

Irina V. Palamarchuk^{*ID}, Ivan V. Kulakov^{ID}, Svetlana S. Volkova

School of Natural Sciences, University of Tyumen, Tyumen, Russia
(*Corresponding author's e-mail: ivpalamarchuk@utmn.ru)

Synthesis and Optical Properties of Substituted Derivatives of Oxazolo[5,4-b]Pyridine

In continuation of our work on the synthesis and study of new properties of 4-substituted 3-aminopyridin-2-(1*H*)-ones, we carried out the synthesis and subsequent cyclization of the corresponding oxalyl amides. The aminolysis reaction of diethyl oxalate with 3-aminopyridin-2-(1*H*)-ones was carried out by boiling without solvent at a temperature of 150 °C. In this case, intermediate oxalic acid monoamides with the remainder of the ester group were also recorded and separately identified. It was shown that under the action of phosphorus oxychloride the synthesized oxalic acid diamides undergo fairly smooth intramolecular cyclization into symmetrical bis-derivatives of oxazolo[5,4-b]pyridine. The photoluminescent properties of our newly obtained oxazolo[5,4-b]pyridine derivatives **5-8a-c** and 2,2'-bisoxazolo[5,4-b]pyridines **4a-c** were studied, including such parameters as maximum absorption (λ), molar absorption coefficient (ϵ), Stokes shift, and quantum yield. All compounds were found to luminesce with a bluish-blue color and exhibit maximum absorption wavelengths in the range of 299–333 nm (in acetonitrile) and 281–317 nm (in toluene), which is associated with the π - π^* electron transition. A fairly large Stokes shift (83–128 nm) is observed for all compounds. It was also found that the presence of a carboxyl linker at the C-2 position of compounds **5-8a-c** does not significantly affect the shift of the absorption band maxima and other spectral characteristics of the molecules. It should be noted that symmetrical conjugated 2,2'-bisoxazolo[5,4-b]pyridines **4a-c**, featuring two oxazolo[5,4-b]pyridine rings, exhibit fairly high quantum yield values ($\phi \approx 0.70$ – 0.82) compared to the known standard quinine sulfate ($\phi \approx 0.55$), allowing their potential application as effective fluorophores.

Keywords: 3-aminopyridin-2(1*H*)-ones, oxazolo[5,4-b]pyridines, intramolecular heterocyclization, biological activity, UV spectroscopy, optical properties, quantum yield, Stokes shift

Introduction

The oxazole-fused pyridine derivatives, oxazolo[5,4-b]- and oxazolo[4,5-b]pyridines, are of great interest due to their application in various fields of chemistry. The condensed pyridine fragment is acceptor and polar, thereby ensuring enhanced solubility of oxazolopyridines in water, concomitantly promoting the formation of additional interactions with the target receptor protein through a hydrogen bond with a heteroatom [1]. Oxazolopyridine derivatives have proven to serve as inhibitors of sphingomyelin synthase (SMS) (compound A, Fig. 1) [2]. The activity of this enzyme is associated with the progression of atherosclerosis, as well as inhibitors of I κ B kinase (compound B) [3], which promotes the activation of immunoregulatory factors during inflammation.

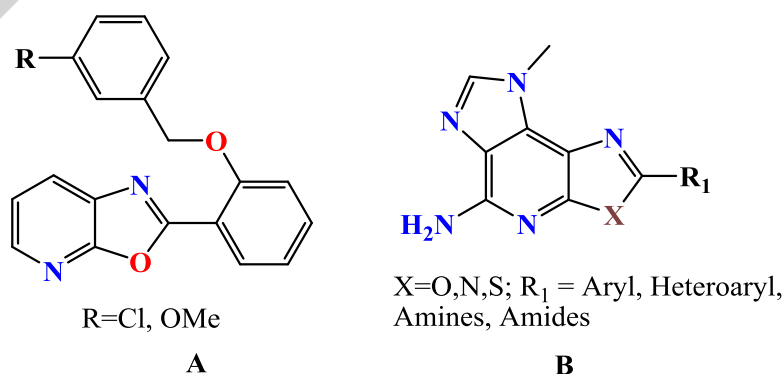
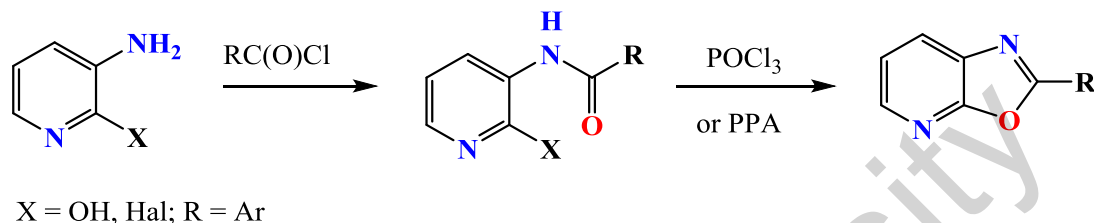


Figure 1. Inhibitors of sphingomyelin synthase (**A**) and inhibitors of I κ B kinase (**B**)

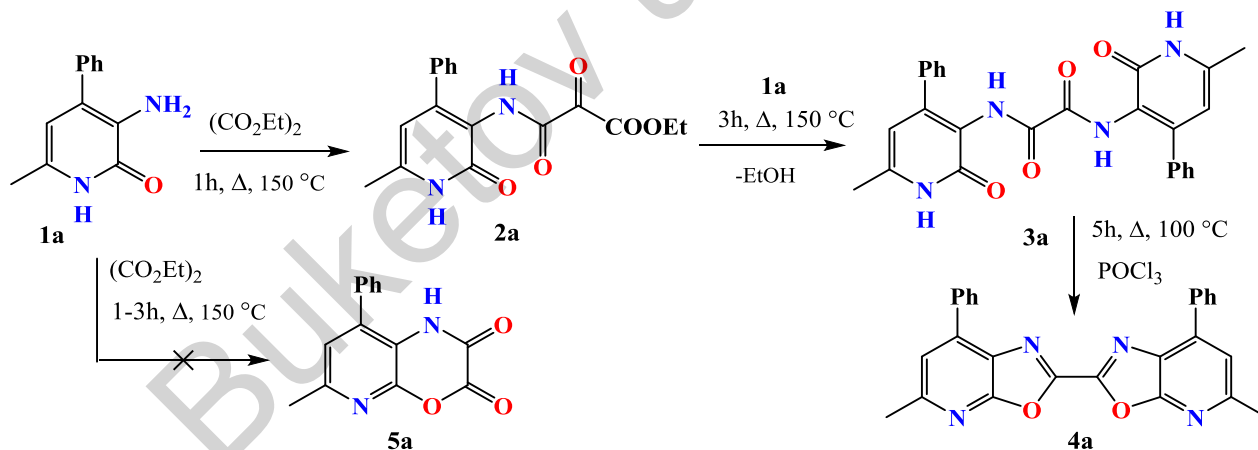
Being structural isosteres of the purine bases—adenine and guanine, these compounds exhibit a wide range of biological activity: anti-cancer, antimicrobial, antidiabetic, anti-inflammatory, etc. [4–12]. Furthermore, the potential for application as organic luminophores and biomarkers is also noteworthy [13–16]. For example, in 2011 [17], a study was conducted using oxazolopyridine derivatives as amyloid- β ligands in positron emission tomography (PET). This analysis allows the *in vivo visualisation* of amyloid- β fibrillary plaques, which are indicative of the pathology of Alzheimer's disease.

The most common method for synthesis of oxazolo[5,4-b]pyridines (Scheme 1) is the use of 3-amino-5-hydroxy- or 3-amino-5-halopyridines as initial compounds. The first step is the Schotten–Baumann reaction. At the second step the obtained amides cyclized into oxazolopyridines under the action of polyphosphoric acid or phosphorus oxychloride [18–20].



