Received: May , 2014

SYNTHESIS AND ANTIBACTERIAL ACTIVITY OF SERIES FLUORINE-SUBSTITUTED ACRIDONEACETIC ACID DERIVATIVES

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Abstract: *Some new derivatives of various fluoroacridoneacetic acids were obtained, their antimicrobial activity against a group of test strains of microorganisms was investigated, as well as the influence of the structure of the obtained compounds on their bactericidal action.*

Keywords: *Fluorine-substituted acridoneacetic acids, esters, amides, antimicrobial action*

Continuing the search for biologically active compounds in the series of fluorine-substituted acridoneacetic acids (AAA) [1], we were tasked to synthesize a series of new products containing the condensed system of acridone coupled with additional pharmacophore heterocyclic moiety through an amide or ester bond. As these pharmacophores were taken 2-aminothiazole , 2-(2-methyl-5-nitro-1H-imidazol-1-yl)ethanol , 2-(hydroxymethyl)furan, tetrahydro-2-furanmethanol , 4-methyl-5-(2-hydroxyethyl)thiazole and 5-(4-hydroxyphenyl)-3H-1,2-dithiole-3- thione.

The choice of heterocyclic pharmacophore groups was caused by the following reasons: some 2-aminothiazole derivatives have an antibacterial activity [2,3], the fragment of this compound also contains in structure of such known antimicrobial agents as sulfathiazole, nitazolum, carumonam, aztreonam, tenonitrozole, ceftriaxone [4].

Antimicrobial and antiprotozoal drug metronidazole (2-(2-methyl-5-nitro-1H-imidazol-1-yl)ethanol) is widely used in clinical practice. This compound causes DNA damage due to formation of complexes or strand breaks and is effective against *Trichomonas vaginalis*, *Entamoeba histolytica* and obligate anaerobes, which are converted metronidazole into a reactive hydroxylamine metabolite, that lead to irreversible changes in the DNA structure [5,6].

The derivatives of 4-methyl-5-(2-hydroxyethyl)thiazole, which can be regarded as part of thiamine molecule (vitamin B_1), have some useful pharmacological properties. Thus, the drug clomethiazole (5-(2-chloroethyl)-4-methylthiazole ethanedisulphonate) has sedative, hypnotic and anticonvulsant effects and fluorinated analogs of 4-methyl-5-(2-hydroxyethyl)thiazole show bacteriostatic activity [7,8].

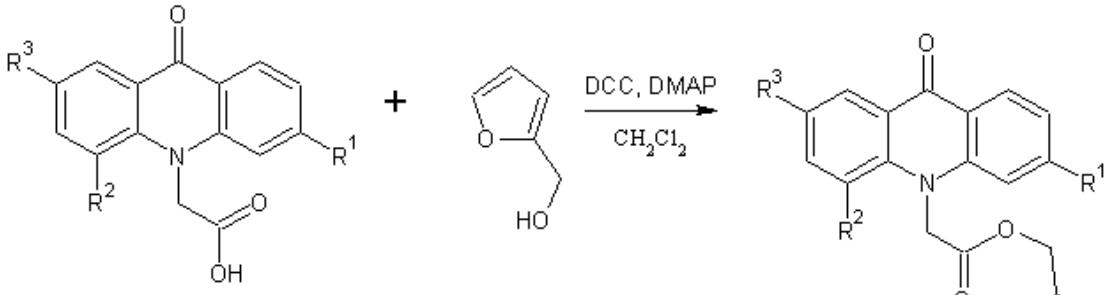
The derivatives of 5-(4-hydroxyphenyl)-3H-1,2-dithiole-3-thione (ADT-OH), which is widely used as H_2S-releasing compound in the organisms for the synthesis of pharmaceutical hybrids, were actively studied last years. It was found that 4-(3H-1,2-dithiole-3-thione-5-yl)phenyl esters of various carboxylic acids show anti-inflammatory and antitumor activity [9-11].

Fragments of 2-(hydroxymethyl)furan and tetrahydro-2-furanmethanol also contains in many biologically active substances[12,13].

One of the general procedure for synthesis of esters and amides is carbodiimide activation of carboxylic acid. In these reactions various carbodiimides are used, N,N-dicyclohexylcarbodiimide (DCC) is the most simple and cheap among them. This synthetic method was used to obtain the title compounds.

