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Synthesis and some chemical transformations of novel 1-oxo-3,4-dihydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazine-8-carboxylic acids and their benzoannelated analogues

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Carbox(sulfone)amides

A B S T R A C T

A preparatively convenient method is proposed for the synthesis of new 1-oxo-3,4-dihydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazine-8- **4a-e** and 4-oxo-4*H*-pyrrolo[2,1-*c*][1,4]benzoxazine-3-carboxylic acids **5a-f** that is based on the interaction of methyl (2-oxomorpholin-3-ylidene)ethanoates **1a-e** and methyl (2-oxo-2*H*-1,4-benzoxazine-3(4*H*)-ylidene)ethanoates **2a-f** with 2-bromo-1,1-diethoxyethane. Obtained acids were transformed into the corresponding *tert*-butyl carbamates **6a-e**, **7a-f** and *N*-alkyl(aryl)carboxamides **11a-i**, **12a-d**. By treating *tert*-butyl carbamates **6a-e**, **7a-f** with hydrogen chloride, 8-amino-3,4-dihydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-1-ones **8a-e** and 3-amino-4*H*-pyrrolo[2,1-*c*][1,4]benzoxazin-4-ones **9a-f** were obtained. By acylation of amines **8a-e**, **9a-f** with acetic anhydride, benzoyl chloride, methanesulfonyl chloride, and *p*-toluenesulfonyl chloride, corresponding *N*-acetamides **13a,b**, **14**, *N*-benzamides **15**, **16**, *N*-methanesulfonamides **17**, **18**, and *N*-*p*-toluenesulfonamides **19**, **20** were synthesized. In total, 30 new derivatives of 1-oxo-3,4-dihydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazinones and 27 new 4-oxo-4*H*-pyrrolo[2,1-*c*][1,4]benzoxazinones were obtained.

1. Introduction

Pyrrolo[2,1-*c*][1,4]oxazin-1-ones are a type of condensed biheterocyclic compounds that are the key structural elements of Lukianol A and B[1] alkaloids isolated from marine organisms and have attracted the attention of researchers due to their various biological properties.[2] In particular, they show anticancer activity when tested on human epidermaoid carcinoma,[1] leukemia, lymphoma, adenocarcinoma, human HeLa–S[3] uterine and glioma.[3,4] Additionally, Lukianol A is a promising platform for further functionalization and development of anticancer drugs insensitive to Multidrug Resistance,[5] and Lukianol B was shown to be an active aldose reductase inhibitor.[6] Synthetic derivatives of 1*H*-pyrrolo[2,1-*c*][1,4]oxazin-1-ones which reduce the production of TNF-α in the corresponding cells are as important.[7] Benzoannelated analogues of 1*H*-pyrrolo[2,1-*c*][1,4]oxazin-1-one, 4*H*-pyrrolo[2,1-*c*][1,4]benzoxazin-4-ones, also demonstrated their biological activity as selective antagonists of estrogen receptors and may be useful for the development of new pharmacological methods for the treatment of breast cancer.[8] Derivatives of 4*H*-pyrrolo-[2,1-*c*][1,4]benzoxazine also exhibit antihypertensive and depressant effects on the central nervous system[9] and show antioxidant activity (See **Fig. 1**).[10]