Scheme 1. General approach for the synthesis of oxazolo[5,4-b]pyridines

Thus, we have previously shown that that certain amides (acetamide, chloroacetamide of 3-aminopyridones) undergo cyclisation when exposed to a mixture of phosphorus oxide and phosphorus oxychloride, resulting in the formation of the corresponding oxazolo[5,4-b]pyridines [21]. Herein we report a method for the preparation of bis-oxazolopyridine **4a** was described. The first step is acylation of 3-amino-6-methyl-4-phenylpyridin-2-(1*H*)-one **1a** with a 1.5-fold excess of diethyl oxalate upon heating to 150 °C (Scheme 2). The diamide **3a** obtained in two stages, when heated with phosphorus oxychloride, forms symmetrical 5,5'-dimethyl-7,7'-diphenyl-2,2'-bis-(oxazolo[5,4-b]pyridine **4a** [22].



Scheme 2. Synthesis of 3-amino-6-methyl-4-phenylpyridin-2-(1*H*)-one **1a** [22]

It should be noted that the reaction of 3-amino-6-methyl-4-phenylpyridin-2-(1*H*)-one **1a** (which is essentially a binucleophile due to additional lactim-lactam tautomerism) with excess of diethyl oxalate we planned to obtain 1*H*-pyrido[2,3-*b*][1,4]oxazine-2,3-dione.

Experimental

Materials

The obtained compounds were analyzed on an Agilent 1260 Infinity II chromatograph connected to an Agilent 6545 LC/Q-TOF high-resolution mass spectrometer equipped with an AJS ESI dual ion source operating in positive ion mode. Mass spectra with LC/MS precision were obtained in the range of 100–1000 *m/z*, at a scan rate of 1.5 spectra per second.

The ^1H and ^{13}C NMR spectra in DMSO- d_6 solutions were recorded on Bruker AVANCE 400 (400 MHz, 100 MHz) and Magritek spinsolve 80 carbon ultra (81 MHz, 20 MHz) spectrometers.

Melting points of synthetic compounds were determined on a Stuart SMP10 hot bench. All reactions were monitored by thin-layer chromatography (TLC) and identified by UV or iodine vapor.

UV-visible spectra were recorded in the range of 200–600 nm in a quartz cell with an optical path length of 1 cm using a Shimadzu UV-2600 spectrophotometer. Fluorescence spectrum of the studied compounds was recorded in the range of 300–700 nm at room temperature using a Shimadzu RF 5301 PC spectrofluorimeter. The solvents used were of analytical grade (for UV spectroscopy).

3-Aminopyridine-2(1*H*)-ones were prepared according to a similar literature procedure [28].

Synthesis and Spectral Analysis of Synthesized Compounds

The synthesis of **oxazolo[5,4-*b*]pyridine derivatives 5-8a-c** [23] involved heating a mixture of 1 mmol of 3-amino-pyridin-2-(1*H*)-one and 5 mmol of the corresponding anhydrides (succinic, maleic, glutaric, phthalic anhydrides) in 5 mL of acetic acid at reflux with vigorous stirring for 10 hours. The mixture was then cooled and poured into 25 mL of water. The resulting precipitates were filtered and recrystallized from a mixture of hexane, 2-propanol, and dichloromethane.

N^1, N^2 -bis(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)oxalamide (3b) 0.4 ml (3.0 mmol) of diethyl oxalate is added to 276 mg (2.0 mmol) of 3-amino-4,6-dimethylpyridin-2(1*H*)-one **1b** and the mixture is boiled for 3 hours under reflux. Then 1 ml of 2-propanol is added and the mixture is boiled for another 1 hour. The precipitate that forms upon cooling is filtered, washed with cold 2-propanol and dried. 102 mg of a finely crystalline white powder is obtained (yield 53 %). An analytically pure sample is obtained by recrystallization from a mixture of DMF and 2-propanol, m.p. = 210–211 °C. IR spectrum (KBr) ν , cm^{-1} : 1642–1693 (NC=O); 3466 (NH). ^1H NMR spectrum (400 MHz, DMSO- d_6 , δ , ppm): 2.03 s (6H, 4,4'- CH_3); 2.16 s (6H, 6,6'- CH_3); 5.90 s (2H, C(5,5')-H); 9.35 br. s (2H, 3,3'-NHCO), 11.49 br. s (2H, NHCO). ^{13}C NMR spectrum (101 MHz, DMSO- d_6 , δ , ppm): 17.79 (4, 21- CH_3), 18.04 (6, 19- CH_3), 106.33 (C-5, 20), 120.89 (C-3, 16), 141.85 (C-4, 21), 145.26 (C-6, 19), 157.93 (2, 17- CONH), 159.17 (9, 13-NHCO). Found, %: C, 58.56; H, 5.85; N, 17.38. $\text{C}_{16}\text{H}_{18}\text{N}_4\text{O}_4$. Calculated, %: C, 58.17; H, 5.49; N, 16.96.

Ethyl 3-((6-methyl-2-oxo-4-(thiophen-2-yl)-1,2-dihydropyridin-3-yl)amino)-2,3-dioxopropanoate (2c). 200 mg (1.0 mmol) of 3-amino-4-(thiophen-2-yl)pyridin-2-one **1c** was boiled With 2 ml of diethyl oxalate (15 mmol) for about 5 hours. After cooling, the precipitated product is filtered, washed with a mixture of 2-propanol and hexane, and dried. After recrystallization, 258 mg (yield 78 %) is obtained with M.p. = 220–222 °C.

^1H NMR (80 MHz, DMSO- d_6 , δ , ppm): 1.3 t (3H, $J = 6.4$ Hz, CH_2CH_3), 2.2 s (3H, 6- CH_3); 4.3 q (2 H, $J = 6.2$ Hz, CH_2CH_3); 6.4 s (1H, H-5); 7.2 s (1H, H-4' thiophen); 7.7 br. s (2H, H — 3',5' thiophen); 10.1 br. s, 1H, 3-NHCO); 11.8 br. s (1H, NHCO). ^{13}C NMR spectrum (21 MHz, DMSO- d_6 , δ , ppm): 14.1 (CH_2CH_3), 18.54 (CH_3), 63.3 (OCH_2), 102.9, 118.6, 127.3 (3-C thiophene), 129.1 (4-C thiophene), 130.0 (5-C thiophene), 137.1, 141.1, 143.6, 159.2 (COO), 160.3 (CONH), 161.8 (-NHCO). Found, %: C, 54.89; H, 4.61; N, 9.14. $\text{C}_{14}\text{H}_{14}\text{N}_2\text{O}_4\text{S}$. Calculated, %: C, 54.44; H, 4.26; N, 8.87.

N^1, N^2 -bis(6-methyl-2-oxo-4-(thiophen-2-yl)-1,2-dihydropyridin-3-yl)oxalamide (3c) Obtained similarly **3b** from 200 mg (1.0 mmol) 3-amino-4-(thiophen-2-yl)pyridin-2-one **1c**, 0.2 ml (1.5 mmol) of diethyl oxalate. 225 mg (48 %) of a finely crystalline white powder are obtained. An analytically pure sample is obtained by recrystallization from a mixture of DMF and propanol-2 solvents. M.p. > 350 °C. ^1H NMR spectrum (80 MHz, DMSO- d_6 , δ , ppm): 2.20 s (6H, 2 CH_3); 6.37 s (2H, 2 H-5); 7.11 dd (2H, $J = 4.8, 4.0$ Hz, H-4' thiophen); 7.64 t (4 H, $J = 4.5$ Hz, 2 H-3',5' thiophen); 9.51 br. s, (2 H, 2 3-NH CO); 11.74 br. s (2H, 2NHCO). ^{13}C NMR spectrum (20 MHz, DMSO- d_6 , δ , m. d.): 18.5 (2 CH_3), 103.2 (2 C-5), 119.4 (2 C-3), 127.4 (2 3-C Th), 129.0 (2 4-C Th), 129.6 (2 5-C Th), 137.5 (2 C), 140.7 (2 C), 143.2 (2 C), 162.7 (2 NHCO), 166.9 (2 NHCO).