Tetrahydrofuran and furan-2-ylmethyl esters of various fluoroacridoneacetic acids were prepared in dichloromethane in the presence of DCC and a catalytic amount of N, N-dimethylaminopyridine

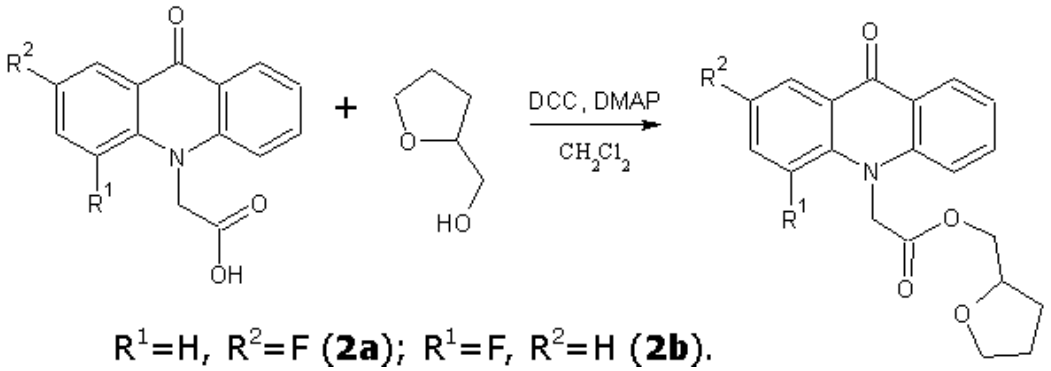
(DMAP) at room temperature for 6 hours. The precipitate of N, N-dicyclohexylurea was filtered, the solvent was evaporated and the crude obtained products were purified by column chromatography (silica gel 60-Merck, eluent toluene: acetone: ethanol at a volume ratio 10:3:2).



R^1=H, R^2=H, R^3=F (**1a**);

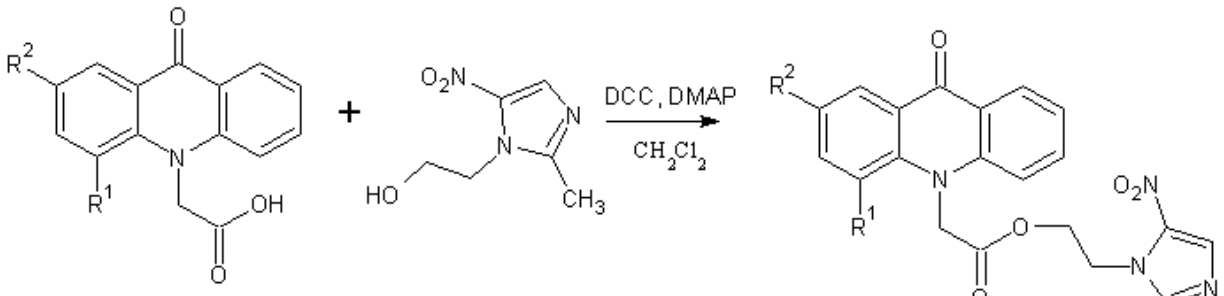
R^1=H, R^2=F, R^3=H (**1b**);

R^1=NO_2, R^2=H, R^3=F (**1c**).

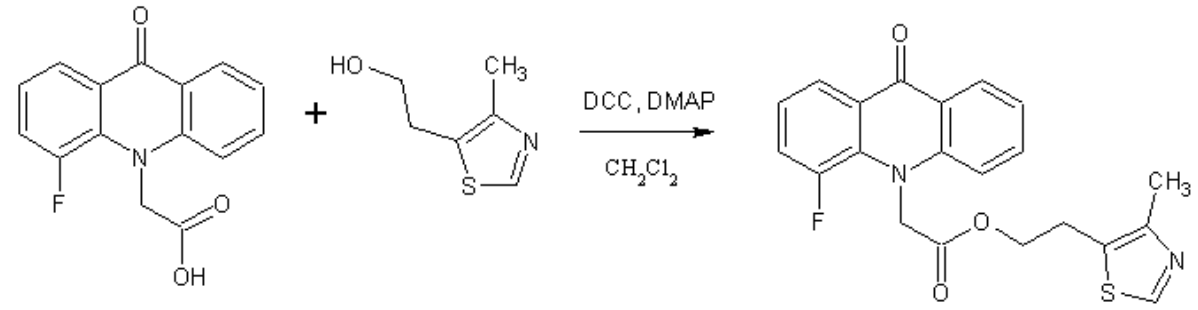


R^1=H, R^2=F (**2a**); R^1=F, R^2=H (**2b**).

Similarly 2-(2-methyl-5-nitro-1H-imidazol-1-yl)ethyl and 2-(4-methyl-1,3-thiazol-5-yl)ethyl esters of 2- and 4-fluoroacridoneacetic acids were synthesized.

