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Synthesis of *N*-Derivatives of Cytisine, Anabasine, and Salsoline Alkaloids with Pharmacophore 3-Aminopyridine-2(1*H*)-one and 5-Methyl-7-phenyloxazole[5,4-*b*]pyridine Cycles

I. V. Palamarchuk[a,*], D. N. Ogurtsova[b], T. M. Seilkhanov[c], and I. V. Kulakov[a]

[a] *Institute of Chemistry, Tyumen State University, Tyumen, 625003 Russia*
[b] *Omsk O.M. Dostoevskii State University, Omsk, 644077 Russia*
[c] *Ualikhanov Kokshetau State University, Kokshetau, 020000 Kazakhstan*
**e-mail: i.v.palamarchuk@utmn.ru*

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Abstract—The reaction of nucleophilic substitution of 2-chloro-*N*-(6-methyl-2-oxo-4-phenyl-1,2-dihydropyridin-3-yl)acetamide and 2-(chloromethyl)-5-methyl-7-phenyloxazolo[5,4-*b*]pyridine with cytisine, anabasine, and salsoline alkaloids has afforded the corresponding derivatives. Structure of the obtained compounds has been confirmed by means of ^{1}H and ^{13}C NMR spectroscopy.

Keywords: alkaloid, cytisine, anabasine, salsoline, 3-amino-4-phenylpyridine-2(1*H*)-one, chloroacetamide, oxazolo[5,4-*b*]pyridine, nucleophilic substitution

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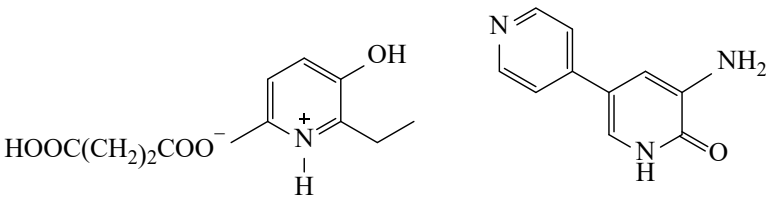
Combination of two or more pharmacophore fragments (one of them being a natural compound) in a single molecule is a main route to the design of novel biologically active compounds. Basic synthetic pharmacophores include derivatives of pyridine which are components of vital vitamins (B_5 and B_6), drugs exhibiting diverse therapeutic activity (antibacterial, antituberculous, antidepressant, antihistaminic, analgesic, psychotropic, nootropic, etc.) [1–3], and agricultural chemicals (efficient fungicides, herbicides, and growth promotors) [4, 5]. Structural features are important in determining the pharmacological effect of the active substances, since the change in the fragments position or the formation of additional bonds can alter the range of the activity. The presence of electron-donating hydroxyl and alkyl groups in pyridine derivatives leads to the antioxidant activity. For example, the Mexidol drug (3-oxy-6-methyl-2-ethylpyridinium succinate **1**, see the figure) shows antioxidant and membrane-protecting action. Exchange of the OH group with the NH_2 one alters its biological activity. For example, the 3-aminopyridine-2(1*H*)-ones include the drugs like Amrinon **2** (see the figure) [6]. The presence of an amino acid fragment makes 3-aminopyridine-2(1*H*)-ones promising as building blocks for the synthesis of peptidomimetics [7, 8].

Derivatives of pyridine fused at the C^2 and C^3 positions, for example, bicyclic oxazolo[5,4-*b*]pyridines also exhibit wide range of biological activity including antimicrobial, antitumor, anti-inflammatory, and analgesic [9–11].

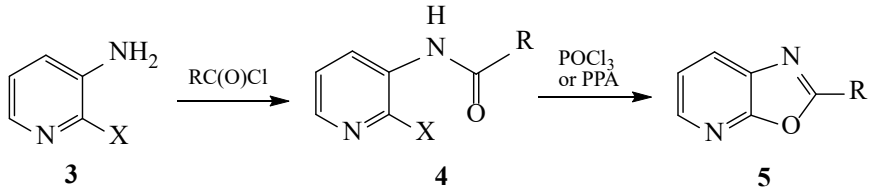
The synthetic routes to oxazolo[5,4-*b*]pyridines **5** [12–14] include condensation of benzamides **4** in an acidic medium (polyphosphoric acid or phosphorus oxychloride); the benzamides **4** being obtained from



1 **2**

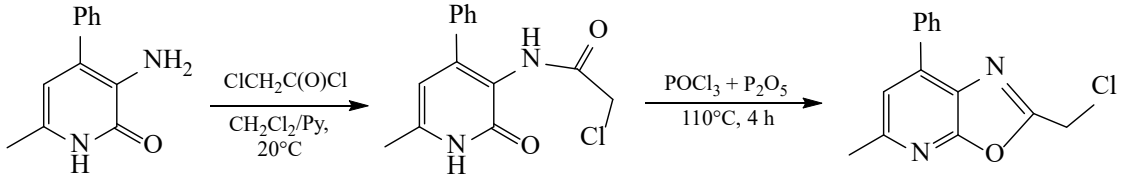
Structures of Mexidol **1** and Amrinon **2**.