5,5'-Dimethyl-7,7'-diphenyl-2,2'-bioxazolo[5,4-*b*]pyridine (4a) was obtained by methodology [22]: A mixture of 0.227 g (0.5 mmol) oxalylamide **1a** and 1.0 ml POCl_3 heat up to 100 °C within 9 hours. Excess oxychloride phosphorus evaporate, residue are being processed ice water. The resulting precipitate was filtered off and crystallized from a mixture of 2-propanol and DMF solvents. Yield: 0.185 g (88 %), white powder, mp 263–265 °C. IR spectrum (KBr), ν , cm^{-1} : 1608, 1675; ^1H NMR spectrum (400 MHz, DMSO- d_6 , δ , ppm): 2.71 (6H, s, 5- CH_3 , 5'- CH_3); 7.59 (2H, d, $^3J = 7.3$ Hz, H-4, 4'Ph); 7.66 (4H, t, $^3J = 7.3$ Hz, H-3, 3',5, 5' Ph); 7.86 (2H, s, H-6,6'); 8.26 (2H, d, $^3J = 7.3$ Hz, H-2, 2', 6, 6' Ph). ^{13}C NMR spectrum (DMSO- d_6), δ , ppm: 24.2 (5- CH_3 , 5'- CH_3); 119.4 (C-6, C-6'); 127.6 (C-7a, C -7a'); 128.9 (C-4,4',6,6' Ph); 130.1 (C-4,4' Ph);

129.0 (C-2, 2', 6, 6' Ph); 133.6 (C-1,1' Ph); 141.0 (C-7, C-7'); 150.2 (C-5, C-5'); 157.6 (C-3a, 3a'); 159.4 (C-2, 2'). Found, %: C 74.44; H 4.50; N 13.52. $C_{26}H_{18}N_4O_2$. Calculated, %: C 74.63; H 4.34; N 13.39.

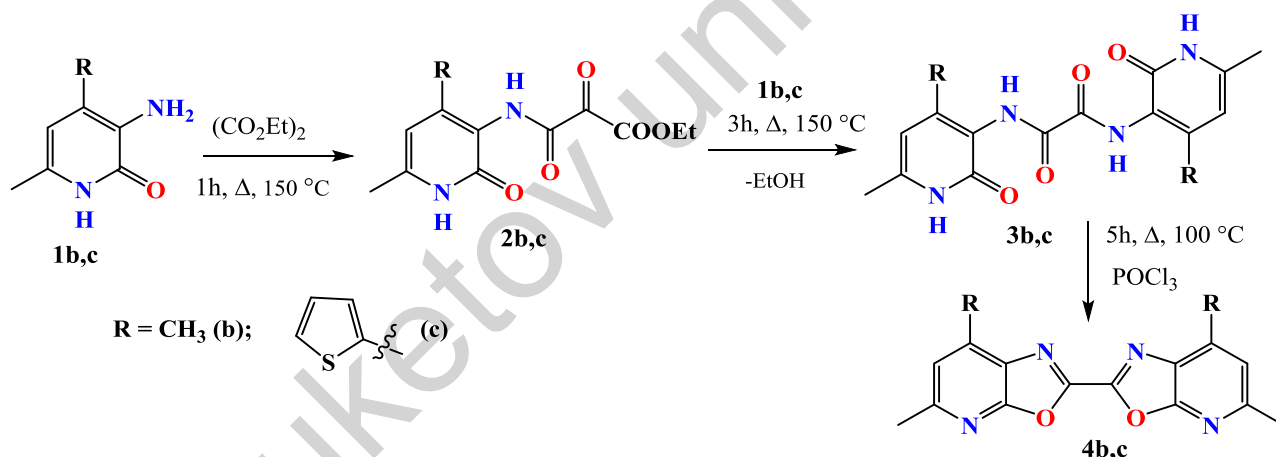
5,5',7,7'-tetramethyl-2,2'-bioxazolo[5,4-b]pyridine (4b). A mixture of 330.3 mg (1 mmol) of oxalylamide (**3b**) and 1.0 ml (10 mmol) of phosphorus oxychloride was heated under reflux for 9 h. The excess phosphorus oxychloride was distilled off under vacuum. The reaction mixture was treated with cold distilled water. The formed precipitate was filtered off, washed with water and air-dried. The mass of the product was 170 mg (yield 58 %) with M.p. > 330 °C. 1H NMR spectrum (80 MHz, DMSO- d_6 , δ , ppm): 2.00 s (6H, 4,4'- CH_3); 2.14 s (6H, 6,6'- CH_3); 7.37 s (2H, C-(7,7')-H). Mass spectrum (direct injection), m/z (I_{rel} %): 294 [M] $^+$ (100). Found, %: C, 65.30; H, 4.79; N, 19.04. $C_{16}H_{14}N_4O_2$. Calculated, %: C, 65.74; H, 5.01; N, 18.83.

5,5'-dimethyl-7,7'-di(thiophen-2-yl)-2,2'-bioxazolo[5,4-b]pyridine (4c) was obtained similar to **4**. The yield was 238 mg (51 %) with a mp > 330 °C (2-propanol-DMF). 1H NMR spectrum (80 MHz, DMSO- d_6 , δ , ppm): 2.79 s (6H, 2 CH_3); 7.33 br. d (2H, J = 4.0 Hz, 2 H-4' thiophen); 7.53 s (2H, 2 H-7); 7.59 t (2H, J = 4.0 Hz, 2H-3' thiophen); 8.40 d (2H, J = 3.3 Hz, 2 H-5' thiophen). ^{13}C NMR spectrum (20 MHz, DMSO- d_6 , δ , ppm): 24.7 (2 CH_3), 117.5 (2 C-7), 128.8 (2 3-C Th), 129.1 (2 4-C Th), 131.3 (2 5-C Th), 136.4 (2 C), 138.7, 141.6 (2 C), 143.5, 149.8 (2 C), 158.7. Found, %: C, 61.38; H, 3.28; N, 13.01. $C_{22}H_{14}N_4O_2S_2$. Calculated, %: C, 61.71; H, 3.56; N, 12.84.

Results and Discussion

Chemistry

In order to obtain new derivatives of bis-(oxazolo[5,4-b]pyridine) type **4a** with various substituents on the pyridine ring and to study their optical properties, we carried out the following similar transformations based on new 3-amino-6-methyl-4-methyl- and (2-thienyl)-pyridin-2-(1H)-ones **1b**, **1c** (Scheme 3).