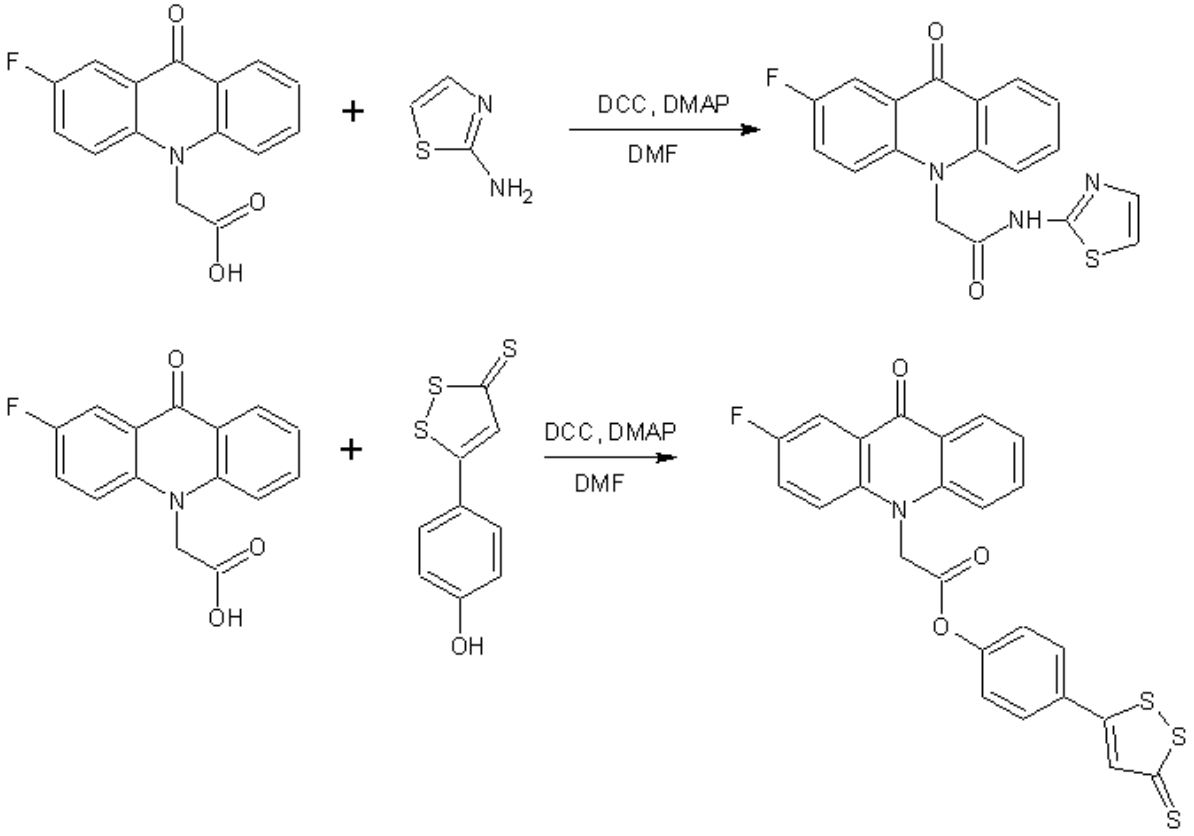


R^1=H, R^2=F (**3a**); R^1=F, R^2=H (**3b**).



It should be noted that one of possible synthetic way for furan-2-ylmethyl and 2-(4-methyl-1,3-thiazol-5-yl)ethyl ester is transesterification of methyl, ethyl or butyl esters of the AAA by the corresponding alcohol with a five-membered heterocyclic moiety catalyzed $NaOCH_3$. However, we found that a similar reaction with tetrahydro-2-furanmethanol leads to low yield of target ester.

Synthesis of 2-aminothiazole and ADT-OH derivatives was carried out more long time (8-10 hours). The final products have a poor solubility in dichloromethane, therefore the reaction was performed in DMF. The crude products were washed with hot $CHCl_3$ solution to remove impurities of starting materials, N,N-dicyclohexylurea and N, N-dicyclohexylcarbamimidates of fluoroacridoneacetic acids.



The signals of protons corresponding acridone tricyclic system, as well as signals relating to the coupled pharmacophore heterocyclic moiety present in the ^{1}H-NMR spectra of the obtained compounds.

In a previous paper [1] we studied the antimicrobial action of some 2-fluoroacridoneacetic acid derivatives, so it was of considerable interest to evaluate activity of substances with a fluorine atom in the 4-position of acridone ring. The antibacterial activity of compounds **2b, 3b** and **4** (1% and 2% solution in DMSO) was investigated on a series of test strains of microorganisms, results are shown in Table 1.

