (d, 1H, J=8.2 Hz, H-6), 7.61 (t, 1H, J=7.2 Hz, H-7), 7.77 (d, 1H, J=7.0 Hz, H-5), 8.14 (s, 1H, H-4); ¹³C NMR (100 MHz, DMSO-d₆): δ: 12.4, 116.4, 119.4, 119.5, 122.2, 125.1, 129.1, 132.4, 138.2, 143.3, 153.5, 159.0, 165.6. LC-MS, m/z: 259 [M+H]⁺. Mp 216 – 218 °C. Anal. Caled for C₁₁H₁₂N₂O₂S: C, 60.45; H, 3.90; N, 10.85. Found: C, 60.56; H, 4.05; N, 10.74.

3-(2-Amino-5-methyl-1,3-thiazol-4-yl)-8-methoxy-2H-chromen-2-one (4b). The compound was obtained in 82 % yield as a yellow powder; ¹H NMR (400 MHz, DMSO-d₆): δ 2.17 (s, 3H, CH₂), 3.92 (s, 3H, OCH₃), 6.97 (br. s, 2H, NH₃), 7.27-7.33 (m, 3H, H Ar), 8.09 (s, 1H, H-4); ¹³C NMR (100 MHz, DMSO-d₆): δ 11.9, 56.0, 114.0, 119.0, 119.5, 121.7, 124.2, 124.5, 138.7, 142.3, 142.7, 146.2, 158.2, 164.9. LC-MS, m/z: 289 [M+H]⁺. Mp 205 – 207 °C. Anal. Caled for C₁₂H₁₃N₂O₃S: C, 58.32; H, 4.20; N, 9.72. Found: C, 58.51; H, 4.14; N, 9.69.

N-[5-methyl-4-(2-oxo-2H-chromen-3-yl)-1,3-thiazol-2-yl]acetamide (4c).

The compound was obtained in 86 % yield as a yellow powder; ¹H NMR (400 MHz, DMSO-d₆): δ 2.13 (s, 3H, CH₃), 2.32 (s, 3H, CH₃), 7.38 (t, 1H, J=7.1 Hz, H-8), 7.44 (d, 1H, J=8.2 Hz, H-6), 7.63 (t, 1H, J=7.6 Hz, H-7), 7.78 (d, 1H, J=7.6 Hz, H-5), 8.17 (s, 1H, H-4), 12.12 (br. s, 1H, NH); ¹³C NMR (100 MHz, DMSO-d₆): δ: 11.9, 22.8, 116.4, 119.4, 122.8, 125.1, 125.4, 129.1, 132.4, 139.4, 143.5, 153.6, 154.7, 159.0, 168.8. LC-MS, m/z: 301 [M+H]⁺. Mp 257 – 258 °C. Anal. Caled for C₁₄H₁₂N₂O₃S: C, 59.99; H, 4.03; N, 9.33. Found: C, 60.18; H, 4.22; N, 9.50.
N-[4-(8-methoxy-2-oxo-2H-chromen-3-yl)-5-methyl-1,3-thiazol-2-yl]acetamide (4d). The compound was obtained in 91% yield as a yellow powder; 1H NMR (400 MHz, DMSO-d6): δ 2.15 (s, 3H, CH3), 2.34 (s, 3H, CH3), 3.97 (s, 3H, OCH3), 7.24-7.35 (m, 3H, H Ar), 8.09 (s, 1H, H-4), 11.80 (br. s, 1H, NH); 13C NMR (100 MHz, DMSO-d6): δ 11.4, 22.3, 56.1, 114.2, 119.4, 121.0, 121.5, 122.2, 123.2, 125.0, 130.6, 139.9, 142.9, 143.4, 146.8, 148.4, 158.8, 160.8. LC-MS, m/z: 395 [M+H]+. Mp 193 – 195 °C. Anal. Calcd for C21H17N2O4S: C, 63.95; H, 4.60; N, 7.10. Found: C, 64.23; H, 4.61; N, 7.29.