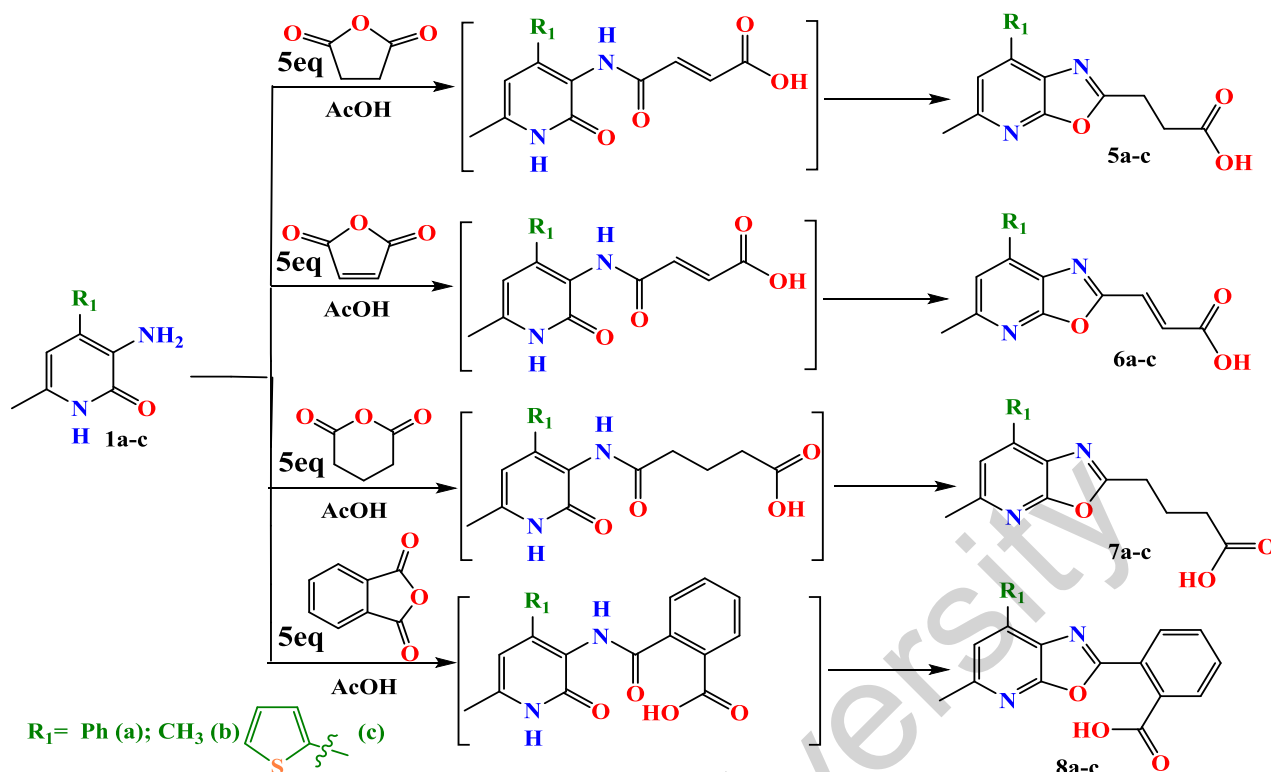


Scheme 3. Synthesis of symmetrical 5,5'-dimethyl-7,7'-diphenyl-2,2'-bis-(oxazolo[5,4-b]pyridine **4b**, **c**

Intermediate monoamides **2b**, **2c** were easily obtained by the reaction with an excess of diethyl oxalate and detected spectrally.

The characteristic chemical signals of the amide NH protons in initial diamides **3b** and **3c** (at 9.35–9.42 and 11.49–11.83 ppm) are no longer present in the 1H NMR spectra of compounds **4b** and **4c**. Furthermore, a shift of the aromatic proton to a weak field was also observed.

For possible comparison of the optical properties of bis-(oxazolo[5,4-b]pyridines), we also synthesized oxazolo[5,4-b]pyridines (**5-8 a-c**) using the previously described method [23], containing one oxazolo[5,4-b]pyridine scaffold and a carboxyl linker.

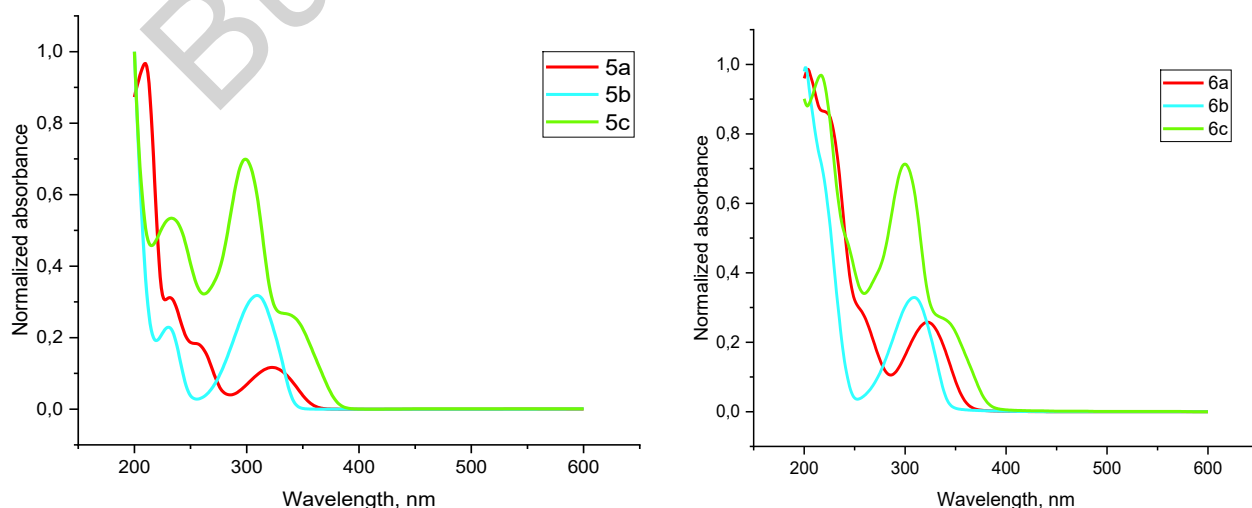


Scheme 4. Cyclization reaction of 3-aminopyridones **1a-c** with into the corresponding oxazolo[5,4-b]pyridine **5-8a-c**

Photophysical Properties of Compounds

Previous work by the research group of Alexander S. Fisyuk has demonstrated [24] that heterocyclic derivatives based on 3-amino-6-methyl-4-phenylpyridin-2(1*H*)-one **1a** are characterized by a high fluorescence quantum yield in the blue region of the visible spectrum ($\phi \approx 0.76$), suggesting their potential as efficient fluorophores.

Within the scope of the present study, our primary objective was to investigate the photophysical properties of the synthesized 3-amino-6-methyl-4-(methyl-, aryl)pyridin-2(1*H*)-one derivatives (**1a-c**) and to elucidate the impact of linker structure on their spectral characteristics, including the absorption maximum (λ_{max}), Stokes shift, and quantum yield. To initiate this, the absorption spectra of oxazolo[5,4-b]pyridine derivatives (**5-8a-c**) were recorded in two aprotic solvents—toluene (nonpolar) and acetonitrile (polar)—at a concentration of 6×10^{-4} M. The resulting absorption spectra are presented in Figures 2–4, while the spectral characteristics of the compounds are summarized in Table 1.



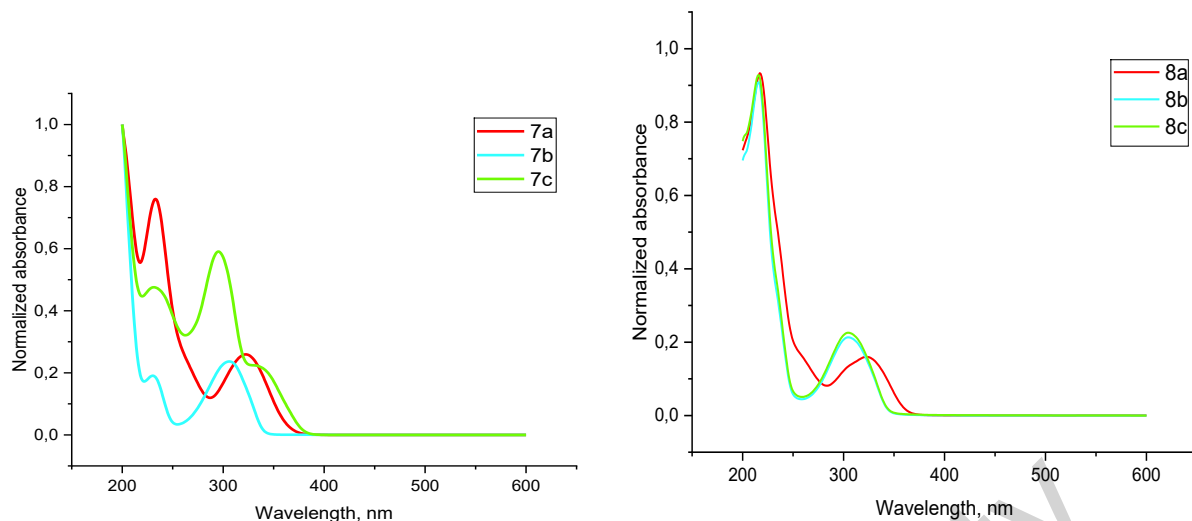


Figure 2. Normalized absorption spectra of oxazolo[5,4-b]pyridine derivatives **5-8a-c** in acetonitrile solution (6×10^{-4} mol/L)

