Synthesis and antimicrobial activity of acridine carboxylic acid derivatives containing a piperazine moiety

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A convenient method for the synthesis of new acridine derivatives containing a piperazine moiety was developed. Antimicrobial activity against some pathogenic microorganisms was established for a series of the synthesized compounds.

Key words: acridine, piperazine, nitrofuran, antibacterial activity.

Biological activity of 9-oxoacridines is presently being studied actively.[1] The antibacterial properties characteristic of compounds of this class are attributed to the intercalating abilities of the acridine cycle. At the same time, the 9-oxoacridine derivatives exhibit antitumor, antiviral, and other types of biological activity.[2—7]

Search for novel drugs performed by the modification of known pharmaceuticals is one of trends aimed at improving drugs, enhancing therapeutical efficiency, and diminishing possible side effects. In continuation of our studies[8] on the synthesis and investigation of antibacterial activity of new compounds in the series of 9-oxoacridines, we obtained new derivatives of acridoneacetic acid (AAA), 9-oxo-9,10-dihydroacridine-2-carboxylic acid, 9-oxo-9,10-dihydroacridine-4-carboxylic acid, and acridine-9-carboxylic acid containing the pharmacophoric moiety of 5-nitrofuran.

It is known that the 5-nitrofuran derivatives possess a wide range of biological activity against bacterial, viruses, and protozoa and can act on strains resistant to many antibiotics.[9—11] For example, Furacilin (nitrofural, semicarbazone-5-nitrofurfural) is among widely used pharmaceuticals of this series.

An important task in the synthesis of target compounds is to choose the unit connecting the acridine and 5-nitrofuran moieties. We chose the piperazine cycle, which is makes it possible, being fairly convenient moiety for the construction of organic molecules, to functionalize the molecule of acridinecarboxylic acids for further procedures.

It was found that AAA (**1**) and acridine-9(10*H*)-one-4-carboxylic acid (4-carboxyacridone, **2**) rapidly react with 1,1′-carbonyldiimidazole (CDI) in dimethylformamide (DMF) to form imidazolide, which reacts readily with aliphatic and aromatic amines and alcohols. Unlike other methods of carboxyl group activation (for example, using dicyclohexyl carbodiimide) the by-product (imidazole) is easily washed off with water to give the pure product without additional purification stages. Intermediates products **3** and **4** were thus synthesized and then subjected to quaternization to the corresponding quaternary salts **5a**,**b** and **6a**,**b** (Scheme 1).

However, we failed to activate acridine-9-carboxylic (**7**) and 9-oxo-9,10-dihydroacridine-2-carboxylic (2-carboxyacridone) (**8**) acids with CDI and, hence, derivatives **9** and **10** of these acids were obtained *via* the corresponding acid chlorides, which were further transformed into the corresponding quaternary salts **11a**,**b** and **12a**,**b** (Scheme 2).

Note that an excess of thionyl chloride is needed for the synthesis of acridine-9-carboxylic acid chloride. At the same time, 9-chloroacridine-2-carbonyl chloride is formed by the treatment of 2-carboxyacridone with thionyl chloride excess and, therefore, equivalent amounts of thionyl chloride and 2-carboxyacridone should be used to obtain acridone-2-carbonyl chloride. Since the starting compounds **3**, **4**, **9**, and **10** are highly soluble in acetonitrile, quaternization proceeds almost quantitatively and the quaternary salts formed in the reaction precipitate. As a result, high yields and purity of the products can be achieved.

For the synthesis of the acridine derivatives containing the 5-nitrofuran-2-carboxylic acid and 2-methyl-5-nitrofuran moiety, the studied acridinecarboxylic acids were amidated with 1-(*tert*-butoxycarbonyl)piperazine. Then the *tert*-butoxycarbonyl group (Boc) was removed using trifluoroacetic acid (TFA). As a result, the synthetic blocks (**13a—c**) bearing the highly reactive secondary amino group were obtained in good yields. Unlike the NH group of acridone, the secondary amino group was easily both acylated by 5-nitrofuranecarboxylic acid and alkylated by 2-bromomethyl-5-nitrofuran (Scheme 3).