4. Results

The key intermediates – 3-((2-bromopropanoyl)-2H-chromen-2-ones 2 were prepared by bromination of the known 3-propanoyl-2H-chromen-2-ones 1 in order to synthesize novel 3-(2-N-arylamino-1,3-thiazol-4-yl)-2H-chromen-2-ones derivatives and study their antimicrobial activity (Fig. 1). The obtained compounds 2 are crystalline solids. Their 1H NMR spectra contain signals of CH3CHBr- fragment as a doublet at 1.85-1.88 ppm and a quartet at 5.91-5.95 ppm with 6.5 Hz spin-spin coupling constant.

For construction of the thiazole cycle of 3-(2-N-arylamino-1,3-thiazol-4-yl)-2H-chromen-2-ones 3, the reaction of 2 with substituted thioureas 3 was performed (Fig. 1). The synthesis was carried out in 2-propanol media at reflux. The target compounds 4 were isolated after the treatment of the reaction mixture with aqueous solution of ammonia. The obtained 3-(2-N-arylamino-5-alkyl-1,3-thiazol-4-yl)-2H-chromen-2-ones 4 in 1H NMR spectra have the signals of amino-group protons in the region 6.85 – 6.97 ppm for the derivatives 4a,b while for the aryl-substituted compounds 4c,d the signal of NH-group is shifted downfield to 9.38 – 10.07 ppm and for the acetamides 4e,f the NH-group signal is observed in the region 11.80 – 12.12 ppm.

The antimicrobial activity of the obtained compounds 4 was studied by agar well diffusion method using the standard strains of microorganisms [18]. It was found that compounds 4b, 4c, and 4e inhibit the growth of the S. aureus strain. As far as compounds 4b and 4e are concerned, they also inhibit growth of E. coli, but their activity is smaller than it is for the reference drug Streptomycin (Table 1).

The compounds 4b, 4c, and 4f showed similar activity against P. aeruginosa. The antimicrobial activity against the E. coli strain of the compound 4f appeared to be higher than the activity of the reference drug Streptomycin.

The obtained results of antimicrobial activity screening revealed the growth-inhibitory activity of the most of compounds 4 against the P. aeruginosa bacterial strain, which is known to be highly resistant for a variety of modern antibiotics. They do not have bactericidal activity for this microorganism which quickly adapts for a new antibiotic [23]. Therefore we decided to perform the computer docking study of the obtained compounds with the aim to see whether they could be selective inhib-

Fig. 1. Synthesis of 3-(2-N-(aryl/acyl)amino-5-methyl-1,3-thiazol-4-yl)-2H-chromen-2-ones: 1a R=H; 1b R=8-OCH3; 2a R=H; 2b R=8-OCH3; 3a R1=R2=H; 3b R1=R2=COCH3; 3c R1=Ph; 3d R1=2-(OCH3)C6H4; 4a R=H, R′=H; 4b R=8-OCH3, R′=H; 4c R=H, R′=COCH3; 4d R=8-OCH3, R′=COCH3; 4e R=8-OCH3, R′=Ph; 4f R=8-OCH3, R′=2-(OCH3)C6H4
itors of tRNA (guanine37-N1)-methyltransferase (EC2.1.1.228; TrmD), which is known to be the crucial enzyme for survival of bacterial (also *Pseudomonas aeruginosa*) at a moment of stress [24].