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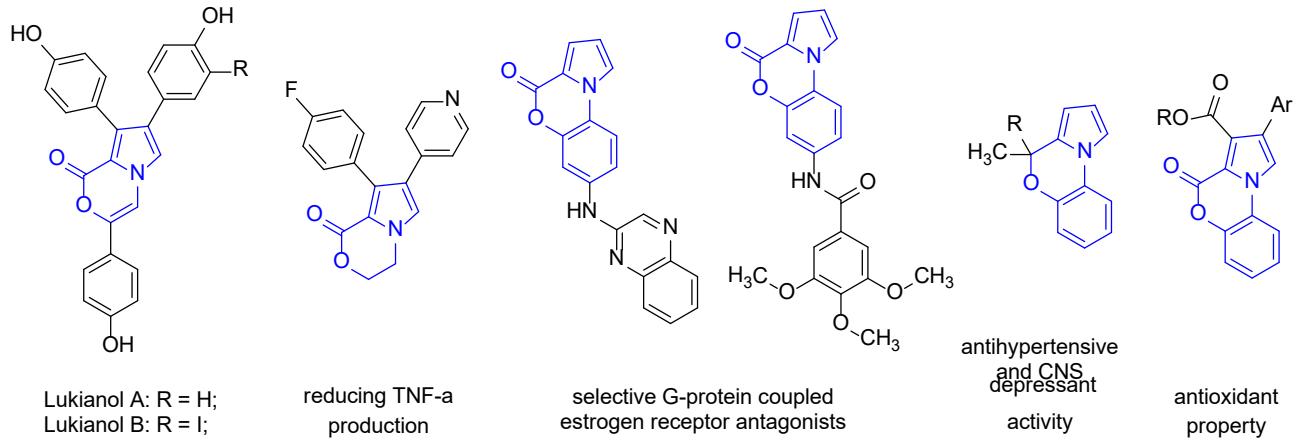


Fig. 1. Bioactive pyrrolo[2,1-*c*][1,4]oxazines and pyrrolo[2,1-*c*][1,4]benzoxazines

The analysis of literature sources showed that the dominant approach to the synthesis of 3,4-dihydropyrrolo[2,1-*c*][1,4]oxazine derivatives is based on the annulation of the oxazine ring to the functionalized pyrrole cycle. Derivatives of 1-(2-hydroxyethyl)-1*H*-pyrrole-2-carboxylic acids which are cyclized under the action of EDC,[7] H_2SO_4,[11] $POCl_3$\PCl_5,[12] PPA[13, 14] and PTSA,[15] are most often used as starting substrates. Quite often, alcohols can be formed as intermediate compounds, such that are immediately prone to further cyclization under the reaction conditions.[12, 13, 16-20] The use of 1-(2-chloroethyl-[21] or propargyl[22]) substituted pyrrole-2-carboxylates in a similar type of cyclocondensation is also described. Intramolecular cyclization of 1-propargylpyrrolo-2-carboxylic acids under the action of Au^{3+}, Ag^{+} salts[23] or iodine[24] was successfully used to obtain 3-ylidene-substituted 3,4-dihydropyrrolo[2,1-*c*][1,4]oxazines-1-ones. Ir-Catalyzed asymmetric cascade allylation/lactonization of ethyl 1*H*-pyrrole-2-carboxylates under the action of vinyl ethylene carbonate deserves particular attention which enables easy synthesis of chiral 3,4-dihydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-1-ones with excellent enantioselectivity.[25]

An approach involving annelation of the pyrrole core to the [1,4]-benzoxazine ring is widely used to construct 4-oxo-4*H*-pyrrolo[2,1-*c*][1,4]benzoxazine systems.[26] For this, the interaction of *o*-aminophenols with dialkyl acetylenedicarboxylates is most often used to form intermediate alkyl (2-oxo-2*H*-1,4-benzoxazine-3(4*H*)-ylidene)ethanoates, which are further treated with such cyclizing agents as *β*- nitrostyrenes,[10, 27-29] ethyl bromopyruvate,[30] aroylmethylidenemalonates,[31] 2-hydroxy-2-(2-oxo-2-arylethyl)-1*H*-indene-1,3(2*H*)-dione[32] and 3-(2-oxo-2-arylethylidene)-1,3-dihydro-2*H*-indol-2-on[33,34] converted into 4-oxo-4*H*-pyrrolo[2,1-*c*][1,4]benzoxazines derivatives.