Table 1. Antimicrobial activity of compounds **2b**, **3b**, **4.**

Compound	C, %	*E. coli* (ATCC 25922)	*Ps. aeruginosa* (ATCC 27853)	*Pr.vulgaris* (ATCC 4636)	*S. aureus* (ATCC 25923)	*B.subtilis* (ATCC 6633)	*Candida albicans* (NCTC2625)
		Growth inhibition areas, mm.					
3b	1	10.50B±0.40	8.50B±0.73	10.50B±0.61	8.00B±0.45	20.50B±0.92	11.00B±0.54
	2	9.00B±0.79	7.00B±0.56	10.50B±0.67	8.00B±0.70	22.50B±0.85	11.00B±0.69
Metro-nidazole	1	11.50B±0.39	20.00B±0.74	14.00B±0.42	22.00B±0.70	14.50B±0.37	20.00B±0.63
	2	12.00B±0.35	21.00B±0.61	22.00B±0.73	25.00B±0.68	15.00B±0.40	25.00B±0.75
2b	1	10.50B±0.54	10.50B±0.66	10.00B±0.60	9.00B±0.58	7.00B±0.38	12.00B±0.75
	2	11.50B±0.71	11.50B±0.80	9.00B±0.47	9.00B±0.77	7.00B±0.42	11.00B±0.59
4	1	10.50B±0.84	8.00B±0.59	7.50B±0.63	8.00B±0.38	8.00B±0.40	10.50B±0.70

	2	12.50B±0.62	8.50B±0.50	8.00B±0.45	8.50B±0.56	9.50B±0.81	12.00B±0.68
Rivanol	1	12.75B±0.47	12.00B±1.14	12.50B±0.83	17.00B±1.02	14.05B±0.94	13.50B±0.56
	2	14.50B±0.57	15.00B±0.93	15.00B±0.66	20.00B±0.97	15.00B±1.14	15.00B±0.96

It was of greatest interest to determine the antimicrobial activity of 4-fluoroacridoneacetic acid 2-(2-methyl-5-nitro-1H-imidazol-1-yl)ethyl ester, because it was previously found that a similar ester of unsubstituted AAA inhibits the growth of microorganisms more effective than the starting drug metronidazole. [14]

However, the obtained product **3b** generally showed lower activity than 2-(2-methyl-5-nitro-1H-imidazol-1-yl)-ethyl ester of AAA and only for values of growth inhibition areas of *B.subtilis* exceeded metronidazole. Introduction of fluorine in the 4-position of acridone ring also led to a reduction of the antibacterial action in case of the compounds **2b** and **4**. Table 2 shows the comparative activity of 2-(4-methyl-1,3-thiazol-5-yl)ethyl esters unsubstituted, 2- and 4-fluoroAAA.

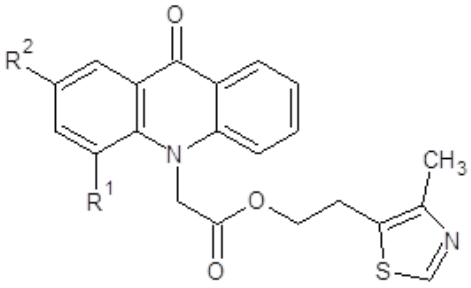


Table 2. Comparative antimicrobial activity of 2-(4-methyl-1,3-thiazol-5-yl)ethyl esters of various acridoneacetic acids.

Compound	C, %	*E. coli* (ATCC 25922)	*Ps. aeruginosa* (ATCC 27853)	*Pr.vulgaris* (ATCC 4636)	*S. aureus* (ATCC 25923)	*B.subtilis* (ATCC 6633)	*Candida albicans (NCTC2625)*
		Growth inhibition areas, mm.					
R^1=H, R^2=H	1	9.00B±0.34	12.25B±1.04	9.00B±0.36	9.00B±0.46	10.00B±0.33	12.50B±0.47
	2	9.00B±0.51	13.50B±0.56	10.00B±0.39	9.25B±0.52	10.50B±0.72	14.00B±0.32
R^1=H, R^2=F	1	8.80B±0.71	10.05B±0.94	11.50B±0.32	14.00B±0.75	10.00B±0.37	13.50B±0.94
	2	9.00B±0.75	13.50B±0.66	15.00B±1.09	14.50B±0.97	11.50B±0.32	15.00B±1.09
R^1=F, R^2=H	1	10.50B±0.84	8.00B±0.59	7.50B±0.63	8.00B±0.38	8.00B±0.40	10.50B±0.70
	2	12.50B±0.62	8.50B±0.50	8.00B±0.45	8.50B±0.56	9.50B±0.81	12.00B±0.68

It should be noted that 2-(4-methyl-1,3-thiazol-5-yl)ethyl ester of 2-fluoro AAA has a slightly higher antimicrobial activity than the unsubstituted analog, whereas the biological activity of a 4-fluoroAAA derivative generally decreased.

Compounds **2b** and **4** on some indicators of activity are comparable to standard drug rivanol (closest structurally antibacterial drug вЂ“ 2-ethoxy-6,9-diaminoacridine lactate).