**Table 1**

| Compd. number | Diameters of growth inhibition zones in mm. |
|---------------|---------------------------------------------|
|               | **S. aureus** | **E. coli ATCC 25922** | **P. vulgaris ATCC 4636** | **P. aeruginosa ATCC 27853** | **B. subtilis ATCC 6633** | **C. albicans ATCC 653/885** |
| 4a            | 19, 19, 20    | 20, 19, 19              | 17, 16, 16                | 19, 19, 20                    | 19, 18, 19                | 18, 17, 17                    |
| 4b            | 24, 25, 25    | 23, 24, 24              | 20, 20, 19                | 23, 22, 22                    | 20, 21, 22                | 22, 21, 21                    |
| 4c            | 22, 23, 22    | 18, 19, 18              | 17, 16, 16                | 22, 20, 21                    | 21, 21, 20                | 19, 19, 20                    |
| 4d            | 18, 19, 19    | 17, 17, 18              | 16, 15, 17                | 20, 21, 21                    | 20, 21, 21                | 17, 17, 17                    |
| 4e            | 24, 24, 25    | 23, 24, 24              | 17, 16, 17                | 22, 23, 22                    | 23, 23, 22                | 20, 18, 29                    |
| 4f            | 19, 20, 19    | 27, 28, 28              | 17, 17, 17                | 23, 24, 23                    | 19, 19, 20                | 17, 16, 16                    |
| Strept.*      | 30, 31, 29    | 24, 24, 25              | 25, 26, 24                | 25, 24, 25                    | 27, 26, 25                | 14, 13, 14                    |

*Streptomycin*

**Table 2**

| Compd. number | affinity, kcal/mole | ligand binding with the active site (+/-) | amino acids of the active site interacting with the ligand |
|---------------|---------------------|------------------------------------------|---------------------------------------------------------|
| 4a            | -7.4                | PRO-94; TYR-120; VAL-142; ASP-178; GLY-179; LEU-180; LEU-181; ASP-182 |
| 4b            | -6.7                | PRO-94; ARG-119; TYR-120; VAL-142; LEU-143; GLY-145; ARG-159; ASP-178 |
| 4c            | -8.1                | PRO-94; GLN-95; TYR-120; VAL-142; LEU-143; GLN-101; ARG-105; ASP-178; GLY-179; LEU-180; LEU-181; ASP-182 |
| 4d            | -8.0                | PRO-94; TYR-120; ASP-140; TYR-141; ASP-178; GLY-179; LEU-180; ASP-182 |
| 4e            | -8.9                | PRO-94; GLN-95; TYR-120; VAL-142; GLN-101; ARG-159; ASP-178; GLY-179; LEU-181; ASP-182; HIS-185 |
| 4f            | -9.1                | TYR-91; PRO-94; GLN-95; ARG-119; TYR-120; GLY-122; TYR-141; VAL-142; GLY-179; LEU-180; LEU-181; ASP-182; LEU-228 |

The results of antimicrobial activity screening for compounds 4 (concentration 100 µg per mL) present the research where 3-(thiazol-4-yl)-2H-chromen-2-ones inhibited the growth of *S. aureus* ATCC 25923 and *H. influenzae* ATCC 10211 strains at higher level than Tetracycline and were even able to inhibit *M. tuberculosis* H37Rv ATCC 27294. Although the inhibitory concentration for the tested compounds was tenfold higher than those of Isoniazid.

The computer docking results for binding of compounds 4 with PaTrmDc in comparison with its known selective inhibitor showed that all of them are able to bind the active site of the enzyme (Table 2). On the other hand the decrease in polarity of the substituent at position 2 of the thiazole increases the affinity of the ligand towards the target.

**5. Discussion**

The previously reported results [10] show that the derivatives of 8-ethoxy-2H-chromen-2-one bearing the fragment of thiazole at position 3 can inhibit the growth of *B. bronchiseptica* ATCC 4617 and *B. pumilus* ATCC 14884 better than the reference drug Ampicillin. The promising antibacterial inhibitory concentrations were reported for the compounds with the similar structures bearing 5-methoxy-2H-chromen-2-one fragment and 2-bromophenylamino or 3,4-dichlorophenyl in 2-aminothiazole moiety (60-73 µM) [9]. The other paper [11] presents the research where 3-(thiazol-4-yl)-2H-chromen-2-ones inhibited the growth of *S. aureus* ATCC 25923 and *H. influenzae* ATCC 10211 strains at higher level than Tetracycline and were even able to inhibit *M. tuberculosis* H37Rv ATCC 27294. Although the inhibitory concentration for the tested compounds was tenfold higher than those of Isoniazid.