Other, less common methods of synthesis of pyrrolo[2,1-*c*][1,4]benzoxazine derivatives concern the anneling of the [1,4]-benzoxazine ring to the pyrrole nucleus by intramolecular cyclization of 1-[2-hydroxyphenyl]pyrrole-2-carboxylates,[35] 2-(1*H*-pyrrol-1-yl)phenol derivatives[36-38] and 2-iodophenyl-1*H*-pyrrole-2-carboxylate under microwave irradiation in the presence of catalytic amounts of Cu.[39]

Considering the biological potential of compounds with pyrrolo[2,1-*c*][1,4]oxazine and pyrrolo[2,1-*c*][1,4]benzoxazine skeletons, the search for new preparatively convenient approaches to the construction of their derivatives with synthetically powerful functional groups, which in the future can be successfully used for directed structural modification, is an urgent task. Given that the carboxyl functional group is the most successful and convenient for such a purpose, the subject of our research was previously unknown derivatives of pyrrolo[2,1-*c*][1,4]oxazine-8-carboxylic acids **I** and their benzoannelated analogues – pyrrolo[2,1-*c*][1,4]benzoxazine-3-carboxylic acids **II** (See **Fig. 2**).

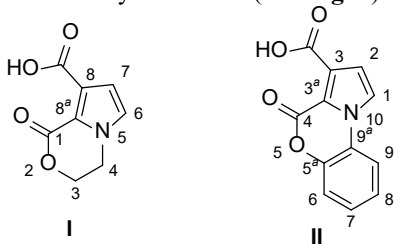


Fig. 2. Structures of pyrrolo[2,1-*c*][1,4]oxazine-8-carboxylic acids **I** and pyrrolo[2,1-*c*][1,4]benzoxazine-3-carboxylic acids **II**