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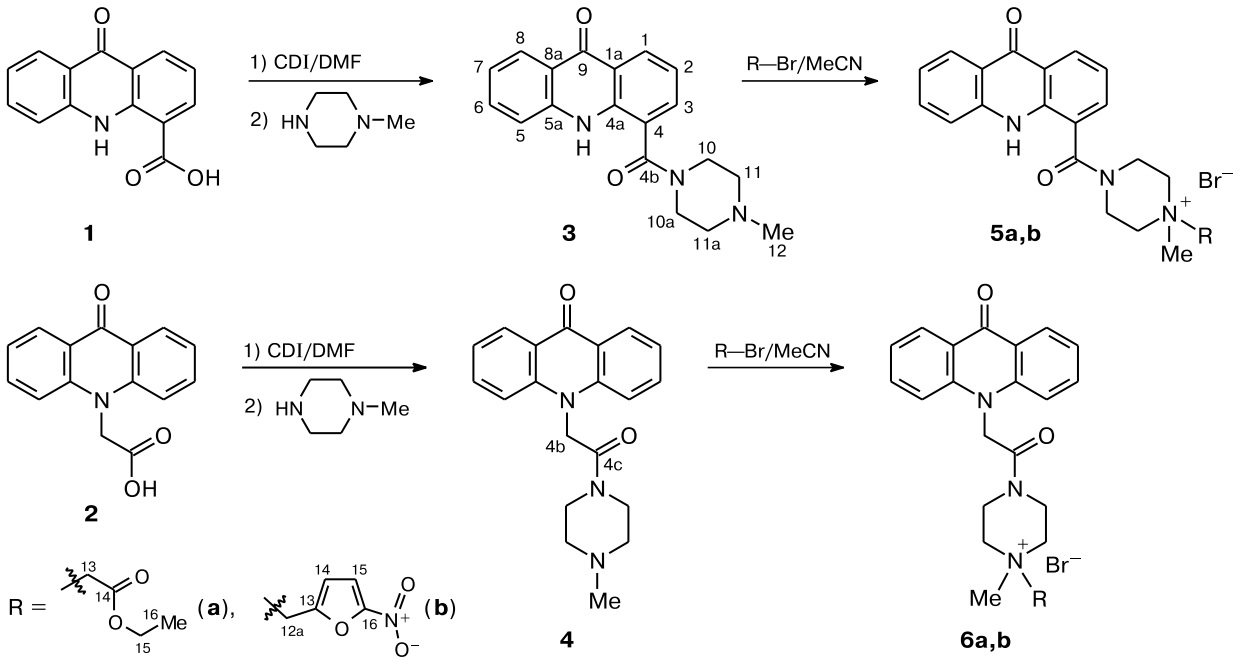
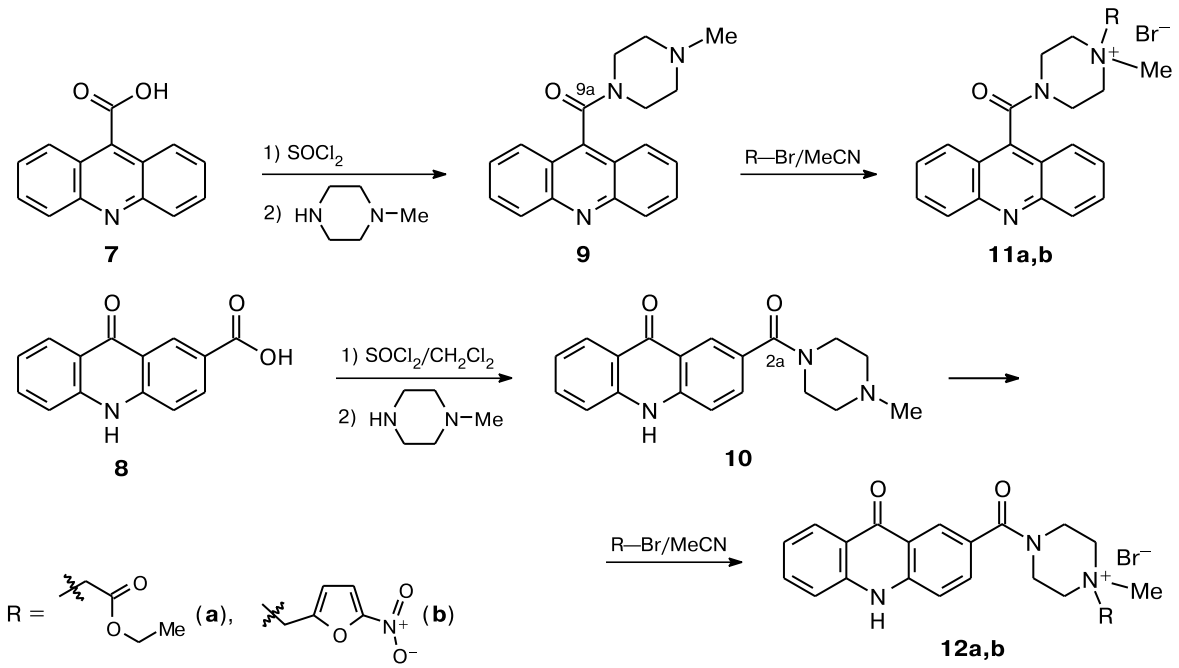
Scheme 1



Scheme 2

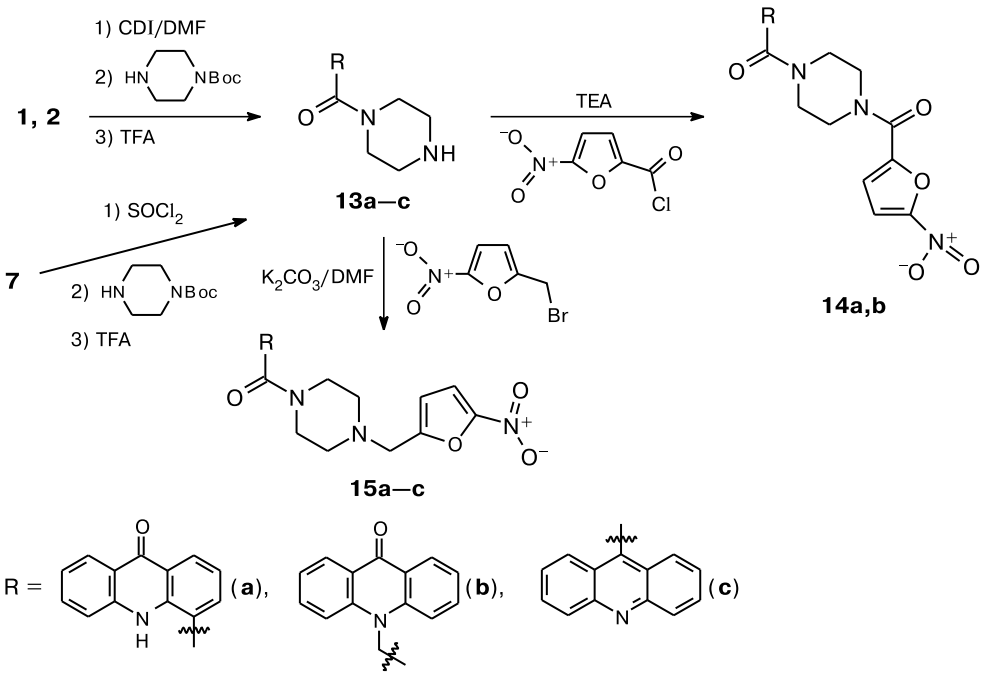


By-products were formed in the alkylation and acylation reactions of derivatives **13a**—**c**. Therefore, the final compounds were purified using preparative chromatography, which made it possible to achieve maximum yields of the compounds.

The antimicrobial activity was tested *in vitro* for heterocyclic derivatives **5b**, **6a**,**b**, **12b**, **14b**, and **15c** against multiple test strains *E. Coli*, *Ps. Aeruginosa*, *Pr. Vulgaris*, *S. Aureus*, *B. Subtilis*, and *Candida albicans* using lactate ethacridine (Rivanol)[2] as a standard. Rivanol is applied in medicine as an antibacterial pharmaceutical. The data obtained are presented in Table 1.

The antimicrobial activity of compounds **5b** and **12b** is comparable with that of Rivanol (pharmaceutical of the

Scheme 3



acridine series), and compound **5b** is characterized by a higher inhibition effect relative to the chosen test strains of microorganisms compared to the standard. Compounds **14b** and **15c** showed moderate activity. Compound **6a** bearing no 5-nitrofuran moiety, as it was assumed, demonstrated the lowest activity among the samples studied.