The results of our chemical experiments show the successful bromination of 3-propanoyl-2H-chromen-2-ones, and also perfect results in the Hantzsch thiazole synthesis as the key-step for preparation of the novel target 3-(2-N-(arylacetyl)amino-5-methyl-1,3-thiazol-4-yl)-2H-chromen-2-ones. Therefore, our research revealed the possibility of synthesis of 3-(thiazol-4-yl)-2H-chromen-2-ones' analogues with the methyl group at position 5 of thiazole. It has been also shown that the synthesized compounds can effectively inhibit the growth of *S. aureus* ATCC 25923, *E. coli* ATCC 25922 and *P. aeruginosa* ATCC 27853 and are also able to
show better inhibitory results than the reference drug Streptomycin.

The results of the docking studies of the target compounds as the ligands for bacterial tRNA (guanine37-N1)-methyltransferase obviously show that the introduction of the substituted phenyl substituents to amino-group of the thiazole moiety in the core 3-(2-amino-5-methyl-1,3-thiazol-4-yl)-2H-chromen-2-one is favourable for interaction with the enzyme. It also correlates with the results of agar-well diffusion screening results because the compounds 4e and 4f, which display promising docking results, also have the largest growth inhibition zones. Therefore, the docking modelling of interaction of the 3-(2-amino-5-methyl-1,3-thiazol-4-yl)-2H-chromen-2-one derivatives with tRNA (guanine37-N1)-methyltransferase could be useful at the stage of pre-screening filtration of virtual libraries of the compounds planned for further antimicrobial activity search.

**Study limitations.** As far as this research contains only primary screening results on the activity of 3-(2-amino-5-methyl-1,3-thiazol-4-yl)-2H-chromen-2-ones against the standard strains of microorganisms the clear obstacle for the research expand is the availability of the clinical strains of the corresponding bacteria.

**Prospects for further research.** The developed methods for synthesis of 3-(2-amino-5-methyl-1,3-thiazol-4-yl)-2H-chromen-2-ones allow to vary the substituents in both heterocyclic fragments. Therefore, the promising strategy of the further investigation is the synthesis of the lead compounds identified after the preliminary screening of the virtual libraries of 3-(2-amino-5-methyl-1,3-thiazol-4-yl)-2H-chromen-2-ones as to their ability to bind the active site of the bacterial tRNA (guanine37-N1)-methyltransferase.

**6. Conclusions**

By the Hantzsch thiazole synthesis, the derivatives of 2H-chromen-2-ones having the fragment of 2-N-(aryl,acyl)amino-5-methyl-1,3-thiazol at the position 3 were obtained. The study of antimicrobial activity of the synthesized compounds allowed for identification of the 2H-chromen-2-ones derivatives as compounds of similar of better activity than the reference drug Streptomycin. The docking studies revealed that the synthesized compound may be inhibitors of tRNA (guanine37-N1)-methyltransferase, which is a crucial enzyme for survival of different bacteria e.g. *P. aeruginosa* during stress conditions.

**Conflict of interests**

The authors declare that they have no conflict of interests.

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**References**

1. Singh, L. R., Avula, S. R., Rai, S., Srivastava, A., Palnati, G. R., Tripathi, C. K. M. et. al. (2017). Coumarin-benzimidazole hybrids as a potent antimicrobial agent: synthesis and biological elevation. The Journal of Antibiotics, 70 (9), 954–961. doi: http://doi.org/10.1038/ja.2017.70

2. Fotso, G. W., Ngamenni, B., Storr, T. E., Ngadjui, B. T., Mafu, S., Stephenson, G. R. (2020). Synthesis of Novel Stilbene–Coumarin Derivatives and Antifungal Screening of Monotes kerstingii-Specialized Metabolites Against Fusarium oxysporum. Antibiotics, 9 (9), 537. doi: http://doi.org/10.3390/antibiotics9090537