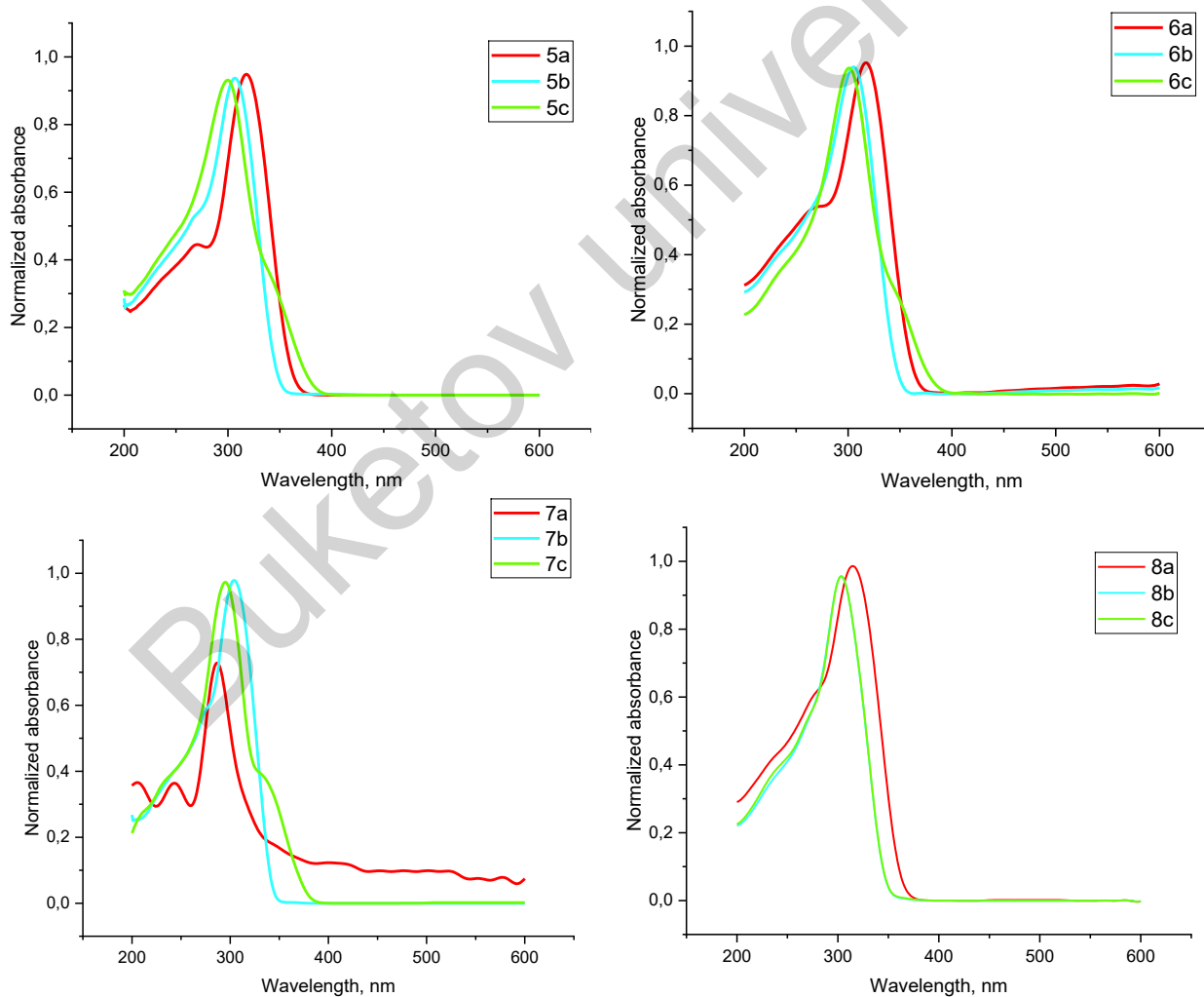


Figure 3. Normalized absorption spectra of oxazolo[5,4-b]pyridine derivatives **5-8a-c** in toluene solution (6×10^{-4} mol/L)

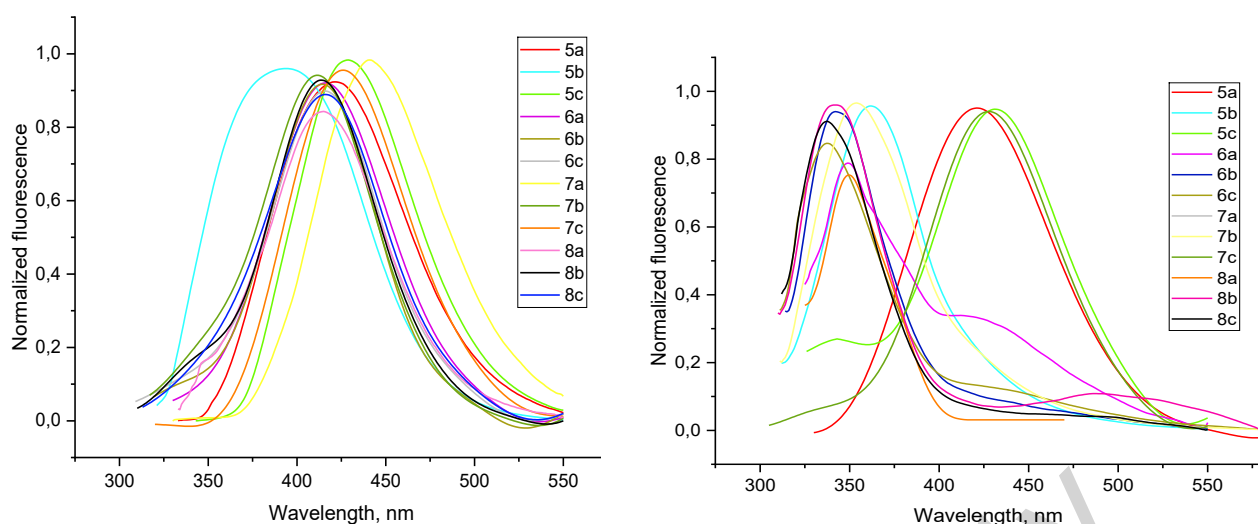


Figure 4. Normalized fluorescence spectra of oxazolo[5,4-b]pyridine derivatives **5-8a-c** in acetonitrile (left) and toluene (right) solutions (6×10^{-4} mol/L)

It was established that, for all the compounds studied, the absorption maxima fall within the range of 299–333 nm in an acetonitrile solution and in the range of 281–317 nm in a toluene solution, which is associated with the π - π^* electron transition in the conjugated system of the oxazopyridine moiety. A comparative analysis of the absorption spectra of compounds **5a-c** and **7a-c** in acetonitrile revealed that the presence of a thiophene or phenyl substituent at the C-4 position of the oxazopyridine ring induces a slight bathochromic shift in the absorption band compared to the corresponding methyl derivative (Table 1). Moreover, the largest bathochromic shift is observed for compound **7c**. The observed bathochromic shift in the absorption bands of compounds **5a, c** and **7a, c** is attributed to the presence of the thiophene ring, which participates in p - π conjugation, and the phenyl ring, which engages in π - π conjugation with the oxazopyridine moiety. However, within each homologous series containing an identical substituent at the C-4 position (methyl, phenyl, or thiophen-2-yl), modifications to the acidic fragment at the C-2 position had no produce a discernible effect on the shift of the absorption maxima.