To conclude, new series of acridine derivatives containing piperazine and nitrofuryl moieties were synthesized, and the possibility to functionalize acridinecarboxylic acids and use them as blocks for further synthetic procedures was shown. The antimicrobial activity of the acridine derivatives was tested. It was found that compound **5b** exerts a higher inhibition effect against the microorganisms than the standard. It follows from this that the 9-oxoacridine derivatives are promising for the synthesis of biologically active compounds.

Experimental

Acridinecarboxylic acids were synthesized according to earlier described procedures.[7,12—14]

The ^1H and ^{13}C NMR spectra of solutions of the tested compounds in DMSO-d_6 were recorded on a Bruker AM-600 spectrometer at a working frequency of 600.13 MHz using Me_4Si as an internal standard. Elemental analysis was carried out on a Thermo Element 2 instrument. Preparative chromatography was conducted on a puriFlash 450 instrument (column 120 g, silica gel 15 μm, eluent $MeCl_2 \rightarrow MeCl_2$—MeOH (95 : 5), flow rate 50 mL min^{-1}).

Synthesis of compounds 3 and 4 (general procedure). Acid **1** or **2** (0.01 mol) was dispersed in DMF (20 mL), CDI (0.01 mol) was added by portions, the mixture was stirred until CO_2 stopped evolving (~20 min), and amine (0.01 mol) was added. The reaction mixture was stirred for 24 h, poured into water (150 mL),

Table 1. Antimicrobial activity of compounds **5b**, **6a,b**, **12b**, **14b**, and **15c**

Tested compound*	Size of bacteriostasis zone/mm					
	E. coli (ATCC 25922)	*Ps. Aeruginosa* (ATCC 27853)	*Pr. vulgaris* (ATCC 4636)	*S. aureus* (ATCC 25923)	*B. subtilis* (ATCC 6633)	*Candida albicans* (NCTC2625)
5b	20±1.1	11.5±1.1	18.5±1.5	20±1.1	19.5±1.5	20±1.3
6a	11.5±0.5	11±0.4	10.5±0.5	9.5±0.5	8.5±0.5	11±0.6
6b	10.5±0.5	13.5±0.5	13	12.5±0.5	15	12.5±0.5
12b	14±0.5	16.5±1.2	18.5±1.5	12.5±0.5	18±0.7	11±1.0
14b	9.5±0.5	9±0.3	12.5±0.5	11±0.6	18±1.0	11.5±0.5
15c	10±0.4	16.5±1.5	13±0.5	12.5±0.5	18±0.7	12.5±0.5
Rivanol	14±0.5	15±0.4	15±0.5	20±0.7	15±0.6	15±0.5

* Concentration 2%.

and cooled down. The precipitated product was filtered off, washed with water, and dried.

4-(4-Methylpiperazine-1-carbonyl)acridin-9(10*H*)-one (3). The yield was 85%, yellow crystals, m.p. 144—146 °C. Found (%): C, 71.52; H, 5.64; N, 12.78. $C_{19}H_{19}N_3O_2$. Calculated (%): C, 71.01; H, 5.96; N, 13.08. ^{1}H NMR, δ: 2.12—2.36 (m, 5 H, C(11)H_2, C(12)H_3); 2.39—2.61 (m, 2 H, C(11a)H_2); 3.09—3.31 (m, 2 H, C(10)H_2); 3.64—3.68 (m, 2 H, C(10a)H_2); 7.28—7.34 (m, 2 H, C(2)H, C(6)H); 7,66 (dd, 1 H, C(5)H, J_1 = 7.2 Hz, J_2 = 1.6 Hz); 7.75 (ddd, 1 H, C(7)H, J_1 = 8.4 Hz, J_2 = 6.9 Hz, J_3 = 1.6 Hz); 7.9 (d, 1 H, C(3)H, J = 8.5 Hz); 8.24 (dd, 1 H, C(8)H, J_1 = 8.0 Hz, J_2 = 1.5 Hz); 8.34 (dd, 1 H, C(1)H, J_1 = 8.0 Hz, J_2 = 1.5 Hz); 10.83 (s, 1 H, NH). ^{13}C NMR, δ: 42.07 (C(10)); 46.09 (C(12)); 47.2 (C(10a)); 54.26 (C(11a)); 55.1 (C(11)); 118.63 (C(8a)); 120.94 (C(5)); 121.1 (C(2)); 121.57 (C(1a)); 122.11 (C(7)); 125.01 (C(4)); 126.26 (C(8)); 127.82 (C(3)); 132.54 (C(6)); 134.16 (C(1)); 137.72 (C(5a)); 141.5 (C(4a)); 166.59 (C(4b)); 177.08 (C(9)).

10-[2-(4-Methylpiperazin-1-yl)-2-oxoethyl]acridin-9(10*H*)-one (4). The yield was 90%, white powder, m.p. 247—249 °C. Found (%): C, 71.95; H, 6.71; N, 12.84. $C_{20}H_{21}N_3O_2$. Calculated (%): C, 71.62; H, 6.31; N, 12.53. ^{1}H NMR, δ: 2.27 (s, 3 H, C(12)H_3); 2.32—2.37 (m, 2 H, C(11a)H_2); 2.49—2.55 (m, 2 H, C(11)H_2); 3.48—3.54 (m, 2 H, C(10a)H_2); 3.7—3.76 (m, 2 H, C(10)H_2); 5.50 (s, 2 H, C(4b)H); 7.34 (t, 2 H, C(2)H, C(7)H, J = 7.4 Hz); 7.53 (d, 2 H, C(4)H, C(5)H, J = 8.7 Hz); 7.77—7.81 (m, 2 H, C(3)H, C(6)H); 8.36 (dd, 2 H, C(1)H, C(8)H, J_1 = 8.0 Hz, J_2 = 1.7 Hz). ^{13}C NMR, δ: 42.08 (C(10)); 44.73 (C(10a)); 46.21 (C(12)); 47.81 (C(4b)); 54.81 (C(11a)); 55.27 (C(11)); 116.54 (C(4), C(5)); 121.78 (C(2), C(7)); 122.02 (C(1a), C(8a)); 126.92 (C(1), (8)); 134.42 (C(3), C(6)); 142.94 (C(4a), C(5a)); 165.2 (C(4c)); 177.2 (C(9)).

