ISSN 1070-3632, Russian Journal of General Chemistry, 2019, Vol. 89, No. 1, pp. 157–159. © Pleiades Publishing, Ltd., 2019.
Russian Text © T.N. Kudryavtseva, K.V. Bogatyrev, P.I. Sysoev, L.G. Klimova, 2019, published in Zhurnal Obshchei Khimii, 2019, Vol. 89, No. 1, pp. 148–151.

LETTERS TO THE EDITOR

Synthesis and Antibacterial Activity of New N^9-Substituted Acridine-9-amines

T. N. Kudryavtseva[a]*, K. V. Bogatyrev[a], P. I. Sysoev[a], and L. G. Klimova[b]

[a] *Kursk State University, ul. Radishcheva 33, Kursk, 305000 Russia*
**e-mail: labos.kgu@mail.ru*

[b] *Kursk State Medical University, Kursk, Russia*

Received June 21, 2018; revised June 21, 2018; accepted June 26, 2018

Abstract—A method for the synthesis of N^9-substituted acridine-9-amines by reacting 9-chloroacridines with 2-(2-methyl-5- nitro-1*H*-imidazol-1-yl)ethanamine was developed. The synthesized compounds showed high antibacterial ability against *B. subtilis* bacteria compared with rivanol and metronidazole.

Keywords: acridine-9-amines, metronidazole, antibacterial activity

DOI: 10.1134/S1070363219010298

Continuing the search for new biologically active substances with antibacterial activity in the series of acridine and acridine derivatives [1–3], we studied new N^9-substituted acridine-9-amines, the most interesting representatives of the acridine class, with a wide spectrum of different biological activities such as anti-tumor, antiviral, antibacterial, and anti-inflammatory. In pharmacology, such drugs as acriquine, amsacrine and rivanol [4–9] are actively used. Currently, a number of 9-aminoacridines continues to be actively studied.

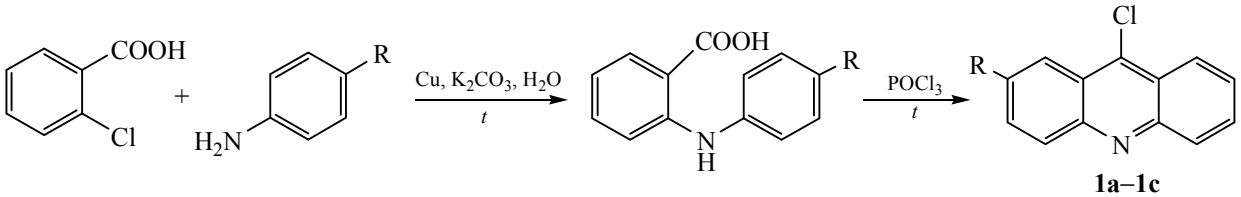
We synthesized compounds bearing 2- (2-methyl-5-nitro-1*H*-imidazol-1-yl)ethane fragment bound with the acridine structural fragment by N^9 nitrogen atom. It should be noted that the preparation of O^9-substituted derivatives by direct reacting 9-chloroacridine with 2-(2-methyl-5-nitro-1*H*-imidazol-1-yl)ethanol did not seem appropriate, since 9-hydroxy derivatives of acridine are unstable compounds. For the synthesis of N^9-substituted acridine-9-amines, 9-chloroacridine was used because of its high reactivity associated with the mobility of the chlorine atom in the position 9. The conditions of the reactions with various amines vary depending on the synthesis conditions and the chemical activity of the starting materials.

The starting 9-chloroacridines **1a–1c** were obtained by known methods from commercially available anilines and *o*-chlorobenzoic acid (Scheme 1).

The target N^9-substituted acridine-9-amines **2a–2c** (as hydrochlorides) were obtained by reacting 9-chloro-acridines **1a–1c** with 2-(2-methyl-5-nitro-1*H*-imidazol-1-yl)ethanamine in DMF at 110°C for 4 h with yields of 60–70% (Scheme 2).

An alternative synthesis method based on the alkylation of 9-aminoacridine with the corresponding halogen derivatives, turned out to be ineffective, since the amino group at the position 9 of acridine has a low nucleophilicity. Thus, the reaction of 9-aminoacridine with 1-(2-bromoethyl)-2-methyl-5-nitro-1*H*-imidazole did not proceed under similar conditions.