Scheme 1.



X = OH; Hal; R = Ar.

Scheme 2.



the corresponding 3-amino-2-hydroxy- or 3-amino-2-halopyridines **3** (Scheme 1).

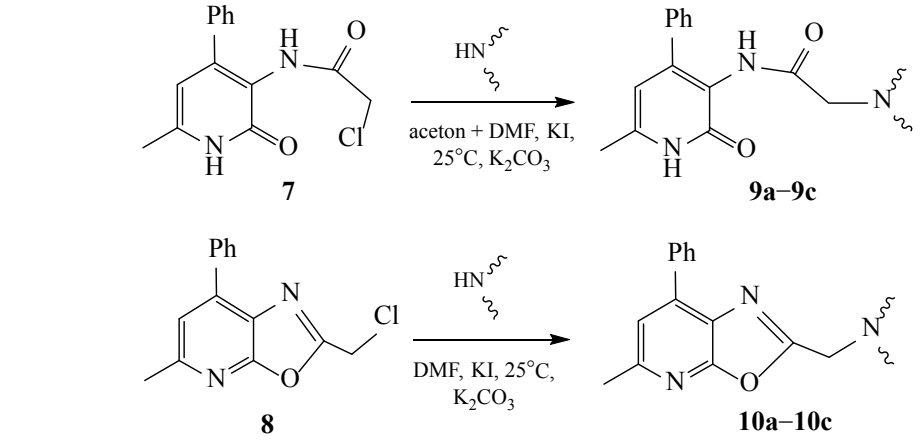
The derivatives containing bicyclic oxazolo[5,4-*b*] pyridine moiety and physiologically active alkaloids (cytisine, anabasine, salsoline) as substituents have not been reported in the literature.

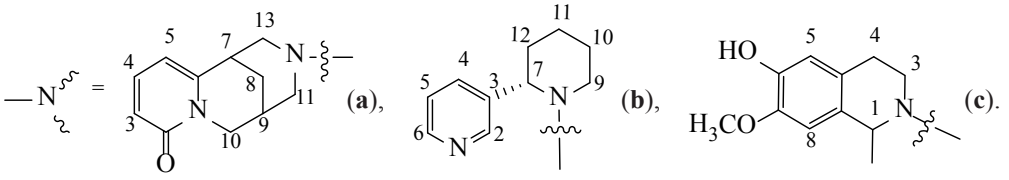
The following substrates were used as the starting materials for the modification with natural alkaloids: 3-aminopyridine-2(1*H*)-one **6** [15], 2-chloro-*N*-(6-methyl-2-oxo-4-phenyl-1,2-dihydropyridin-3-yl)acetamide **7**, and 2-(chloromethyl)-5-methyl-7-phenyloxazolo[5,4-*b*]-pyridine **8** [16, 17] (Scheme 2).

The use of compound **7** in the synthesis of 2-methylamino-substituted oxazolo[5,4-*b*]pyridine via nucleophilic substitution with different amines has been earlier demonstrated [17].

Extending our studies on the synthesis of novel derivatives based on cytisine, anabasine, and salsoline alkaloids [18–21], we used the classical reaction of nu-

Scheme 3.





cleophilic substitution of chlorine atom in compounds **7** and **8** (Scheme 3).

The reaction in a mixture of the alkylating agent and alkaloid (anabasine was used as the hydrochloride) was performed at room temperature (for compounds **9a**–**9c**) or at reflux (for compounds **10a**–**10c**) in anhydrous acetone in the presence of potassium carbonate, 10 vol% of DMF, and small amount of potassium iodide. The addition of DMF allowed dissolution of anabasine hydrochloride and significantly accelerated the nucleophilic substitution. The target products were isolated from the reaction mixture in the form of the bases. The use of DMF only at heating (60°C) for the synthesis of compounds **9a**–**9c** led to the formation of 1*H*-pyrido[2,3-*b*][1,4]oxazine-2(3*H*)-one via cyclization of compound **7** as side product. The formation of that compound in basic medium has been described previously [16].