Acridin-9-yl(4-methylpiperazin-1-yl)methanone (9). A mixture of acid **7** (10 mmol) and thionyl chloride (10 mL) was refluxed for 4 h. Thionyl chloride excess was distilled off *in vacuo*, benzene (10 mL) was added to the residue, and the solvent was distilled off again. A solution of triethylamine (20 mmol) and *N*-methylpiperazine (10 mmol) in dichloromethane (5 mL) was added to a mixture (cooled to 0 °C) of the acid chloride dried *in vacuo* and dichloromethane (15 mL). The mixture was stirred for 24 h, the solvent was distilled off, water (20 mL) was added, and the mixture was triturated. The precipitate was filtered off and dried. The yield was 95%, yellow crystals, m.p. 167—169 °C. Found (%): C, 75.12; H, 6.56; N, 14.12. $C_{19}H_{19}N_3O$. Calculated (%): C, 74.73; H, 6.27; N, 13.76. ^{1}H NMR, δ: 2.07—2.12 (m, 2 H, C(11)H_2); 2.19 (s, 3 H, C(12)H_3); 2.54—2.59 (m, 2 H, C(11a)H_2); 2.94—2.99 (m, 2 H, C(10)H_2); 3.94—4.01 (m, 2 H, C(10a)H_2); 7.71(ddd, 2 H, C(3)P, C(6)P, J_1 = 8.33 Hz, J_2 = = 6.89 Hz, J_3 = 1.14 Hz); 7.89—7.94 (m, 4 H, C(2)H, C(4)H, C(5)H, C(7)H); 8.21—8.24 (m, 2 H, C(1)H, C(8)H). ^{13}C NMR, δ: 42.08 (C(12)); 44.73 (C(10)); 46.65 (C(10a)); 53.34 (C(11)); 54.8 (C(11a)); 121.88 (C(1a), C(8a)); 125.61 (C(2), C(7)); 127.68 (C(1), C(8)); 130.00 (C(3), C(6)); 131.3 (C(9)); 141.14 (C(4), C(5)); 148.59 (C(4a), C(5a)); 165.24 (C(9a)).

2-(4-Methylpiperazine-1-carbonyl)acridin-9(10*H*)-one (10). A mixture of acid **8** (10 mmol) and thionyl chloride (11 mmol) in dichloromethane (20 mL) was refluxed for 9 h. The solvent was distilled off *in vacuo*, benzene (10 mL) was added, and the solvent was distilled off again. A solution of triethylamine (20 mmol) and *N*-methylpiperazine (10 mmol) in dichloromethane (5 mL) was added to a mixture (cooled to 0 °C) of the acid chloride dried *in vacuo* and dichloromethane (15 mL). The mixture was stirred for 24 h, the solvent was distilled off, water (20 mL) was added, and the mixture was triturated. The precipitate was filtered off and dried. The yield was 77%, yellow crystals, m.p. 187—189 °C. Found (%): C, 71.49; H, 6.16; N, 13.47. $C_{19}H_{19}N_3O_2$. Calculated (%): C, 71.01; H, 5.96; N, 13.08. ^{1}H NMR, δ: 2.22 (s, 3 H, C(12)H_3); 2.28—2.42 (m, 4 H, C(11)H_2, C(11a)H); 3.44—3.73 (m, 4 H, C(10)H_2, C(10a)H); 7.29—7.32 (m, 1 H, C(7)H); 7.55—7.61 (m, 2 H, C(5)H, C(6)H); 7.74—7.8 (m, 2 H, C(3)H, C(4)H); 8.21—8.26 (m, 2 H, C(1)H, C(8)H); 11.95 (s, NH). ^{13}C NMR, δ: 40.5 (C(10), C(10a)); 46.1 (C(12)); 55.04 (C(11), C(11a)); 118.01 (C(5)); 118.08 (C(4)); 120.02 (C(8a)); 121.12 (C(1a)); 122.07 (C(7)); 125.71 (C8)); 126.51 (C(1); 128.46 (C(2)); 132.93 (C(6)); 134.3 (C(3)); 141.31 (C(5a)); 141.94 (C(4a)); 168.99 (C(2a)); 177.07 (C(9)).

Synthesis of compounds 5a,b, 6a,b, 11a,b, and 12a,b (general procedure). A quaternizing agent (3 mmol) was added to a solution of compound **3**, **4**, **9**, or **10** (2 mmol) in acetonitrile (7 mL). The reaction mixture was stirred for 24 h. As a result, the product precipitated, filtered off, washed with acetonitrile and diethyl ether, and dried *in vacuo*.

1-Methyl-1-(2-ethoxy-2-oxoethyl)-4-(9-oxo-9,10-dihydroacridine-4-carbonyl)piperazin-1-ium bromide (5a). The yield was 93%, white crystals, m.p. 190—192 °C. Found (%): C, 56.97; H, 5.66; N, 8.93. $C_{23}H_{26}BrN_3O_4$. Calculated (%): C, 56.56; H, 5.37; N, 8.60. ^{1}H NMR, δ: 1.26 (t, 3 H, C(16)H_3, J = 7.2 Hz); 3.38 (s, 3 H, C(12)H_3); 3.52—4.09 (m, 8 H, C(10)H_2, C(10a)H_2, C(11)H_2, C(11a)H_2); 4.25 (q, 2 H, C(15)H_2, J = 7.2 Hz); 4.66 (br.s, 2 H, C(13)H_2); 7.31 (ddd, 1 H, C(7)H, J_1 = 8.1 Hz, J_2 = 7.0 Hz, J_3 = 1.1 Hz); 7.36 (dd, 1 H, C(6)H, J_1 = 8.5 Hz, J_2 = 7.2 Hz); 7.73—7.79 (m, 2 H, C(2)H, C(5)H); 7.95 (d, 1 H, C(3)H, J = 8.5 Hz); 8.24 (dd, 1 H, C(8)H, J_1 = 8.1 Hz, J_2 = 1.5 Hz); 8.38 (dd, 1 H, C(1)H, J_1 = 8.0 Hz, J_2 = 1.1 Hz); 10.88 (s, 1 H, NH). ^{13}C NMR, δ: 14.29 (C(16)); 47.89 (C(10), C(10a)); 60.25 (C(12)); 61.14 (C(11), C(11a)); 62,62 (C(13)); 65.4 (C(15)); 118.75 (C(8a)); 121.02 (C(5)); 121.12 (C(2)); 121.75 (C(1a)); 122.25 (C(7)); 123.45 (C(4)); 126.26 (C(8)); 128.5 (C(6)); 132.8 (C(1)); 134.16 (C(3)); 137.81 (C(5a)); 141.46 (C(4a)); 164.89 (C(14)); 167 (C(4b)); 177.06 (C(9)).