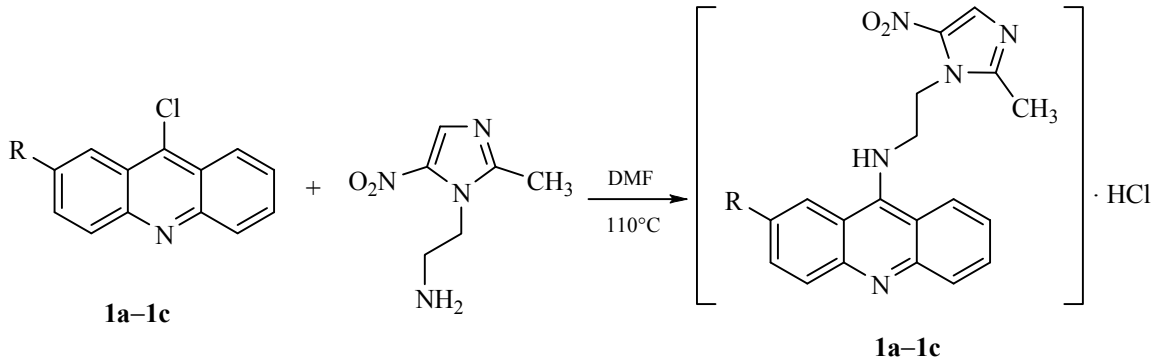
Scheme 1.



1a–1c

R = H (**a**), CH_3 (**b**), OCH_3 (**c**).

Scheme 2.



R = H (**a**), CH_3 (**b**), OCH_3 (**c**).

The ^{1}H NMR spectra of compounds **2a–2c** contain the signals corresponding to the protons of acridine (CH groups, 7.23–8.49 ppm) and imidazole fragments (CH_3 and CH groups, 2.49 and 8.07 ppm respectively), as well as the quartet and triplet signals related to the CH_2–CH_2 unit at 3.21 and 4.53 ppm. In the IR spectra there are the absorption bands of the N–H bond (3437 cm^{-1}) and the nitro group (1535 cm^{-1}).

For the previously obtained acridone and acridine derivatives, it was found that the introduction of the methyl group slightly affects the antimicrobial activity, so the activity of compound **2b** was not studied. The antimicrobial activity of compounds **2a** and **2c** was studied *in vitro* against test strains of *E. coli*, *Ps. aeruginosa*, *Pr. vulgaris*, *S. aureus*, *B. subtilis*, and *Candida albicans* microorganisms according to the method [10] when using ethacridine lactate (rivanol) and 2-(2-methyl-5-nitro-1*H*-imidazol-1-yl)ethanol (metronidazole) used in medicine as antibacterial agents as a reference (see the table). The obtained data show that compounds **2a** and **2c** have a high inhibitory activity against *B. subtilis* bacteria, significantly exceeding by comparison with the reference drugs rivanol and metronidazole (almost 3 times). For other microorganisms, compounds **2a** and **2c** are also superior or comparable to 2-(2-methyl-5-nitro-1*H*-imidazol-1-yl) ethanol. It should be noted that the activity of the 2-methoxyacridine derivative is slightly higher than that of the unsubstituted analog.

General procedure for the synthesis of compounds 2a–2c. To a solution of 4.7 mmol of the corresponding 9-chloroacridine in 25 mL of anhydrous DMF was added 4.7 mmol of the corresponding amine. The resulting mixture was stirred at 110–120°C for 3–4 h, the reaction progress was monitored with TLC. An excess of DMF was distilled off, the residue