Experimental

TLC was performed on plates B«SorbfilB» PTLC-P-B-UV, eluent вЂ“ toluene: acetone: ethanol in volume ratio of 10:3:2. IR spectra were obtained using a spectrometer FSM 1201 Monitoring, KBr tablets. Mass spectra were recorded on system ACQUITY UPLC H-Class with UV / mass detectors ACQUITY SQD Waters. ^{1}H NMR spectra were recorded on spectrometer Bruker AV-600, solvent DMSO-d_6.

The synthesis of various fluoroacridoneacetic acids and determination of antimicrobial activity were performed by the methods described previously [1]. Heterocyclic amines and alcohols used in this work вЂ“ commercially available reagents.

General procedure for the synthesis of compounds 1-4

A mixture of the corresponding fluoroacridoneacetic acid (3 mmol), the alcohol, containing five-membered heterocyclic fragment, (3 mmol), 0.61 g (3 mmol) N,N-dicyclohexylcarbodiimide, 0.04 g (0.33 mmol) N,N-dimethylaminopyridine and 30 ml CH_2Cl_2 was stirred at room temperature for 5 - 6 hours. The precipitate N,N'-dicyclohexylurea was filtered off, the solvent was evaporated. Technical obtained product was purified by column chromatography on silica gel-60 Merck, eluent вЂ“ toluene: acetone: ethanol at volume ratio 10:3:2.

General procedure for the synthesis of compounds 5,6

A mixture of the corresponding fluoroacridoneacetic acid (3 mmol), 2-aminothiazole or ADT-OH (3 mmol), 0.61 g (3 mmol) N,N-dicyclohexylcarbodiimide, 0.04 g (0.33 mmol) N,N-dimethylaminopyridine and 25 ml DMF was stirred at room temperature for 8-10 hours. The precipitate N,N'-dicyclohexylurea was filtered, the filtrate was poured into 50 ml of water. The formed precipitate was filtered off and washed with a hot solution of $CHCl_3$ (3x20 mL).

Furan-2-ylmethyl(2-fluoro-9-oxoacridin-10(9H)-yl)acetate (1a)

Dark yellow crystalline solid. Yield: 83 %, m.p. 179-180 В°C. R_f = 0.81. MS, *m/z* (I_{rel} (%)): 352 [Рњ+H]$^+$ (100), 272 [$C_{15}H_{10}FNO_3$ + H]$^+$ (20), 226 [$C_{14}H_{10}FNO$ вЂ“ H]$^+$ (84). IR (KBr) OS, СЃm^{-1}: 3120вЂ“2856 (СвЂ”H); 1744 (C=$O_{est.}$); 1623 (C=$O_{acridone}$); 1603, 1493, 1470 (C-$C_{P\circ r}$). ^{1}H-NMR (DMSO-d_6, Оґ, ppm, J/ Hz): 5.22 (s, 2 H, C(2a)H_2); 5.52 (s, 2 H, C(1a)H_2); 6.49 (t, 1 H, C(2b)H, J = 3.1, J =1.8); 6.56 (d, 1 H, C(1b)H, J = 3.1); 7.38 (t, 1 H, C(7)H, J = 7.4); 7.64 (d, 1 H, C(4)H, J = 8.8); 7.71 вЂ“ 7.77 (m, 3 H, C(3)H, C(5)H, C(3b)H); 7.81(t, 1 H, C(6)H, J = 7.9); 7.99 (dd, 1 H, C(1)H, J = 8.7, J = 2.8); 8.34 (d, 1 H, C(8)H, J = 7.9).

Furan-2-ylmethyl(4-fluoro-9-oxoacridin-10(9H)-yl)acetate (1b)

Brown crystalline solid. Yield: 85 %, m.p. 151-152 В°C. R_f = 0.84 . MS, *m/z* (I_{rel} (%)): 352 [Рњ+H]$^+$ (75), 272 [$C_{15}H_{10}FNO_3$ + H]$^+$ (31), 226 [$C_{14}H_{10}FNO$ вЂ“ H]$^+$ (100). IR (KBr) OS, СЃm^{-1}: 3108вЂ“2855 (СвЂ”H); 1744 (C=$O_{est.}$); 1638 (C=$O_{acridone}$); 1603, 1499, 1463 (C-$C_{P\circ r}$). ^{1}H-NMR (DMSO-d_6, Оґ, ppm, J/ Hz): 5.27 (s, 2 H, C(2a)H_2); 5.30 (s, 2 H, C(1a)H_2); 6.50 (t, 1 H, C(2b)H, J = 3.0, J =1.8); 6.60 (d, 1 H, C(1b)H, J = 2.9); 7.31 вЂ“ 7.35 (m, 1 H, C(2)H); 7.39 (t, 1 H, C(7)H, J = 7.4); 7.61 (d, 1 H, C(5)H, J = 8.8); 7.67 (dd, 1 H, C(3)H, J = 15.3, J = 7.8); 7.73 (s, 1 H, C(3b)H); 7.81 (t, 1 H, C(6)H, J = 7.8); 8.15 (d, 1 H, C(1)H, J = 8.1); 8.28 (d, 1 H, C(8)H, J = 8.1).