1-Methyl-1-[(5-nitrofuran-2-yl)methyl]-4-(9-oxo-9,10-dihydroacridine-4-carbonyl)piperazin-1-ium bromide (5b). The yield was 83%, yellow crystals, m.p. 213—215 °C. Found (%): C, 55.21; H, 4.57; N, 10.73. $C_{24}H_{23}BrN_4O_5$. Calculated (%): C, 54.66; H, 4.40; N, 10.62. ^{1}H NMR, δ: 3.29 (s, 3 H, C(12)H_3); 3.40—4.55 (m, 8 H, C(10)H_2, C(10a)H_2, C(11)H_2, C(11b)H_2); 5.11 (s, 2 H, C(12a)H_2); 7.28 (d, 1 H, C(14)H, J = 3.8 Hz); 7.34—7.39 (m, 2 H, C(5)H, C(7)H); 7.73—7.79 (m, 2 H, C(2)H, C(6)H); 7.83 (d, 1 H, C(15)H, J = 3.8 Hz); 7.9 (d, 1 H, C(3)H, J = 8.4 Hz); 8.24 (dd, 1 H, C(8)H, J_1 = 8.1 Hz, J_2 = 1.5 Hz); 8.37 (dd, 1 H, C(1)H, J_1 = 8.01 Hz, J_2 = 1.14 Hz); 10.84 (s, 1 H, NH). ^{13}C NMR, δ: 45.3 (C(10), C(10a)); 46.88 (C(12)); 49.05 (C(12a)); 58.96 (C(11), C(11)a); 113.72 (C(14)); 118.62 (C(15)); 120.81 (C(8a)); 121.04 (C(5)); 121.15 (C(2)); 121.76 (C(1a)); 122.23 (C(7)); 123.55 (C(4)); 126.26 (C(8)); 128.45 (C(6)); 132.82 (C(1)); 134.09 (C(3)); 137.76 (C(5a)); 141.46 (C(4a)); 145.96 (C(13)); 153.41 (C(16)); 167.02 (C(4b)); 177.07 (C(9)).

1-Methyl-1-(2-ethoxy-2-oxoethyl)-4-[2-(9-oxoacridin-10(9*H*)-yl)acetyl]piperazin-1-ium bromide (6a). The yield was 88%, white crystals, m.p. 221—223 °C. Found (%): C, 57.69; H, 5.73; N, 8.56. $C_{24}H_{28}BrN_3O_4$. Calculated (%): C, 57.38; H, 5.62; N, 8.36. ^{1}H NMR, δ: 1.29—1.32 (m, 3 H, C(16)H_3); 3.44 (s, 3 H, C(12)H_3); 3.71—4.27 (m, 8 H, C(10)H_2, C(10a)H_2, C(11)H_2, C(11a)H_2); 4.30 (q, 2 H, C(15)H_2, J = 7.1 Hz); 4.72

(s, 2 H, C(13)H_2); 5.56—5.70 (m, 2 H, C(4b)H_2); 7.36 (td, 2 H, C(2)H, C(7)H, J_1 = 7.5 Hz, J_2 = 0.7 Hz); 7.59 (d, 2 H, C(4)H, C(5)H, J = 8.7 Hz); 7.8 (ddd, 2 H, C(3)H, C(6)H, J_1 = 8.7 Hz, J_2 = 6.9 Hz, J_3 = 1.7 Hz); 8.36 (dd, 2 H, C(1)H, C(8)H, J_1 = 7.9 Hz, J_2 = 1.7 Hz). ^{13}C NMR, δ: 36.03 (C(16)); 38.8 (C(10), C(10a)); 47.84 (C(12)); 60.09 (C(4b)); 60.38 (C(11), C(11a)); 61.11 (C(13)); 62.69 (C(15)); 116.59 (C(4), C(5)); 121.93 (C(2), C(7)); 122.06 (C(1a), C(8a)); 127.00 (C(1), C(8)); 134.42 (C(3), C(6)); 142.85 (C(4a), C(5a)); 164.98 (C(14)); 165.93 (C(4c)); 177.2 (C(9)).

1-Methyl-1-[(5-nitrofuran-2-yl)methyl]-4-[2-(9-oxoacridin-10(9*H*)-yl)acetyl]piperazin-1-ium bromide (6b). The yield was 93%, yellow crystals, m.p. 230—232 °C. Found (%): C, 55.89; H, 4.75; N, 10.56. $C_{25}H_{25}BrN_4O_5$. Calculated (%): C, 55.46; H, 4.65; N, 10.35. ^{1}H NMR, δ: 3.29 (s, 3 H, C(12)H_3); 3.57—4.38 (m, 8 H, C(10)H_2, C(10a)H_2, C(11)H_2, C(11a)H_2); 5.09—5.12 (m, 2 H, C(4b)H_2); 5.57—5.76 (m, 2 H, C(12a)H_2); 7.31 (d, 1 H, C(14)H, J = 3.8 Hz); 7.36 (t, 2 H, C(2)H, C(7)H, J = 7.4 Hz); 7.6 (d, 2 H, C(4)H, C(5)H, J = 8.8 Hz); 7.78—7.82 (m, 2 H, C(3)H, C(6)H); 7.83 (d, 1 H, C(15)H, J = 3.8 Hz); 8.37 (dd, 2 H, C(1)H, C(8)H, J_1 = 8.0 Hz, J_2 = 1.7 Hz). ^{13}C NMR, δ: 36.04 (C(10)); 36.25 (C(10a)); 38.86 (C(12)); 46.44 (C(11)); 47.86 (C(4b)); 58.85 (C(12a)); 59.29 (C(11a)); 113.71 (C(15)); 116.6 (C(4), C(5)); 120.67 (C(14)); 121.93 (C(2), C(7)); 122.06 (C(1a), C(8a)); 127.01 (C(1), C(8)); 134.42 (C(3), C(6)); 142.87 (C(4a), C(5a)); 146.02 (C(13)); 162.78 (C(16)); 165.92 (C(4c)); 177.20 (C(9)).