Structure of the obtained compounds was confirmed by means of ^{1}H and ^{13}C NMR spectroscopy. The spectra of compounds **9a**–**9c** and **10a**–**10c** contained the products of the alkaloid fragments in the characteristic ranges as well as diastereotropic bridging methylene protons (as two doublets with high spin-spin interaction constants) and the protons of aromatic 3-aminopyridine and 7-phenyloxazolo[5,4-*b*]pyridine cycles. The obtained derivatives are interesting objects with potential anti-inflammatory activity.

EXPERIMENTAL

^{1}H and ^{13}C NMR spectra were recorded using a Jeol JNM-ECA 400 instrument (400 and 100 MHz, respectively) in $CDCl_3$ with TMS as internal reference. TLC analysis was performed using Sorbfil plates with propanol-2–benzene–ammonia (10 : 5 : 2) as eluent and iodine vapor as developer.

Compounds 9a–9c (*general procedure*). A mixture of 138 mg (0.5 mmol) of compound **7**, 0.5 mmol of the corresponding alkaloid (cytisine, anabasine hydrochloride, or salsoline), 20 mg of potassium iodide, and 138 mg (1.0 mmol) of potassium carbonate in 5 mL of acetone and 0.5–1.0 mL of DMF was stirred at room temperature during 10–15 h. The reaction course was monitored by means of TLC. The reaction mixture was filtered to separate salts precipitate, washed with acetone, and recrystallized from a hexane : methylene chloride mixture (3 : 1) after the solvent removal.

***N*-(6-Methyl-2-oxo-4-phenyl-1,2-dihydropyridin-3-yl)-2-(8-oxo-1,5,6,8-tetrahydro-2*H*-1,5-methanopyrido[1,2-*a*][1,5]diazocin-3(4*H*)-yl)acetamide (9a).** Yield 153 mg (71%), white crystals, mp 157–160°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.77 and 1.86 two br. d [2H, H-8, $J_{8,7}$, $J_{8,9}$ = 12.2 Hz], 2.35 s (3H, CH_3), 2.38–2.48 m (4H, H-9, H-7,H-11*a*, H-13*a*), 2.92–3.01 m (4H, N-CH_2, H-11*e*, H-13*e*), 3.80 d. d [1H, H-10*a*, $^2J_{10a,10e}$ = 15.3 Hz, $J_{10a,9}$ = 6.1 Hz), 4.01 d [1H, H-10*e*, $^2J_{10e,10a}$ = 15.3 Hz], 5.72 d [1H, H-5, $J_{5,4}$ = 7.0 Hz], 6.02 s (1H, H-5'), 6.34 d [1H, H-3, $J_{3,4}$ = 9.2 Hz], 7.13 d. d [1H, H-4, $J_{4,5}$ = 7.0, $J_{4,3}$ = 9.2 Hz], 7.29–7.40 m (6H, 5H Ph, NH), 12.61 br. s (1H, NH). ^{13}C NMR spectrum, δ, ppm: 18.9, 25.3, 27.9, 35.1, 49.6, 59.9, 60.2, 61.3, 105.0, 107.9, 116.8, 119.8, 127.7 (2C Ph), 128.2 (2C Ph), 128.3, 137.6, 138.6, 143.5, 150.0, 151.0, 161.8, 163.2, 169.8. Found, %: C 69.42; H 6.48; N 13.43. $C_{25}H_{26}N_4O_3$. Calculated, %: C, 69.75; H, 6.09; N, 13.01.

***N*-(6-Methyl-2-oxo-4-phenyl-1,2-dihydropyridin-3-yl)-2-(2-(pyridin-3-yl)piperidin-1-yl)acetamide (9b).** Yield 90 mg (45%), pale beige crystals, mp 131–134°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.40–1.87 m [6H, H-10, H-11, H-12], 2.18–2.25 m (1H, H-9*a*), 2.36 s (3H, 6-CH_3), 2.53 d [1H, N-CH_a, $^2J_{ab}$ = 16.8 Hz], 2.98 d [1H, N-CH_b, $^2J_{ba}$ = 16.8 Hz], 3.22 br. d (1H, H-9*e*, *J* = 10.7 Hz), 3.28 br. d (1H, H-7, *J* = 9.2 Hz), 6.13 s (1H, H-5'), 7.23 d. d (1H, H-5, $^3J_{5,4}$ = 7.6 Hz, $^3J_{5,6}$ = 4.6 Hz), 7.29–7.36 m (5H, Ph), 7.71 d (1H, H-4, $^3J_{4,5}$ = 7.6 Hz), 8.52 d (1H, H-6, $^3J_{6,5}$ = 4.6 Hz), 8.57 s (1H, H-2), 8.88 s (1H, NH), 13.31 br. s (1H, NH). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 18.7, 24.6, 26.0, 36.6, 55.2, 58.7, 65.4, 108.23, 120.3, 123. 8, 127.1 (2C Ph), 128.2, 128.3 (2C Ph), 134.6, 138.2, 139.2, 142.0, 148.5, 148.9, 149.2, 162.4, 169.1. Found, %: C 72.03; H 6.13; N 13.49. $C_{24}H_{26}N_4O_2$. Calculated, %: C 71.62; H 6.51; N 13.92.