Furan-2-ylmethyl(2-fluoro-6-nitro-9-oxoacridin-10(9H)-yl)acetate (1c)

Dark orange crystalline solid. Yield: 74 %, m.p. 153-154 В°C. R_f = 0.86. MS, *m/z* (I_{rel} (%)): 397 [Рњ+H]$^+$ (64), 271 [$C_{14}H_9FN_2O_3$ вЂ“ H]$^+$ (100). IR (KBr) OS, СЃm^{-1}: 3103вЂ“2857 (СвЂ”H); 1728 (C=$O_{est.}$); 1651 (C=$O_{acridone}$); 1611, 1483, 1462 (C-$C_{P\circ r}$), 1534 (NO_2). ^{1}H-NMR (DMSO-d_6, Оґ, ppm, J/ Hz): 5.24 (s, 2 H, C(2a)H_2); 5.67 (s, 2 H, C(1a)H_2); 6.47 (t, 1 H, C(2b)H, J = 3.3, J =1.5); 6.56 (d, 1 H, C(1b)H, J = 3.3); 7.69 (s, 1 H, C(3b)H); 7.78 вЂ“ 7.82 (m, 2 H, C(3)H, C(4)H); 7.98 (d, 1 H, C(1)H, J = 8.4); 8.05 (d, 1 H, C(7)H, J = 8.8); 8.47 (s, 1 H, C(5)H); 8.51 (d, 1 H, C(8)H, J = 8.4).

Tetrahydrofuran-2-ylmethyl(2-fluoro-9-oxoacridin-10(9H)-yl)acetate (2a)

Pale yellow crystalline solid. Yield: 77 %, m.p. 147-148 В°C. R_f = 0.79. MS, *m/z* (I_{rel} (%)): 356 [Рњ+H]$^+$ (100), 272 [$C_{15}H_{10}FNO_3$+H]$^+$ (94), 226 [$C_{14}H_{10}FNO$ вЂ“ H]$^+$ (35). IR (KBr) OS, СЃm^{-1}: 3070вЂ“2855 (СвЂ”H); 1751 (C=$O_{est.}$); 1627 (C=$O_{acridone}$); 1603, 1493, 1466 (C-$C_{P\circ r}$), 1074 (C-O-C in tetrahydrofuran fragment). ^{1}H-NMR (DMSO-d_6, Оґ, ppm, J/ Hz): 1.44 вЂ“ 1.50 (m, 1 H, C(2b)H); 1.67 вЂ“ 1.75 (m, 2 H, C(2b)H, C(3b)H); 1.82 вЂ“ 1.88 (m, 1 H, C(3b)H); 3.55 вЂ“ 3.60 (m, 2 H, C(4b)H_2); 4.01 вЂ“ 4.05 (m, 1 H, C(1b)H); 4.08 вЂ“ 4.11 (m, 1 H, C(2a)H); 4.17 (dd, 1 H, C(2a)H, J=11.5, J=3.6); 5.49 (s, 2 H, C(1a)H_2); 7.37 (t, 1 H, C(7)H, J=7.6); 7.66 (d, 1 H, C(4)H, J=8.6); 7.71 вЂ“ 7.78 (m, 2 H,

C(3)H, C(5)H); 7.82 (t, 1 H, C(6)H, J=7.6); 7.98 (dd, 1 H, C(1)H, J=8.6, J=2.6); 8.33 (d, 1 H, C(8)H, J=8.1).

Tetrahydrofuran-2-ylmethyl(4-fluoro-9-oxoacridin-10(9H)-yl)acetate (2b)