4-(Acridine-9-carbonyl)-1-(2-ethoxy-2-oxoethyl)-1-methylpiperazin-1-ium bromide (11a). The yield was 90%, white crystals, m.p. 203—205 °C. Found (%): C, 58.96; H, 5.65; N, 8.98. $C_{23}H_{26}BrN_3O_3$. Calculated (%): C, 58.48; H, 5.55; N, 8.90. ^{1}H NMR, δ: 1.25 (t, 3 H, C(16)H_3); 3.37—3.56 (m, 7 H, C(11a)H_2, C(15)H_2, C(12)H_3); 3.91—4.05 (m, 2 H, C(11)H_2); 4.20—4.26 (m, 2 H, C(13)H_2); 4.27—4.51 (m, 2 H, C(10)H_2); 4.63—4.76 (m, 2 H, C(10a)H_2); 7.71—7.75 (m, 2 H, C(4)H, C(5)H); 7.94 (ddd, 2 H, C(3)H, C(6)H, J_1 = 8.7 Hz, J_2 = 6.7 Hz, J_3 = 1.3 Hz); 7.99—8.05 (m, 2 H, C(2)H, C(7)H); 8.25 (d, 2 H, C(1)H, C(8)H). ^{13}C NMR, δ: 14.28 (C(16)); 35.4 (C(10), C(10a)); 47.96 (C(12)); 59.96 (C(11)); 60.22 (C(11a)); 60.45 (C(13)); 62.63 (C(15)); 122.03 (C(1a), C(8a)); 125.29 (C(2), C(7)); 127.88 (C(1), C(8)); 130.04 (C(3), C(6)); 131.37 (C(9)); 139.58 (C(4), C(5)); 148.58 (C(4a), (5a)); 164.63 (C(14)); 165.87 (C(9a)).

4-(Acridine-9-carbonyl)-1-methyl-1-[(5-nitrofuran-2-yl)-methyl]piperazin-1-ium bromide (11b). The yield was 75%, yellow crystals, m.p. 167—170 °C. Found (%): C, 55.98; H, 4.43; N, 10.74. $C_{24}H_{23}BrN_4O_4$. Calculated (%): C, 56.37; H, 4.53; N, 10.96. ^{1}H NMR, δ: 3.23 (s, 3 H, C(12)H_3); 3.42—3.59 (m, 2 H, C(11a)H_2); 3.74—3.92 (m, 2 H, C(11)H_2); 4.13—4.21 (m, 2 H, C(10)H); 4.60—4.67 (m, 2 H, C(10a)H); 4.98—5.09 (m, 2 H, C(12a)H_2); 7.22 (d, 1 H, C(14)H, J = 3.8 Hz); 7.69—7.76 (m, 2 H, C(4)H, C(5)H); 7.78 (d, 1 H, C(15)H, J = 3.8 Hz); 7.92—8.11 (m, 4 H, C(2)H, C(3)H, C(6)H, C(7)H); 8.28—8.23 (m, 2 H, C(1)H, C(8)H). ^{13}C NMR, δ: 41.55 (C(12)); 46.65 (C(10), C(10a)); 58.91 (C(12a)); 59.37 (C(11), C(11a)); 120.62 (C(14)); 121.99 (C(15)); 122.12 (C(1a), C(8a)); 125.72 (C(2), C(7)); 127.88 (C(1), C(8)); 130.07 (C(3), C(6)); 131.35 (C(9)); 139.63 (C(4), C(5)); 148.62 (C(4a), C(5a)); 148.87 (C(13)); 153.42 (C(16)); 165.89 (C(9a)).

1-Methyl-1-(2-ethoxy-2-oxoethyl)-4-(9-oxo-9,10-dihydroacridine-2-carbonyl)piperazin-1-ium bromide (12a). The yield was 93%, white crystals, m.p. 225—227 °C. Found (%): C, 56.94; H, 5.42; N, 8.71. $C_{23}H_{26}BrN_3O_4$. Calculated (%): C, 56.56; H, 5.37; N, 8.60. ^{1}H NMR, δ: 1.26 (td, 3 H, C(16)H_3, J_1 = 7.2, J_2 = 0.8); 3.40 (s, 3 H, C(12)H_3); 3.65—4.15 (m, 8 H, C(10)H_2, C(10a)H_2, C(11)H_2, C(11a)H_2); 4.25 (q, 2 H, C(15)H_2, J = 7.2 Hz); 4.69 (br.s, 2 H, C(13)H_2); 7.29—7.33 (m, 1 H, C(7)H); 7.64 (d, 1 H, C(5)H, J = 8.4 Hz); 7.69 (dd, 1 H, C(4)H, J_1 = 8.58 Hz, J_2 = 1.72 Hz); 7.76—7.80 (m, 1 H, C(6)H); 7.82 (dd, 1 H, C(3)H, J_1 = 8.58 Hz, J_2 = 2.06 Hz); 8.24 (dd, 1 H, C(8)H, J_1 = 8.0 Hz, J_2 = 0.8 Hz); 8.33 (d, 1 H, C(1)H, J = 1.94 Hz); 12.14 (s, NH). ^{13}C NMR, δ: 14.29 (C(16)); 47.86 (C(10), C(10a)); 60.25 (C(12)); 60.80 (C(11), C(11a)); 62.62 (C(13)); 65.38 (C(15)); 118.05 (C(5)); 118.26 (C(4)); 120.04 (C(8a)); 121.15 (C(1a)); 122.19 (C(7)); 126.25 (C(8)); 126.45 (C(1)); 126.95 (C(2)); 132.86 (C(6)); 134.36 (C(3)); 141.29 (C(5a)); 142.29 (C(4a)); 164.96 (C(14)); 169.30 (C(2a)); 177.08 (C(9)).