2-(6-Hydroxy-7-methoxy-1-methyl-3,4-dihydroisoquinolin-2(1*H*)-yl)-*N*-(6-methyl-2-oxo-4-phenyl-1,2-dihydropyridin-3-yl)acetamide (9c). Yield 89 mg (41%), pale beige crystals, mp 248–251°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.27 d [1H, 1-CH_3, *J* = 6.4 Hz], 2.31 s (3H, 6-CH_3), 2.52–2.57 m (1H, H_a-4), 2.68–2.71 m (2H, H_e-4, H_a-3), 2.96–3.03 m (1H, H_e-3), 3.13 d [1H, N-CH_a, $^2J_{ab}$ = 16.5 Hz], 3.17 d [1H, N-CH_b, $^2J_{ba}$ = 16.5 Hz], 3.73 q [1H, C*H*-CH_3, *J* = 6.4 Hz], 3.84 s (1H, OCH_3), 5.29 s (1H, OH), 6.07 s (1H, H-5'), 6.44 s (1H, H-5), 6.59 s (1H, H-8), 7.35–7.39 m (5H, Ph), 8.82 br. s (1H, NH), 11.45 br. s (1H, NH). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 16.8, 18.3, 24.7, 43.0, 54.0, 54.6, 56.3, 104.3, 108.8, 113.3, 119.2, 123.8, 125.7 (2C Ph), 126.1, 126.3 (2C Ph), 128.0, 136.6, 140.5, 143.0, 144.2, 146.2, 159.0,

167.8. Found, %: C 68.83; H 5.88; N 9.32. $C_{25}H_{27}N_3O_4$. Calculated, %: C 69.27; H 6.28; N 9.69.

Compounds 10a–10c (*general procedure*). A mixture of 130 mg (0.5 mmol) of compound **8**, 0.5 mmol of the corresponding alkaloid (cytisine, anabasine hydrochloride, or salsoline), and 70 mg (0.5 mmol) of potassium carbonate in 5 mL of DMF was stirred at room temperature during 5 h. The reaction course was monitored by means of TLC. The reaction mixture was treated with 150 mL of icy water, filtered to separate the precipitate, washed with water, and recrystallized from a propanol-2 : hexane mixture (1 : 5) after drying in air.

3-{(5-Methyl-7-phenyloxazolo[5,4-*b*]pyridin-2-yl)methyl}-1,2,3,4,5,6-hexahydro-8*H*-1,5-methanopyrido[1,2-*a*][1,5]diazocine-8-one (10a). Yield 113 mg (55%), white crystals, mp 143–146°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.73, 1.87 two br. d [2H, H-8, $J_{8,7}$, $J_{8,9}$ = 12.8 Hz], 2.46 br. s (1H, H-9), 2.69 s (3H, 5'-CH_3), 2.73 br. d [1H, H-7, J = 11.0 Hz], 2.79 d. d [1H, H-11*a*, $J_{11a,11e}$ = 10.8 Hz, $J_{11a,9}$ = 2.1 Hz], 2.97 br. d [1H, H-13*a*, $J_{13a,7}$ = 1.8 Hz], 3.03–3.11m (2H, H-11*e*, H-13*e*), 3.84 d [1H, N-CH_a, ^1J = 15.6 Hz], 3.91 d [1H,N-CH_b, ^1J = 15.6 Hz], 3.93 d [1H, H-10a, $J_{10a,10e}$ = 15.5 Hz], 4.08 d [1H, H-10_e, $J_{10e,10a}$ = 15.5 Hz], 5.99 d. d [1H, H-5, $J_{5,4}$ = 6.9 Hz, $J_{5,3}$ = 1.4 Hz), 6.46 d. d [1H, H-3, $J_{3,4}$ = 9.2 Hz, $J_{3,5}$ = 1.4 Hz], 7.27 d. d [1H, H-4, $J_{4,5}$ = 6.9 Hz, $J_{4,3}$ = 9.2 Hz], 7.38 s (1H, H-6'), 7.47 m (1H, H-4, Ph), 7.54 t [2H, H-3,5 Ph, J = 7.5 Hz], 8.05 d. d (2H, H-2,6 Ph, J = 8.5 Hz, 1.1 Hz). ^{13}C NMR spectrum, δ, ppm: 24.3, 25.2, 27.9, 35.4, 49.8, 54.6, 58.8, 59.3, 104.6, 116.9, 118.3, 127.6, 128.8 (2C Ph), 128.9 (2C Ph), 129.5, 134.7, 138.6, 140.9, 151.0, 154.6, 160.4, 162.0, 163.6. Found, %: C 72.38; H 6.21; N 13.17. $C_{25}H_{24}N_4O_2$. Calculated, %: C 72.80; H 5.86; N 13.58.