Yellow crystalline solid. Yield: 82 %, m.p. 142-143 B°C. R_f = 0.80. MS, *m/z* (I_{rel} (%)): 356 [Рњ+H]$^+$ (100), 272 [$C_{15}H_{10}FNO_3$+H]$^+$ (81), 226 [$C_{14}H_{10}FNO$ вЂ“ H]$^+$ (20). IR (KBr) OS, Cґm^{-1}: 3071вЂ“2847 (СвЂ”H); 1750 (C=$O_{est.}$); 1640 (C=$O_{acridone}$); 1601, 1498, 1461 (C-$C_{P°r}$), 1084 (C-O-C $_{in\ tetrahydrofuran\ fragment}$). ^{1}H-NMR (DMSO-$d_6$, Oґ, ppm, J/ Hz): 1.53 вЂ“ 1.59 (m, 1 H, C(2b)H); 1.73 вЂ“ 1.78 (m, 2 H, C(2b)H, C(3b)H); 1.89 вЂ“ 1.95 (m, 1 H, C(3b)H); 3.61 вЂ“ 3.69 (m, 2 H, C(4b)H_2); 4.06 вЂ“ 4.09 (m, 1 H, C(1b)H); 4.14 вЂ“ 4.17 (m, 1 H, C(2a)H); 4.24 (d, 1 H, C(2a)H, J=11.5); 5.28 (s, 2 H, C(1a)H_2); 7.32 вЂ“ 7.35 (m, 1 H, C(2)H); 7.39 (t, 1 H, C(7)H, J=7.4); 7.62 (d, 1 H, C(5)H, J=8.6); 7.69 (dd, 1 H, C(3)H, J=15.1, J=7.8); 7.82 (t, 1 H, C(6)H, J=7.5); 8.15 (d, 1 H, C(1)H, J=7.7); 8.29 (d, 1 H, C(8)H, J=7.9).

2-(2-methyl-5-nitro-1H-imidazol-1-yl)ethyl(2-fluoro-9-oxoacridin-10(9H)-yl)acetate (3a)

Light yellow crystalline solid. Yield: 62 %, m.p. 224-225 B°C. R_f = 0.68. MS, *m/z* (I_{rel} (%)): 425 [Рњ+H]$^+$ (100), 298 [$C_{17}H_{14}FNO_3$ вЂ“ H]$^+$ (65), 272 [$C_{15}H_{10}FNO_3$ + H]$^+$ (67), 226 [$C_{14}H_{10}FNO$ вЂ“ H]$^+$ (29), 212 [$C_{13}H_8FNO$ вЂ“ H]$^+$ (8). IR (KBr) OS, Cґm^{-1}: 3129 вЂ“ 2847 (СвЂ”H); 1742 (C=$O_{est.}$); 1619 (C=$O_{acridone}$); 1601, 1493, 1462 (C=C, C=N); 1526 (NO_2). ^{1}H-NMR (DMSO-d_6, Oґ, ppm, J/ Hz): 2.28 (s, 3 H, CH_3); 4.53 (t, 2 H, C(3a)H_2, J=5.1); 4.58 (t, 2 H, C(2a)H_2, J=5.0); 5.39 (s, 2 H, C(1a)H_2); 7.38 (t, 1 H, C(7)H, J=7.5); 7.50 (d, 1 H, C(4)H, J=8.7); 7.58 вЂ“ 7.64 (m, 2 H, C(3)H, C(5)H); 7.68 (t, 1 H, C(6)H, J=7.8); 7.79 (dd, 1 H, C(1)H, J=8.8, J=2.7); 7.98 (s, 1 H, C(1b)H); 8.33 (d, 1 H, C(8)H, J=8.0).

2-(2-methyl-5-nitro-1H-imidazol-1-yl)ethyl(4-fluoro-9-oxoacridin-10(9H)-yl)acetate (3b)

Pale brown crystalline solid. Yield: 65 %, m.p. 207-208 B°C. R_f = 0.71. MS, *m/z* (I_{rel} (%)): 425 [Рњ+H]$^+$ (95), 298 [$C_{17}H_{14}FNO_3$ вЂ“ H]$^+$ (100), 272 [$C_{15}H_{10}FNO_3$ + H]$^+$ (28), 254 [$C_{15}H_{10}FNO_2$ вЂ“ H]$^+$ (12), 226 [$C_{14}H_{10}FNO$ вЂ“ H]$^+$ (73), 212 [$C_{13}H_8FNO$ вЂ“ H]$^+$ (13). IR (KBr) OS, Cґm^{-1}: 3129 вЂ“ 2856 (СвЂ”H); 1738 (C=$O_{est.}$); 1636 (C=$O_{acridone}$); 1610, 1601, 1497, 1462 (C=C, C=N); 1519 (NO_2). ^{1}H-NMR (DMSO-d_6, Oґ, ppm, J/ Hz): 2.26 (s, 3 H, CH_3); 4.58 (t, 2 H, C(3a)H_2, J=5); 4.62 (t, 2 H, C(2a)H_2, J=4.8); 5.18 (s, 2 H, C(1a)H_2); 7.32 вЂ“ 7.35 (m, 1 H, C(2)H); 7.39 (t, 1 H, C(7)H, J=7.4); 7.49 (d, 1 H, C(5)H, J=8.8); 7.63 (dd, 1 H, C(3)H, J=15.2, J=7.8); 7.78 (t, 1 H, C(6)H, J=7.8); 7.95 (s, 1 H, C(1b)H); 8.14 (d, 1 H, C(1)H, J=7.8); 8.28 (d, 1 H, C(8)H, J=7.8).