1-Methyl-1-[(5-nitrofuran-2-yl)methyl]-4-(9-oxo-9,10-dihydroacridine-2-carbonyl)piperazin-1-ium bromide (12b). The yield was 91%, yellow crystals, m.p. 217—219 °C. Found (%): C, 54.15; H, 4.35; N, 10.57. $C_{24}H_{23}BrN_4O_5$. Calculated (%): C, 54.66; H, 4.40; N, 10.62. ^{1}H NMR, δ: 3.24 (s, 3 H, C(12)H_3); 3.45—4.40 (m, 8 H, C(10)H_2, C(10a)H_2, C(11)H_2, C(11a)H_2); 5.02 (s, 2 H, C(12a)H_2); 7.25 (d, 1 H, C(14)H, J = 3.8 Hz); 7.32 (m, 1 H, C(7)H); 7.61 (d, 1 H, C(5)H, J = 8.35 Hz); 7.67 (d, 1 H, C(4)H, J = 8.6 Hz); 7.76—7.84 (m, 3 H, C(3)H, C(6)H, C(15)H); 8.25 (dd, 1 H, C(8)H, J_1 = 8.0 Hz, J_2 = 0.8 Hz); 8.36 (d, 1 H, C(1)H, J = 1.8 Hz); 12.06 (s, NH). ^{13}C NMR, δ: 31.16 (C(10), (10a)); 36.07 (C(12)); 46.63 (C(12a)); 59.14 (C(11), C(11a)); 113.66 (C(14)); 118.07 (C(5)); 118.31 (C(4)); 120.02 (C(8a)); 120.61 (C(15)); 121.17 (C(1a)); 122.22 (C(7)); 126.29 (C(8)); 126.49 (C(1)); 126.97 (C(2)); 132.91 (C(6)); 134.64 (C(3)); 141.29 (C(5a)); 142.32 (C(4a)); 145.95 (C(13)); 162.77 (C(16)); 169.41 (C(2a)); 177.10 (C(9)).

Synthesis of compounds 14a,b (general procedure). 1,1′-Carbonyldiimidazole (10 mmol) was added by portions to a suspension of acid **1** or **2** (10 mmol) in DMF (20 mL), and the mixture was stirred until CO_2 stopped evolving. Then 1-(*tert*-butoxycarbonyl)-piperazine (10 mmol) was added. The reaction mixture was stirred for 24 h and poured into water (150 mL). The precipitated product was filtered off, washed with water, and dried. Trifluoroacetic acid was added (1 : 1), the mixture was kept for 24 h and evaporated. The residue was neutralized with a solution of $NaHCO_3$. The precipitate was filtered off, washed with water, dried, and dispersed in dichloromethane (15 mL). Triethylamine (10 mmol) and 5-nitrofuran-2-carboxylic acid chloride (10 mmol) in dichloromethane (5 mL) were added. The solution was stirred for 6 h and washed with water. The organic layer was concentrated and purified by preparative chromatography.

4-[4-(5-Nitrofuran-2-carbonyl)piperazine-1-carbonyl]acridin-9(10*H*)-one (14a). The yield was 54%, yellow crystals, m.p. 206—208 °C. Found (%): C, 62.97; H, 4.43; N, 12.36. $C_{23}H_{18}N_4O_6$. Calculated (%): C, 62.60; H, 4.38; N, 12.17. ^{1}H NMR, δ: 4.01—4.54 (m, 8 H, C(10)H_2, C(10a)H_2, C(11)H_2, C(11a)H_2); 7.25—7.39 (m, 3 H, C(2)H, C(6)H, C(14)H); 7.70—7.81 (m, 3 H, C(5)H, C(7)H, C(15)H); 7.88 (d, 1 H, C(3)H, J = 8.4 Hz); 8.24 (dd, 1 H, C(8)H, J = 7.3 Hz); 8.33—8.38 (m, 1 H, C(1)H); 10.91 (s, 1 H, NH). ^{13}C NMR, δ: 55.38 (C(10), C(10a)); 60.19 (C(11), C11a)); 113.26 (C(14)); 117.66 (C(8a)); 118.56 (C(5)); 121.00 (C(2)); 121.15 (C(1a)); 121.62 (C(15)); 122.15 (C(7)); 124.65 (C(4)); 126.3 (C(8)); 128.06 (C(6)); 132.77 (C(3)); 134.19 (C(1)); 137.72 (C(5a)); 141.59 (C(4a)); 147.76 (C(12)); 151.70 (C(13)); 157.42 (C(16)); 166.92 (C(4b)); 177.08 (C(9)).

10-{2-[4-(5-Nitrofuran-2-carbonyl)piperazin-1-yl]-2-oxoethyl}acridin-9(10*H*)-one (14b). The yield was 67%, yellow crystals, m.p. 229—231 °C. Found (%): C, 62.10; H, 4.32; N, 12.06. $C_{24}H_{20}N_4O_6$. Calculated (%): C, 62.60; H, 4.38; N, 12.17. ^{1}H NMR, δ: 3.58—4.09 (m, 8 H, C(10)H_2, C(10a)H_2, C(11)H_2,

C(11a)H_2); 5.57 (s, 2 H, C(4b)H_2); 7.29—7.41 (m, 3 H, C(2)H, C(7)H, C(14)H); 7.61 (dd, 2 H, C(4)H, C(5)H, J = 8.7 Hz); 7.73—7.86 (m, 3 H, C(3)H, C(6)H, C(15)H); 8.36 (dd, 2 H, C(1)H, C(8)H, J_1 = 7.9 Hz, J_2 = 1.4 Hz). ^{13}C NMR, δ: 42.77 (C(11)); 44.28 (C(11a)); 44.83 (C(10)); 46.58 (C(10a)); 47.94 (C(4b)); 113.40 (C(14)); 116.67 (C(4), C(5)); 117.90 (C(15)); 121.84 (C(2), C(7)); 122.02 (C(1a), C(8a)); 126.92 (C(1), C(8)); 134.45 (C(3), C(6)); 142.94 (C(4a), C(5a)); 148.00 (C(12)); 151.78 (C(16)); 157.49 (C(13)); 165.66 (C(4c)); 177.22 (C(9)).

Synthesis of compounds 15a—c (general procedure). Potassium bicarbonate (1.1 mmol) was added to compound **13a—c** (1 mmol) in DMF (10 mL). Then 2-bromomethyl-5-nitrofuran (1.1 mmol) was added. The reaction mixture was stirred for 24 h, poured into water, and filtered. The precipitate was washed with water, dried, and purified by preparative chromatography.