Table 1

Photophysical properties of compounds **5-8a-c**

Compound	Acetonitrile				Toluene			
	UV-Vis		Photoluminescence		UV-Vis		Photoluminescence	
	$\lambda_{\text{max}}^{\text{abs}}$, [nm]	ϵ , [l/cm ² *mol]	$\lambda_{\text{max}}^{\text{em}}$	Stokes shift, [nm]	$\lambda_{\text{max}}^{\text{abs}}$, [nm]	ϵ , [l/cm ² *mol]	$\lambda_{\text{max}}^{\text{em}}$, [nm]	Stokes shift, [nm]
5a	323	700	427	104	317	622	419	102
5b	311	760	394	83	306	607	362	56
5c	333	602	430	97	300	545	433	133
6a	322	694	416	94	316	560	348	32
6b	310	995	416	106	304	642	344	40
6c	299	1503	415	116	301	1222	329	28
7a	322	660	450	128	281	6.5	423	142
7b	307	810	407	100	303	735	355	52
7c	331	372	423	92	295	860	428	133
8a	323	798	414	91	315	768	347	32
8b	303	723	417	114	302	972	346	44
8c	303	1288	415	112	302	1690	342	40

The fluorescence spectra of all synthesized compounds were recorded in acetonitrile and toluene (6×10^{-4} mol/L) using the absorption maximum of each compound as the excitation wavelength.

The emission maxima of the investigated compounds range from 329 to 450 nm, which corresponds to bluish-blue photoluminescence (Table 1). It should be noted that all compounds in acetonitrile solution exhibit a substantial Stokes shift (83–128 nm).

Given that the synthesized compounds **4a–c** contain two conjugated oxazolo[5,4-b]pyridine ring systems and are of significant interest as potential luminophores, we sought to determine their fluorescence quantum yield.

Upon irradiation with UV light, chloroform solutions of the bis(oxazolopyridine) derivatives **4a–c** emit intense blue-violet light (Fig. 5), indicating high-efficiency photoluminescence in the visible spectral region.

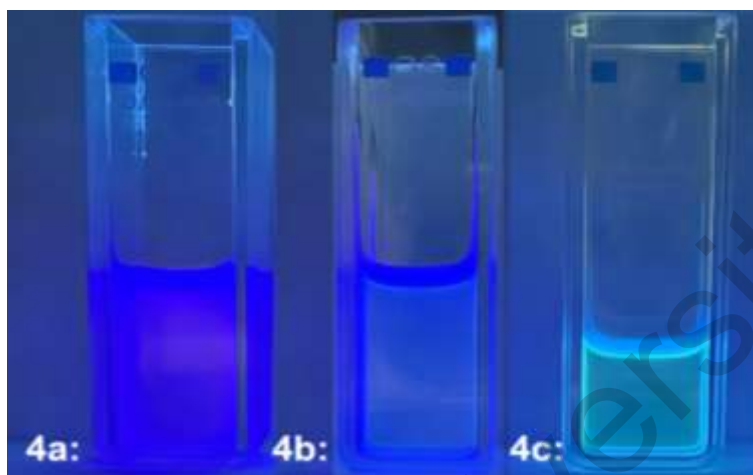


Figure 5. Photographs of compounds **4a–c** in a chloroform solution (2×10^{-5} mol/L) under UV radiation ($\lambda = 365$ nm)

To determine the quantum yield of compounds **4a–c**, their absorption and fluorescence spectra were recorded in chloroform at a concentration of 2×10^{-5} mol/L (Fig. 6). A quinine sulfate solution in 0.1 M H_2SO_4 was utilized as an internal standard.

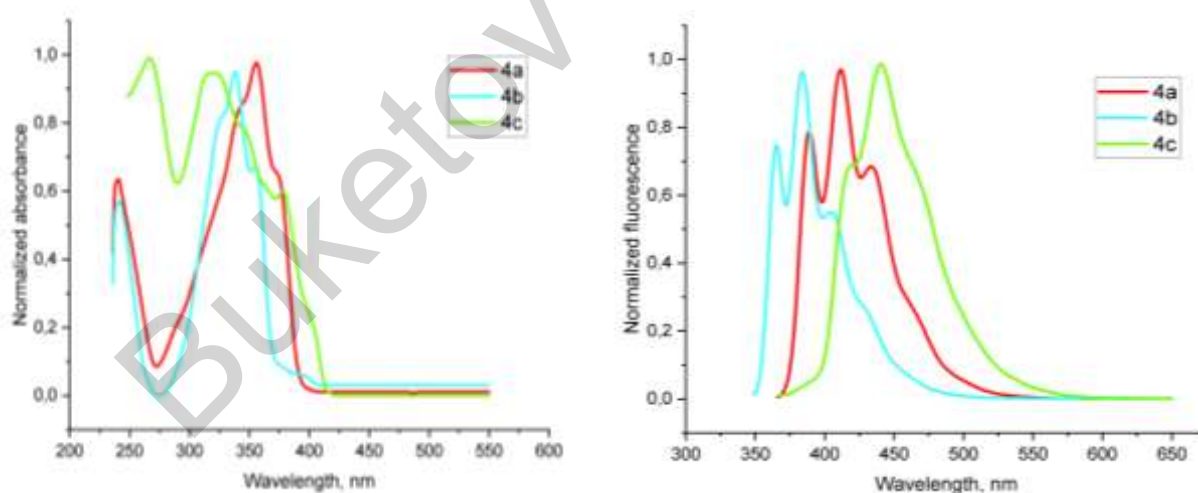


Figure 6. Normalized absorption (left) and fluorescence (right) spectra of oxazolo[5,4-b]pyridine derivatives **4a–c** in chloroform solution (2×10^{-5} mol/L)

The relative quantum yield was calculated using the following formula:

$$\varphi_i = \varphi_{st} \cdot \frac{A_{st}}{A_x} \cdot \frac{F_x}{F_{st}} \cdot \frac{n_x^2}{n_{st}^2},$$

where φ_i is the fluorescence quantum yield of the studied compound; φ_{st} is the fluorescence quantum yield of the standard used (quinine sulfate); A_{st} , A_x are the absorbances at excitation wavelength for the standard sample (st) and the studied compound (**4a–c**); F_{st} , F_x are the areas of fluorescence spec-

trum with spectral correction for the standard sample (st) and the studied compound (**4a-c**); n_{st} , n_x are the refractive index of the standard sample (st) and the studied compound (**4a-c**).

Table 2

Photophysical properties of compounds **4a-c**

Compound	UV-Vis		Photoluminescence		
	$\lambda_{\max}^{\text{abs}}$, [nm]	ϵ , [l/cm ² *mol]	$\lambda_{\max}^{\text{em}}$, [nm]	Stokes shift, [nm]	Quantum yield (ϕ_i) ^a , %
4a	356	40833	389, 411, 435	79	81
4b	339	39583	365, 384, 405	66	82
4c	332	30833	418, 440	108	70

Note: ^aThe fluorescence quantum yield was calculated relative to the standard (quinine sulfate in 0.1 M H₂SO₄, $\phi_i = 0.55$) [25–27].