3. Sanduja, M., Gupta, J., Singh, H., Pagare, P. P., Rana, A. (2020). Uracil-coumarin based hybrid molecules as potent anticancer and anti-bacterial agents. Journal of Saudi Chemical Society, 24 (2), 251–266. doi: http://doi.org/10.1016/j.jscs.2019.12.001

4. Mahmoud, M. R., El-Shahawi, M. M., Abu El-Azm, F. S., Abdeen, M. (2017). Synthesis and Antimicrobial Activity of Polynuclearly Substituted Heterocyclic Compounds Derived from 5-Cinnamoylamino-2-Cyanomethyl-1,3,4-Thiadiazole. Journal of Heterocyclic Chemistry, 54 (4), 2352–2359. doi: http://doi.org/10.1002/jhet.2824

5. Reen, F. J., Gutiérrez-Barranquero, J. A., Parages, M. L., O’Gara, F. (2018). Coumarin: a novel player in microbial quorum sensing and biofilm formation inhibition. Applied Microbiology and Biotechnology, 102 (5), 2063–2073. doi: http://doi.org/10.1007/s00253-018-8778-x

6. Yang, L., Li, S., Qin, X., Jiang, G., Chen, J., Li, B. et. al. (2017). Exposure to Umbelliferone Reduces Ralstonia solanacearum Biofilm Formation, Transcription of Type III Secretion System Regulators and Effectors and Virulence on Tobacco. Frontiers in Microbiology, 8. doi: http://doi.org/10.3389/fmicb.2017.01234

7. Zhang, S., Liu, N., Liang, W., Han, Q., Zhang, W., Li, C. (2016). Quorum sensing-disrupting coumarin suppressing virulence phenotypes in Vibrio splendidus. Applied Microbiology and Biotechnology, 101 (8), 3371–3378. doi: http://doi.org/10.1007/s00253-016-8009-3

8. Ojima, Y., Nunogami, S., Taya, M. (2016). Antibiofilm effect of warfarin on biofilm formation of Escherichia coli promoted by antimicrobial treatment. Journal of Global Antimicrobial Resistance, 7, 102–105. doi: http://doi.org/10.1016/j.jgar.2016.08.003

9. Osman, H., Yusufzai, S. K., Khan, M. S., Abd Razik, B. M., Sulaiman, O., Mohamad, S. et. al. (2018). New thiazolyl-coumarin hybrids: Design, synthesis, characterization, X-ray crystal structure, antibacterial and antiviral evaluation. Journal of Molecular Structure, 1166, 147–154. doi: http://doi.org/10.1016/j.molstruc.2018.04.031

10. Arshad, A., Osman, H., Bagley, M. C., Lam, C. K., Mohamad, S., Zahariuluddin, A. S. M. (2011). Synthesis and antimicrobial properties of some new thiazolyl coumarin derivatives. European Journal of Medicinal Chemistry, 46 (9), 3788–3794. doi: http://doi.org/10.1016/j.ejmech.2011.05.044

11. Mohamed, H. M., El-Wahab, A. H. F. A., Ahmed, K. A., El-Agropy, A. M., Bedair, A. H., Eid, F. A., Khafagy, M. M. (2012). Synthesis, Reactions and Antimicrobial Activities of 8- Ethanocycomarin Derivatives. Molecules, 17 (1), 971–988. doi: http://doi.org/10.3390/molecules17010971

12. Zhuravel, L., Kovalenko, S., Vlasov, S., Chernykh, V. (2005). Solution-phase Synthesis of a Combinatorial Library of 3-[4-(Coumarin-3-yl)-1,3-thiazol-2-ylcarbamoyl]propanoic acid Amides. Molecules, 10 (2), 444–456. doi: http://doi.org/10.3390/10020444