2-(4-methyl-1,3-thiazol-5-yl)ethyl(4-fluoro-9-oxoacridin-10(9H)-yl)acetate (4)

Yellow crystalline solid. Yield: 80 %, m.p. 146-147 B°C. R_f = 0.76. MS, *m/z* (I_{rel} (%)): 397 [Рњ+H]$^+$ (100), 272 [$C_{15}H_{10}FNO_3$+H]$^+$ (88), 226 [$C_{14}H_{10}FNO$ вЂ“ H]$^+$ (30), 213 [$C_{13}H_8FNO$]$^+$ (7). IR (KBr) OS, Cґm^{-1}: 3073вЂ“2855 (СвЂ”H); 1753 (C=$O_{est.}$); 1647 (C=$O_{acridone}$); 1602, 1501, 1462 (C-$C_{P°r}$); 1412 (thiazole ring). ^{1}H-NMR (DMSO-d_6, Oґ, ppm, J/ Hz): 2.26 (s, 3 H, CH_3); 3.15 (t, 2 H, C(3a)H_2, J=6.3); 4.39 (t, 2 H, C(2a)H_2, J=6.3); 5.23 (s, 2 H, C(1a)H_2); 7.32 вЂ“ 7.36 (m, 1 H, C(2)H); 7.39 (t, 1 H, C(7)H, J=7.4); 7.51 (d, 1 H, C(5)H, J=8.8); 7.66 (dd, 1 H, C(3)H, J=15.0, J=7.9); 7.80 (t, 1 H, C(6)H, J=7.9); 8.15 (d, 1 H, C(1)H, J=8.1); 8.29 (d, 1 H, C(8)H, J=7.9); 8.82 (s, 1 H, C(1b)H).

2-(2-fluoro-9-oxoacridin-10(9H)-yl)-N-(1,3-thiazol-2-yl)acetamide (5)

Pale yellow crystalline solid. Yield: 89 %, m.p. 299-300 B°C. R_f = 0.81. MS, *m/z* (I_{rel} (%)): 354 [Рњ+H]$^+$ (100), 254 [$C_{15}H_{10}FNO_2$ вЂ“ H]$^+$ (100). IR (KBr) OS, Cґm^{-1}: 3329 (NвЂ”H); 3164 вЂ“ 2851 (СвЂ”H); 1683 (C=O_{amide}); 1620 (C=$O_{acridone}$); 1603, 1564, 1487, 1462 (C-$C_{P°r}$). ^{1}H-NMR (DMSO-d_6, Oґ, ppm, J/ Hz): 5.54 (s, 2 H, C(1a)H_2); 7.26 (d, 1 H, C(2b)H, J=3.5); 7.37 (t, 1 H, C(7)H, J=7.1); 7.53 (d, 1 H, C(1b)H, J=3.5); 7.67 (d, 1 H, C(4)H, J=8.4); 7.74 (d, 1 H, C(5)H, J=8.6); 7.78 вЂ“ 7.85 (m, 2 H, C(6)H, C(3)H); 8.00 (dd, 1 H, C(1)H, J=7.6, J=2.8); 8.35 (d, 1 H, C(8)H, J=7.5); 12.76 (s, 1 H, NH).

4-(3-thioxo-3H-1,2-dithiol-5-yl)phenyl(2-fluoro-9-oxoacridin-10(9H)-yl)acetate (6)

Dark orange crystalline solid. Yield: 71 %, m.p. 216-217 B°C. R_f = 0,84. MS, *m/z* (I_{rel} (%)): 480 [Рњ+H]$^+$ (100), 226 [$C_{14}H_{10}FNO$ вЂ“ H]$^+$ (10). IR (KBr) OS, Cґm^{-1}: 3061вЂ“2855 (СвЂ”H); 1753 (C=$O_{est.}$); 1642 (C=$O_{acridone}$); 1603, 1485, 1466 (C-$C_{P°r}$). ^{1}H-NMR (DMSO-d_6, Oґ, ppm, J/ Hz): 5.79 (s, 2 H, CH_2); 7.41 (t, 1 H, C(7)H, J = 7.2); 7.47 (d, 2 H, C(1P°)H, C(2P°)H, J = 8.3); 7.76 вЂ“ 7.80 (m, 1 H, C(3)H); 7.83 (s, 1 H, C(5P°)H); 7.87 вЂ“ 7.90 (m, 2 H, C(4)H, C(5)H); 7.98-8.03 (m, 4 H, C(1)H, C(6)H, C(3P°)H, C(4P°)H); 8.36 (d, 1 H, C(8)H, J = 8.0).

This work was financially supported by the Ministry of Education and Science of the Russian Federation.

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Recommended for publication by Prof. A.F. Eleev