5-Methyl-7-phenyl-2-{[2-(pyridin-3-yl)piperidin-1-yl]methyl}oxazolo[5,4-*b*]pyridine (10b). Yield 44 mg (23%), beige crystals, mp 106–110°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.30–1.83 m [6H, H-10, H-11, H-12], 2.26–2.38 m (1H, H-9*a*), 2.71 s (3H, 6-CH_3), 3.18 br. d (1H, H-9*e*, J = 12.2 Hz), 3.53 br. d (1H, H-7, J = 10.7 Hz), 3.62 d [1H, N-CH*a*, $^2J_{ab}$ = 15.3 Hz], 3.87 d [1H, N-CH_b, $^2J_{ba}$ = 15.3 Hz], 7.21 d. d (1H, H-5, $^3J_{5,4}$ = 7.6 Hz, $^3J_{5,6}$ = 4.6 Hz), 7.38 s (1H, H-6'), 7.42–7.55 m (3H, H-3,4,5, Ph), 7.97 d (1H, H-4, $^3J_{4,5}$ = 7.6 Hz), 8.04 d (2H, H-2, 6 Ph, J = 7.6 Hz), 8.54 d (1H, H-6, $^3J_{6,5}$ = 4.6 Hz), 8.71 s (1H, H-2). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 22.7, 24.3, 25.8, 36.6, 52.1, 53.7, 64.4, 118.3, 124.0, 127.5, 128.8 (2C, Ph), 128.9 (2C Ph), 129.5, 129.6, 134.7, 135.8, 139.7, 140.8, 148.5, 149.2, 154.5, 162.8. Found, %: C 74.53; H 6.67; N 14.14. $C_{24}H_{24}N_4O$. Calculated, %: C 74.97; H 6.29; N 14.57.

7-Methoxy-1-methyl-2-{(5-methyl-7-phenyloxazolo[5,4-*b*]pyridin-2-yl)methyl}-1,2,3,4-tetrahydroisoquinolin-6-ol (10c). Yield 91 mg (44%), white crystals, mp 157–159°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.47 d [3H, 1-CH_3, J = 6.1 Hz), 2.69 s (3H, 5-CH_3), 2.71–2.74 m (1H, H_a-4), 2.79–2.86 m (1H, H_e-4), 2.99 d. d. d [1H, H_a-3, ^2J = 11.8 Hz, ^3J = 5.7 Hz, ^3J = 5.3 Hz], 3.27 d. d. d [1H, H_e-3, ^2J = 12.2 Hz, ^3J = 7.6 Hz, ^3J = 4.6 Hz], 3.83 s (1H, OCH_3), 3.97 q (1H, C*H*-CH_3, J = 6.1 Hz), 4.11 d [1H, N-CH_a, J = 15.2 Hz], 4.21 d [1H, N-CH_b, J = 15.2 Hz], 5.54 br. s (1H, OH), 6.53 s (1H, H-5), 6.63 s (1H, H-8), 7.38 s (1H, H-6'), 7.47 t [1H, H-4 Ph J = 6.1 Hz], 7.53 t [2H, H-3,5 Ph, J = 6.9 Hz], 8.07 d [2H, H-2,6, Ph, J = 6.1 Hz]. ^{13}C NMR spectrum, δ, ppm: 20.8, 24.3, 26.7, 45.9, 51.5, 56.0, 56.2, 109.4, 114.1, 118.2, 126.6, 127.9, 128.9 (4C Ph), 129.4, 130.7, 134.8, 140.8, 143.9, 145.0, 154.5, 160.5, 163.4. Found, %: C 71.86; H 6.50; N 9.73. $C_{25}H_{25}N_3O_3$. Calculated, %: C 72.27; H 6.07; N 10.11.

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CONFLICT OF INTEREST

No conflict of interest was declared by the authors.

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