Therefore, the 2,2'-bis(oxazolo[5,4-b]pyridine) derivatives **4a-c** demonstrated photoluminescence quantum yields higher than that of the quinine sulfate standard ($\phi \approx 0.55$).

Conclusions

Aminolysis of diethyl oxalate with three 4-substituted 3-aminopyridin-2-(1*H*)-ones afforded the corresponding oxalylamides. Intermediate oxalic acid monoamides were also detected and separately identified. The resulting oxalic acid diamides were used in cyclization reactions to symmetrical *bis*-derivatives of oxazolo[5,4-b]pyridine under the action of phosphorus oxychloride. For the new oxazolo[5,4-b]pyridine derivatives we obtained. The photoluminescent properties of **5-8a-c** and 2,2'-bisoxazolo[5,4-b]pyridines **4a-c** were studied (maximum absorption λ , molar absorption coefficient (ϵ), Stokes shift, quantum yield). All compounds were found to luminesce with a bluish-blue color and have a maximum absorption length in the wavelength range of 299–333 nm (acetonitrile) and in the range of 281–317 nm (toluene), which is associated with the π - π^* electron transition. A fairly large Stokes shift (83–128 nm) is observed for all compounds. It was also found that the presence of a carboxyl linker at the C-2 position of compounds **5-8a-c** does not significantly affect the shift of the absorption band maxima and other spectral characteristics of the molecules.

It should be noted that symmetrical conjugated 2,2'-bisoxazolo[5,4-b]pyridines **4a-c** with two oxazolo[5,4-b]pyridine rings have fairly high quantum yield values ($\phi \approx 0.70$ – 0.82) compared to the known standard quinine sulfate ($\phi \approx 0.55$), which will allow them to find possible applications as effective fluorophores.

Funding

The study was supported by a grant from the Russian Science Foundation (No. 24-23-00472, “Development of methods for the preparation and practical application of new derivatives of bisoxazolo[5,4-b]pyridine with potential luminescent, complexing and catalytic activity”, <https://rscf.ru/en/project/24-23-00472/>).

Author Information*

*The authors' names are presented in the following order: First Name, Middle Name and Last Name

Irina Valerievna Palamarchuk (corresponding author) — Senior Lecturer, School of Natural Sciences, University of Tyumen, 15a Perekopskaya St., 625003, Tyumen, Russia; e-mail: ivpalamarchuk@utmn.ru; <https://orcid.org/0000-0003-3376-6953>

Ivan Vyacheslavovich Kulakov — Doctor of Chemical Sciences, Associated Professor, School of Natural Sciences, University of Tyumen, 15a Perekopskaya St., 625003, Tyumen, Russia; e-mail: ivkulakov@utmn.ru; <https://orcid.org/0000-0001-5772-2096>

Svetlana Stanislavovna Volkova — Candidate of Chemical Sciences, School of Natural Sciences, University of Tyumen, 15a Perekopskaya St., 625003, Tyumen, Russia; e-mail: s.s.volkova@utmn.ru

Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript. **CRedit**: **Irina Valerievna Palamarchuk** investigation, formal analysis, data

curation and writing — original draft preparation; **Ivan Vyacheslavovich Kulakov** conceptualization, methodology, validation, writing — review and editing and supervision; **Svetlana Stanislavovna Volkova** formal analysis, data curation, methodology, validation.

Acknowledgments

Spectrophotometric studies were carried out using the equipment of the Center for Collective Use “Rational Nature Management and Physicochemical Research” of University of Tyumen.

Conflicts of Interest

The authors declare no conflict of interest.

References

- Demmer, C. S. & Bunch, L. (2015). Benzoxazoles and oxazolopyridines in medicinal chemistry studies. *European Journal of Medicinal Chemistry*, 97, 778–785. <https://doi.org/10.1016/j.ejmech.2014.11.064>
- Qi, X. Y., Cao, Y., Li, Y. L., Mo, M. G., Zhou, L., & Ye, D. Y. (2017). Discovery of the selective sphingomyelin synthase 2 inhibitors with the novel structure of oxazolopyridine. *Bioorganic & Medicinal Chemistry Letters*, 27(15), 3511–3515. <https://doi.org/10.1016/j.bmcl.2017.05.074>
- Kempson, J., Spergel, S. H., Guo, J., Quesnelle, C., Gill, P., Belanger, D., Dyckman, A. J., Li, T., Watterson, S. H., Langevine, C. M., Das, J., Moquin, R. V., Furch, J. A., Marinier, A., Dodier, M., Martel, A., Nirschl, D., Van-Kirk, K. Burke, J.R. Pattoli, M. A., Gillooly, K., McIntyre, K. W., Chen, L., Yang, Z., Marathe, P. H., Wang-Iverson, D., Dodd, J. H., McKinnon, M., Barrish, J. C., & Pitts, W. J. (2009). Novel tricyclic inhibitors of IκB kinase. *Journal of medicinal chemistry*, 52(7), 1994–2005. <https://doi.org/10.1021/jm8015816>
- Bemis, J. E., Vu, C. B., Xie, R., Nunes, J. J., Ng, P. Y., Disch, J. S., Milne, J. C., Carney, D. P., Lynch, A. V., Jin, L., Smith, J. J., Lavu, S., Iffland, A., Jirousek, M. R., & Perni, R. B. (2009). Discovery of oxazolo[4,5-*b*]pyridines and related heterocyclic analogs as novel SIRT1 activators. *Bioorganic & Medicinal Chemistry Letters*, 19(8), 2350–2353. <https://doi.org/10.1016/j.bmcl.2008.11.106>
- Yeh, V. & Iyengar, R. (2008). Oxazoles. *Comprehensive Heterocyclic Chemistry III*, 4, 487–543. <https://doi.org/10.1016/B978-008044992-0.00404-1>
- Yalçın I. & Şener E. (1993). QSARs of some novel antibacterial benzimidazoles, benzoxazoles, and oxazolopyridines against an enteric gram-negative rod; *K. pneumoniae*. *International journal of pharmaceutics*, 98(1–3), 1–8. [https://doi.org/10.1016/0378-5173\(93\)90034-D](https://doi.org/10.1016/0378-5173(93)90034-D)
- Park, H. R., Kim, J., Kim, T., Jo, S., Yeom, M., Moon, B., Choo, I. H., Lee, J., Lim, E. J., Park, K. D., Min, S. J., Nam, G., Keum, G., Lee, C. J., & Choo, H. (2013). Oxazolopyridines and thiazolopyridines as monoamine oxidase B inhibitors for the treatment of Parkinson's disease. *Bioorganic & medicinal chemistry*, 21(17), 5480–5487. <https://doi.org/10.1016/j.bmc.2013.05.066>
- Viaud, M. C., Jamoneau, P., Flouzat, Ch., Bizot-Espiard, J. G., Pfeiffer, B., Renard, P., Caignard, D. H., Adam, G., & Guillaumet, G. (1995). N-Substituted Oxazolo[5,4-*b*]pyridin-2(1*H*)-ones: A New Class of Non-Opiate Antinociceptive Agents. *Journal of Medicinal Chemistry*, 38(8), 1278–1286. <https://doi.org/10.1021/jm00008a006>
- Huang, Z., Zhang, Y., & Song, Y. WO Patent 2011085643.
- Tekiner-Gulbas, B., Temiz-Arpaci, O., Yildiz, I., Aki-Sener, E., & Yalcin, I. (2006). 3D-QSAR study on heterocyclic topoisomerase II inhibitors using CoMSIA. *SAR and QSAR in Environmental Research*, 17(2), 121–132. <https://doi.org/10.1080/10659360600636105>
- Yildiz-Oren, I., Yalcin, I., Aki-Sener, E. & Ucarturk, N. (2004). Synthesis and structure–activity relationships of new antimicrobial active multisubstituted benzazole derivatives. *European Journal of Medicinal Chemistry*, 39(3), 291–298. <https://doi.org/10.1016/j.ejmech.2003.11.014>
- Yalçın, İ., Ören, İ., Şener, E., Akin, A., & Uçartürk, N. (1992). The synthesis and the structure-activity relationships of some substituted benzoxazoles, oxazolo(4,5-*b*)pyridines, benzothiazoles and benzimidazoles as antimicrobial agents. *European journal of medicinal chemistry*, 27(4), 401–406. [https://doi.org/10.1016/0223-5234\(92\)90154-S](https://doi.org/10.1016/0223-5234(92)90154-S)
- Shatsauskas, A. L., Zablotskii, Y. A., Chernenko, S. A., Zheleznova T. Yu., Shuvalov V. Yu., Kostyuchenko A. S., & Fisyuk A. S. (2021). Synthesis and photophysical properties of the products of the reaction of 5-methyl-7-phenyl[1,3]oxazolo[5,4-*b*]pyridin-2(1*H*)-one with amino acids. *Chemistry of Heterocyclic Compounds*, 57(12), 1212–1219. <https://doi.org/10.1007/s10593-021-03045-8>
- Mac M., Baran W., Uchacz T., Baran B., Suder M., & Leśniewski S. (2007). Fluorescence properties of the derivatives of oxazolo[4,5-*b*]pyridine. *Journal of Photochemistry and Photobiology A: Chemistry*, 192(2-3), 188–196. <https://doi.org/10.1016/j.jphotochem.2007.05.023>
- El'chaninov, M. M., Aleksandrov, A. A., & Illenzeer, E. V. (2014). Synthesis and properties of 2-(2-furyl)[1,3]oxazolo[4,5-*b*]pyridine. *Russian Journal of Organic Chemistry*, 50(12), 1826–1828. <https://doi.org/10.1134/S1070428014120197>
- Aleksandrov, A. A., & El'chaninov, M. M. (2015). Synthesis and reactivity of 2-(2-thienyl)oxazolo[4,5-*b*]pyridine. *Russian Journal of General Chemistry*, 85(4), 858–860. <https://doi.org/10.1134/S1070363215040155>