4-{4-[(5-Nitrofuran-2-yl)methyl]piperazin-1-carbonyl]acridin-9(10*H*)-one (15a). The yield was 77%, yellow crystals, m.p. 209—211 °C. Found (%): C, 63.16; H, 4.61; N, 12.86. $C_{23}H_{20}N_4O_5$. Calculated (%): C, 63.88; H, 4.66; N, 12.96. ^{1}H NMR, δ: 2.46—2.34 (m, 2 H, C(11a)H_2); 2.59—2.77 (m, 2 H, C(11)H_2); 3.18—3.30 (m, 2 H, C(10a)H_2); 3.72 (s, 2 H, C(12)H_2); 3.75—3.89 (m, 2 H, C(10)H_2); 6.78 (d, 1 H, C(14)H, J = 3.7 Hz); 7.26—7.33 (m, 2 H, C(6)H, C(7)H); 7.66 (dd, 1 H, C(5)H, J_1 = 7.7 Hz, J_2 = 1.5 Hz); 7.68 (d, 1 H, C(15)H, J = 3.7 Hz); 7.70—7.76 (m, 1 H, C(2)H); 7.84 (d, 1 H, C(3)H, J = 8.4 Hz); 8.23 (dd, 1 H, C(8)H, J_1 = 8.1 Hz, J_2 = 1.3 Hz); 8.33 (dd, 1 H, C(1)H, J_1 = 8.0 Hz, J_2 = 1.5 Hz); 10.83 (s, 1 H, NH). ^{13}C NMR, δ: 53.87 (C10), C(10a)); 55.24 (C(12)); 60.11 (C(11), C(11a)); 113.73 (C(14)); 114.38 (C(15)); 118.59 (C(5)); 120.95 (C(2)); 121.11 (C(8a)); 121.54 (C(1a)); 122.11 (C(7)); 124.96 (C(4)); 126.26 (C(8)); 127.85 (C(6)); 132.60 (C(1)); 134.10 (C(3)); 137.66 (C(5a)); 141.47 (C(4a)); 151.84 (C(13)); 156.84 (C(16)); 166.54 (C(4b)); 177.07 (C(9)).

10-(2-{4-[(5-Nitrofuran-2-yl)methyl]piperazin-1-yl}-2-oxoethyl)acridin-9(10*H*)-one (15b). The yield was 87%, yellow crystals, m.p. 235—237 °C. Found (%): C, 64.96; H, 5.03; N, 12.65. $C_{24}H_{22}N_4O_5$. Calculated (%): C, 64.57; H, 4.97; N, 12.55. ^{1}H NMR, δ: 2.47—2.54 (m, 2 H, C(11a)H_2); 2.66—2.71 (m, 2 H, C(11)H_2); 3.5—3.57 (m, 2 H, C(10)H_2); 3.74—3.80 (m, 4 H, C(10a)H_2, C(12)H_2); 5.5 (s, 2 H, C(4b)H_2); 6.83 (d, 1 H, C(14)H, J = 3.7 Hz); 7.33 (ddd, 2 H, C(2)H, C(7)H, J_1 = 8.0 Hz, J_2 = 7.1 Hz, J_3 = 0.5 Hz); 7.53 (d, 1 H, C(4)H, C(5)H, J = 8.8 Hz); 7.71 (d, 1 H, C(15)H, J = 3.7 Hz); 7.77 (ddd, 2 H, C(3)H, C(6)H, J_1 = 8.7 Hz, J_2 = 6.9 Hz, J_3 = 1.8 Hz); 8.35 (dd, 2 H, C(1)H, C(8)H, J_1 = 8.1 Hz, J_2 = 1.7 Hz). ^{13}C NMR, δ: 42.08 (C(10)); 44.76 (C(10a)); 47.8 (C(11)); 52.36 (C(4b)); 52.87 (C(12)); 54.01 (C(11a)); 113.7 (C(15)); 114.44 (C(14)); 116.54 (C(4), C(5)); 121.78 (C(2), C(7)); 122.01 (C(1a), C(8a)); 126.92 (C(1), C(8)); 134.39 (C(3), C(6)); 142.92 (C(4a), C(5a)); 151.92 (C(16)); 156.98 (C(13)); 165.26 (C(4c)); 177.2 (C(9)).

Acridin-9-yl-{4-[(5-nitrofuran-2-yl)methyl]piperazin-1-yl}-methanone (15c). The yield was 90%, yellow crystals, m.p. 301—303 °C. Found (%): C, 66.85; H, 4.89; N, 13.57. $C_{23}H_{20}N_4O_4$. Calculated (%): C, 66.34; H, 4.84; N, 13.45. ^{1}H NMR, δ: 2.23—2.31 (m, 2 H, C(11a)H_2); 2.69—2.77 (m, 2 H, C(11)H_2); 2.97—3.04 (m, 2 H, C(10a)H_2); 3.71 (s, 2 H, C(12)H_2); 3.95—4.04 (m, 2 H, C(10)H_2); 6.76 (d, 1 H, C(14)H, J = 3.7 Hz); 7.64—7.73 (m, 3 H, C(2)H, C(7)H, C(15)H); 7.87—7.97(m, 4 H, C(3)H, C(4)H, C(5)H, C(6)H); 8.22 (d, 2 H, C(1)H, C(8)H, J = 8.7 Hz). ^{13}C NMR, δ: 41.55 (C(12)); 46.65 (C(10)); 52.41 (C(10a)); 52.99 (C(11)); 53.84 (C(11a)); 113.62 (C(14)); 114.36 (C(15)); 121.87 (C(1a), C(8a)); 125.62 (C(2), C(7)); 127.64 (C(1), C(8)); 130.01 (C(3), C(6)); 131.29 (C(9)); 141 (C(4), C(5)); 148.58 (C(4a), C(5a)); 151.79 (C(13)); 156.85 (C(16)); 165.24 (C(9a)).

Determination of antimicrobial activity.[15] Glass Petri dishes mounted in stages with the rigidly horizontal surface were poured with melted agar medium pre-seeded with test strains of microorganisms.

A suspension of test microbes for seeding on Petri dishes was prepared according to a turbidity standard of 10 EU. Daily cultures were used as inoculum. A suspension of each type of microorganism was seeded on a Petri dish. The microbial load was 1 000 000 microbial cells per 1 mL.

To determine the antimicrobial activity of the tested substances, their solutions with concentrations of 0.5, 1.0, and 2.0% were placed at the center of a cylinder (0.1 mL). Then the dishes were incubated for 18—20 h at 37±1 °C. Standard solutions of Rivanol in the same concentrations were used as reference samples.

The diameter of the bacteriostasis zones for test microbes was measured with a microruler with the accuracy to 1 mm.

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