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13. Khan Yusufzai, S., Osman, H., Khan, M. S., Mohamad, S., Sulaiman, O., Parunasivam, T. et al. (2017). Design, characterization, in vitro antibacterial, antitubercular evaluation and structure–activity relationships of new hydrazinyl thiazolyl coumarin derivatives. Medicinal Chemistry Research, 26 (6), 1139–1148. doi: http://doi.org/10.1007/s00044-017-1820-2

14. Hamdi, M., Talhi, O., Silva, A., Lechani, N., Kheddis-Boutemer, B., Laichi, Y., Bachari, K. (2018). Synthetic Approach Toward Heterocyclic Hybrids of 1,2,4Triazolo[3,4-b][1,3,4]thiadiazines. Synlett, 29 (11), 1502–1504. doi: http://doi.org/10.1055/s-0036-1591991

15. Bag, S., Ghosh, S., Tulsan, R., Sood, A., Zhou, W., Schifone, C. et al. (2013). Design, synthesis and biological activity of multifunctional a,b-unsaturated carbonyl scaffolds for Alzheimer’s disease. Bioorganic & Medicinal Chemistry Letters, 23 (9), 2614–2618. doi: http://doi.org/10.1016/j.bmcl.2013.02.103

16. Banerjee, A., Santra, S. K., Mishra, A., Khatun, N., Patel, B. K. (2015). Copper(i)-promoted cycloalkylation–peroxidation of unactivated alkenes via sp3C–H functionalisation. Organic & Biomolecular Chemistry, 13 (5), 1307–1312. doi: http://doi.org/10.1039/c4ob01962h

17. Widman, O. (1918). Über eine neue Gruppe von Cyclopropan-Derivaten. I: Die Einwirkung von Phenyl-acetylhalogeniden auf 3-Acidyl-cumarine bei Gegenwart von Natriumalkoholat. Berichte Der Deutschen Chemischen Gesellschaft, 51 (1), 533–541. doi: http://doi.org/10.1002/cber.19180510165

18. Coyle, M. B. (2005). Manual of antimicrobial susceptibility testing. Washington, 29–39.

19. Bacteriological Control of Growth Media (2001). Information Letter of the Ukraine Ministry of Health No. 05.4.1/1670. Kyiv.

20. McFarland, J. (1907). The nephelometer: an instrument for estimating the number of bacteria in suspensions used for calculating the opsonic index and for vaccines. JAMA: The Journal of the American Medical Association, 49 (14), 1176–1178. doi: http://doi.org/10.1001/jama.1907.25320140022001f

21. Trot, O., Olson, A. J. (2010). AutoDock Vina: improving the speed and accuracy of docking with a new scoring function, efficient optimization, and multithreading. Journal of Computational Chemistry, 31 (2), 455–461. doi: http://doi.org/10.1002/jcc.21334

22. Zhong, W., Pasunooti, K. K., Balamkundu, S., Wong, Y. W., Nah, Q., Liu, C. F. et al. (2019). Crystal structure of TrmD from Pseudomonas aeruginosa in complex with active-site inhibitor. doi: http://doi.org/10.2210/pdb5zlh/pdb

23. Lazareva, A. V., Tchebotar, I. V., Kryzhanovskaya, O. A., Tchebotar, V. I., Mayanskiy, N. A. (2015). Pseudomonas aeruginosa: Pathogenesis, Pathogenesis and Diseases. Clinical Microbiology and Antimicrobial Chemotherapy, 17 (3), 170–186.

24. Zhong, W., Pasunooti, K. K., Balamkundu, S., Wong, Y. H., Nah, Q., Gadi, V. et al. (2019). Thienopyrimidinone Derivatives That Inhibit Bacterial tRNA (Guanine37-N1)-Methyltransferase (TrmD) by Restructuring the Active Site with a Tyrosine-Flipping Mechanism. Journal of Medicinal Chemistry, 62 (17), 7788–7805. doi: http://doi.org/10.1021/acs.jmedchem.9b00582

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