- 17 Harrison, S. T., Mulhearn, J., Wolkenberg, S. E., Miller, P. J., O'Malley, S. S., Zeng, Z., Williams, D. L., Hostetler, E. D., Sanabria-Bohórquez, S., Gammage, L., Fan, H., Sur, C., Culberson, J. C., Hargreaves, R. J., Cook, J. J., Hartman, G. D. & Barrow, J. C. (2011). Synthesis and evaluation of 5-fluoro-2-aryloxazolo[5,4-*b*]pyridines as β -amyloid PET ligands and identification of MK-3328. *ACS Medicinal Chemistry Letters*, 2(7), 498–502. <https://doi.org/10.1021/ml200018n>
- 18 Doise, M., Dennin, F., Blondeau, D., & Sliwa, H. (1990). Synthesis of novel heterocycles: Oxazolo[4,5-*b*]pyridines and oxazolo[4,5-*d*]pyrimidines. *Tetrahedron Letters*, 31(8), 1155–1156. [https://doi.org/10.1016/S0040-4039\(00\)88750-X](https://doi.org/10.1016/S0040-4039(00)88750-X)
- 19 Doise, M., Blondeau, D., & Sliwa, H. (1992). Syntheses of Oxazolo[4,5-*b*]pyridines and [4,5-*d*]pyrimidines. *Synthetic Communications*, 22(20), 2891–2901. <https://doi.org/10.1080/00397919208021112>
- 20 Myllymäki, M. J. & Koskinen, A. M. P. (2007). A rapid method for the preparation of 2-substituted oxazolo[4,5-*b*]pyridines using microwave-assisted direct condensation reactions. *Tetrahedron Lett.* 48(13), 2295–2298. <https://doi.org/10.1016/j.tetlet.2007.01.161>
- 21 Palamarchuk, I.V., Matsukevich, M. V., Kulakov, I. V., Seilkhanov, T. M., & Fisyuk, A. S. (2019). Synthesis of N-substituted 2-aminomethyl-5-methyl-7-phenyloxazolo[5,4-*b*]pyridines. *Chemistry of Heterocyclic Compounds*, 55(8), 788–791. <https://doi.org/10.1007/s10593-019-02537-y>
- 22 Shatsauskas, A. L., Abramov, A. A., Saibulina, E. R., Palamarchuk, I. V., Kulakov, I. V., & Fisyuk, A. S. (2017). Synthesis of 3-amino-6-methyl-4-phenylpyridin-2(1*H*)-one and its derivatives. *Chemistry of Heterocyclic Compounds*, 53(2), 186–191. <https://doi.org/10.1007/s10593-017-2038-4>
- 23 Palamarchuk, I. V. & Kulakov, I. V. (2024). A New Method for Obtaining Carboxylic Derivatives of Oxazolo[5,4-*b*]pyridine Based on 3-Aminopyridine-2(1*H*)-ones. *Eurasian Journal of Chemistry*, 29(2(114)), 32–44. <https://doi.org/10.31489/2959-0663/2-24-11>
- 24 Shatsauskas, A. L., Shatalin, Y. V., Shubina, V. S., Chernenko, S. A., Kostyuchenko, A. S., & Fisyuk, A. S. (2022). 5-Ethyl-5,6-dihydrobenzo[*c*][1,7]naphthyridin-4(3*H*)-ones — A new class of fluorescent dyes. *Dyes and Pigments*, 204, 110388. <https://doi.org/10.1016/j.dyepig.2022.110388>
- 25 Kostyuchenko, A. S., Zheleznova, T. Y., Stasyuk, A. J., Kurowska, A., Domagala, W., Pron, A., & Fisyuk, A. S. (2017). Synthesis and optical properties of new 5'-aryl-substituted 2,5-bis(3-decyl-2,2'-bithiophen-5-yl)-1,3,4-oxadiazoles. *Beilstein Journal of Organic Chemistry*, 13(1), 313–322. <https://doi.org/10.3762/bjoc.13.34>
- 26 Williams, A. T. R., Winfield, S. A., & Miller, J. N. (1983). Relative fluorescence quantum yields using a computer-controlled luminescence spectrometer. *Analyst*, 108(1290), 1067–1071. <https://doi.org/10.1039/AN9830801067>
- 27 Kurowska, A., Zassowski, P., Kostyuchenko, A. S., Zheleznova, T. Y., Andryukhova, K. V., Fisyuk, A. S., Pron, A., & Domagala, W. (2017). Effect of donor to acceptor ratio on electrochemical and spectroscopic properties of oligoalkylthiophene 1,3,4-oxadiazole derivatives. *Physical Chemistry Chemical Physics*, 19(44), 30261–30276. <https://doi.org/10.1039/C7CP05155G>
- 28 Kulakov, I. V., Matsukevich, M. V., Shulgau, Z. T., Sergazy, S., Seilkhanov, T. M., Puzari, A., & Fisyuk, A. S. (2015). Synthesis and antiradical activity of 4-aryl(hetaryl)-substituted 3-aminopyridin-2(1*H*)-ones. *Chemistry of Heterocyclic Compounds*, 51(11), 991–996. <https://doi.org/10.1007/s10593-016-1809-7>
- 29 Fisyuk, A. S., Kulakov, I. V., Goncharov, D. S., Nikitina, O. S., Bogza, Y. P., & Shatsauskas, A. L. (2014). Synthesis of 3-aminopyridin-2(1*H*)-ones and 1*H*-pyrido[2,3-*b*][1,4]oxazin-2(3*H*)-ones. *Chemistry of Heterocyclic Compounds*, 50(2), 217–224. <https://doi.org/10.1007/s10593-014-1464-9>