Antimicrobial activity of compounds **1** and **3**

Compound	*c*, %	Inhibition 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)
2a	1	14.50±0.76	11.00±0.55	12.50±0.61	19.50±0.38	29.00±0.93	13.50±0.44
	2	16.00±0.81	11.50±0.48	13.50±0.74	23.50±0.52	34.00±0.87	16.50±0.79
2c	1	11.50±0.70	9.00±0.43	13.50±0.76	25.00±0.92	41.00±0.75	15.00±0.56
	2	14.00±0.51	9.50±0.60	17.50±0.49	26.00±0.77	42.00±0.81	15.50±0.63
Metronidazole	1	11.50±0.39	20.00±0.74	14.00±0.42	22.00±0.70	14.50±0.37	20.00±0.63
	2	12.00±0.35	21.00±0.61	22.00±0.73	25.00±0.68	15.00±0.40	25.00±0.75
Rrivanol	1	12.75±0.47	12.00±1.14	12.50±0.83	17.00±1.02	14.50±0.94	13.50±0.56
	2	14.50±0.57	15.00±0.93	15.00±0.66	20.00±0.97	15.00±1.14	15.00±0.96

was dissolved in 50 mL of acetone. The precipitate was filtered off and washed several times with small portions of acetone until the impurities and starting materials disappeared.

***N*-[2-(2-Methyl-5-nitro-1*H*-imidazol-1-yl)ethyl]-acridine-9-amine hydrochloride (2a).** Yield 67%, yellow crystals, mp 198–199°C, R_f 0.05. IR spectrum, ν, cm^{-1}: 3437 (N–H), 3194–2855 (C—H), 1636, 1593, 1566, 1470 (C=C), 1535 (NO_2). ^1H NMR spectrum, δ, ppm (*J*, Hz): 2.49 s (3H, CH_3), 3.20 q (2H, $C^{1a}H_2$, *J* = 6.0), 4.53 t (2H, $C^{2a}H_2$, *J* = 6.5), 7.55 t (2H, C^2H + C^7H, *J* = 8.2), 7.97–8.01 m (4H, C^3H + C^6H + C^4H + C^5H), 8.06 s (1H, $C^{1b}H$), 8.27 d (2H, C^1H + C^8H, *J* = 8.4), 8.59 t (1H, NH, *J* = 5.9). Mass spectrum, *m/z* (I_{rel}, %): 348 (100) $[M + H]^+$, 221 (47) $[C_{15}H_{14}N_2 - H]^+$, 207 (53) $[C_{14}H_{12}N_2 - H]^+$. Found, %: C 59.27; H 4.65; N 18.43. $C_{19}H_{17}N_5O_2 \cdot HCl$. Calculated, %: C 59.45; H 4.73; N 18.25.

2-Methyl-*N*-[2-(2-methyl-5-nitro-1*H*-imidazol-1-yl)ethyl]acridine-9-amine hydrochloride (2b). Yield 64%, yellow crystals, mp 197–198°C, R_f 0.04. IR spectrum, ν, cm^{-1}: 3441 (N–H), 3175–2855 (C–H), 1632, 1574, 1478 (C=C), 1535 (NO_2). ^1H NMR spectrum, δ, ppm (*J*, Hz): 2.43 s (3H, CH_3, acridine), 2.49 s (3H, CH_3, imidazole), 3.22 m (2H, $C^{1a}H_2$), 4.52 t (2H, $C^{2a}H_2$, *J* = 6.8), 7.23 t (1H, C^7H, *J* = 7.5), 7.48 d (1H, C^4H, *J* = 8.5), 7.54–7.58 m (2H, C^3H + C^5H), 7.71 t (1H, C^6H, *J* = 7.7), 7.88 s (1H, C^1H), 8.07 s (1H, $C^{1b}H$), 8.22 d (1H, C^8H, *J* = 8.1), 9.84 m (1H, NH). Mass spectrum, *m/z* (I_{rel}, %): 362 (100) $[M + H]^+$, 235 (51) $[C_{16}H_{16}N_2 - H]^+$, 221 (48) $[C_{15}H_{14}N_2 - H]^+$.

2-Methoxy-*N*-[2-(2-methyl-5-nitro-1*H*-imidazol-1-yl)ethyl]acridine-9-amine hydrochloride (2c). Yield 70%, yellow, mp 248–249°C, R_f 0.07. IR spectrum, ν, cm^{-1}: 3437 (N–H), 3162–2851 (C–H), 1632, 1593, 1570, 1470 (C=C), 1535 (NO_2). ^1H NMR spectrum, δ, ppm (*J*, Hz): 2.49 s (3H, CH_3), 3.20 q (1H, $C^{1a}H$, *J* = 6.0), 3.98 s (3H, OCH_3), 4.53 t (1H, $C^{2a}H$, *J* = 6.8), 4.59 q (1H, $C^{1a}H$, *J* = 6.1), 4.78 t (1H, $C^{2a}H$, *J* = 6.0), 7.49 t (1 H, C^7H, *J* = 7.5), 7.71 d. d (1H, C^3H, *J* = 9.3, 2.6), 7.80 s (1H, C^1H), 7.93–7.97 m (2H, C^4H + C^6H), 8.07 s (1H, $C^{1b}H$), 8.27 d (1H, C^5H, *J* = 7.9), 8.49 d (1H, C^8H, *J* = 8.8), 9.98 t (1H, NH, *J* = 6.1). Mass spectrum, *m/z* (I_{rel}, %): 378 (100) $[M + H]^+$, 251 (34) $[C_{16}H_{16}N_2O - H]^+$, 237 (23) $[C_{15}H_{14}N_2O - H]^+$. Found, %: C 57.85; H 4.93; N 16.74. $C_{20}H_{19}N_5O_3 \cdot HCl$. Calculated, %: C 58.04; H 4.87; N 16.92.

Thin layer chromatography was carried out on Sorbfil PTSH-P-B-UV plates, eluting with toluene–acetone–ethanol, 10 : 3 : 2. IR spectra (KBr) were recorded using an FSM 1201 Monitoring spectrometer. Mass spectra were recorded on an ACQUITY UPLC H-Class system equipped with UV/mass detectors ACQUITY SQD Waters. ^1H and ^{13}C NMR spectra were registered on a Bruker AV-600 spectrometer from DMSO-d_6 solutions. Elemental analysis was performed on a PerkinElmer 2400 CHN analyzer.

Antibacterial activity screening of DMSO solutions of the tested compounds with a concentration of 1.0 and 2.0% was performed in Petri dishes with agar medium, previously seeded with test strains of microorganisms with a microbial load of 106 microbial cells per 1 mL. Diameter of growth inhibition zones was measured with an accuracy of 1 mm after 24 h [10].

FUNDING

This work was financially supported of the Ministry of Education and Science of the Russian Federation (project no. 4.9516.2017 / BC).

CONFLICT OF INTEREST

No conflict of interests was declared by the authors.

REFERENCES

1. Kudryavtseva, T.N., Sysoev, P.I., Popkov, S.V., and Klimova, L.G., *Russ. J. Gen. Chem*., 2017, vol. 87, no. 8, p. 1702. doi 10.1134/S1070363217080102
2. Kudryavtseva, T.N., Lamanov, A.Yu., Klimova, L.G., and Nazarov, G.V., *Russ. J. Gen. Chem*., 2018, vol. 88, no. 4, p. 676. doi 10.1134/S1070363218040102
3. Kudryavtseva, T.N., Lamanov, A.Yu., Klimova, L.G., and Nazarov, G.V., *Russ. Chem. Bull*., 2017, vol. 66, no. 1, p. 123. doi 10.1007/s11172-017-1709-8
4. Howell, L.A., Gulam, R., Mueller, A., O'Connell, M.A., and Searcey, M., *Bioorg. Med. Chem. Lett*., 2010, vol. 20, p. 6956. doi 10.1016/j.bmcl.2010.09.128
5. Denny, W.A., Atwell, G.J., Rewcastle, G.W., and Baguley, B.C., *J. Med. Chem*., 1987, vol. 30, p. 658. doi 10.1021/jm00387a013
6. US Patent 0207909, 2003.
7. US Patent 0069301, 2009.
8. Vogtherr, M., Grimme, S., Elshorst, B., Jacobs, D.M., Fiebig, K., Griesinger, C., and Zahn, R., *J. Med. Chem*., 2003, vol. 46, p. 3563. doi 10.1021/jm034093h
9. Papadopoulou, M.V., Trunz, B.B., Bloomer, W.D., McKenzie, C., Wilkinson, S.R., Prasittichai, C., Brun, R., Kaiser, M., and Torreele, E., *J. Med. Chem*., 2011, vol. 54, p. 8214. doi 10.1021/jm201215n
10. *Gosudarstvennaya farmakopeya Rossiiskoi Federatsii* (State Pharmacopoeia of the Russian Federation), Moscow: MinZdrav RF, 2015, vol. 1, p. 993.