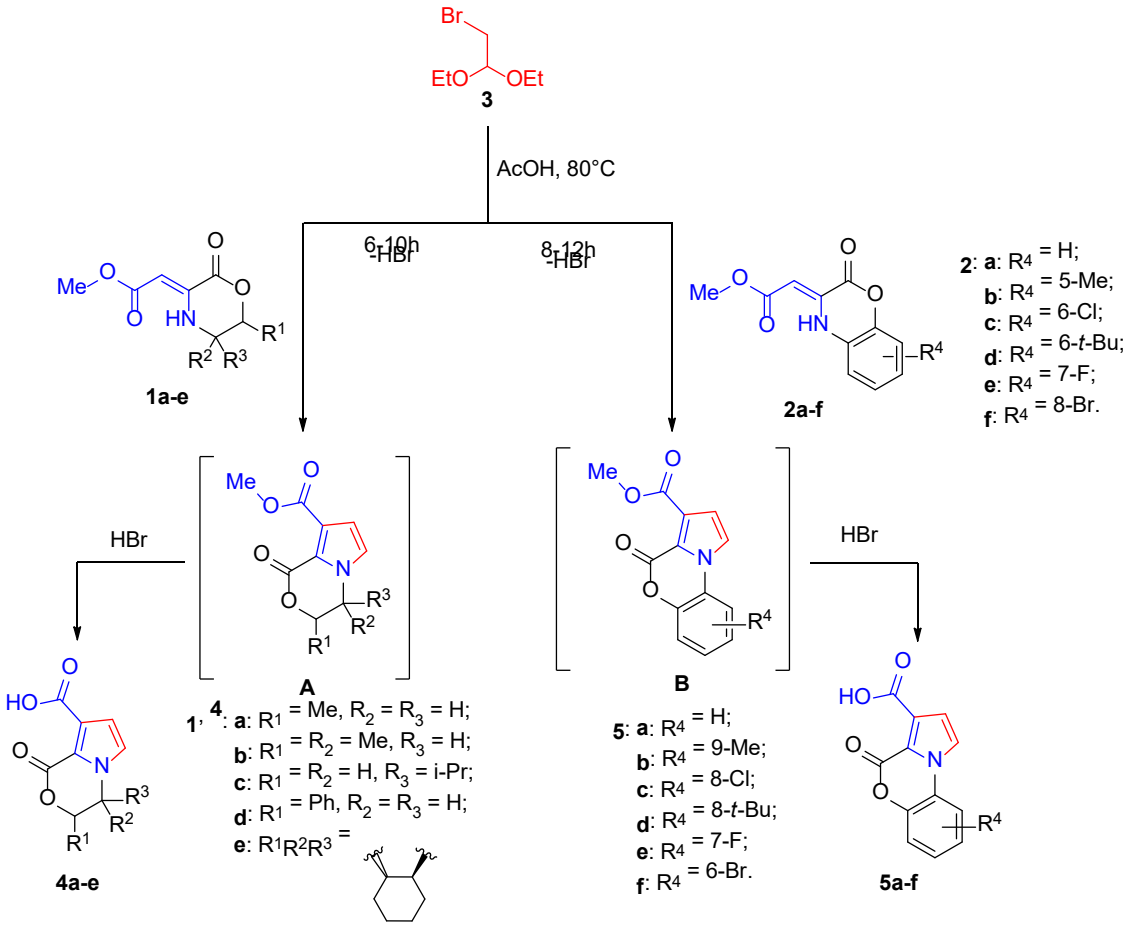
2. Results and Discussion

A general approach to the synthesis of both types of target compounds was proposed which involved the use of easily available (2-oxomorpholine-3-ylidene)ethanoates **1a-e**[40-42] or (2-oxo-1,4-benzoxazine-3(4*H*)-ylidene)ethanoates **2a-f**[42-44] as

substrates. Both types of compounds are readily obtained by cyclocondensation of dimethyl acetylenedicarboxylate (DMAD) with 1,2-aminoalcohols or *o*-aminophenols, respectively. The presence of a 1,3-binucleophilic enamine fragment in their structure creates favorable conditions for pyrroloannelation under the action of various two-centered electrophilic reagents as illustrated above. For directed annelation of the pyrrole nucleus additionally functionalized with a carboxyl group, it seemed appropriate to test bromoacetaldehyde diethyl acetal **3** as a cyclizing reagent which was previously used for the formation of a pyrrole cycle based on enaminones and their synthetic analogues.[45-48]

It was determined that methyl (2-oxomorpholin-3-ylden)ethanoates **1a-e** under the action of bromoacetaldehyde diethyl acetal **3** in acetic acid solution at a temperature of 80°C for 6-10 h are cyclized with the formation of 1-oxo-3,4-dihydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazine-8-carboxylic acids **4a-e** with yields of 67-91%. At the same time, methyl (2-oxo-2*H*-1,4-benzoxazin-3(4*H*)-ylidene)ethanoates **2a-f** require longer heating of 8-12 h, resulting in the formation of 4-oxo-4*H*-pyrrolo[2,1-*c*][1,4]benzoxazine-3-carboxylic acids **5a-f** with yields of 69-93% (See **Scheme 1**). It is most likely that the release of acids **4a-e** and **5a-f** as reaction products occurs due to the hydrolysis of intermediate esters **A** and **B** under the influence of HBr. The latter is formed as a byproduct of the cyclocondensation of ylidenethanoates **1a-e** and **2a-f** with bromoacetaldehyde diethyl acetal **3**. We previously observed a similar transformation for pyrrolo[1,2-*a*]pyrazine-8-carboxylic acid esters.[48]

A one-pot three-component synthesis of acids of type **4** was attempted on the model reaction of DMAD with (2*S*)-2-amino-3-methylbutan-1-ol in acetic acid. It was established that at room temperature methyl [(5*S*)-5-(1-methylethyl)-2-oxomorpholin-3-ylidene]ethanoate **1c** does not form. On the other hand, in the case of 2-aminophenol, methyl (2-oxo-2*H*-1,4-benzoxazine-3(4*H*)-ylidene)ethanoate **2a** is easily formed under such conditions. Subsequent addition of bromoacetal **3** and heating of the reaction mixture for 10 h at 80°C produces 4-oxo-4*H*-pyrrolo[2,1-*c*][1,4]benzoxazine-3-carboxylic acid **5a** with a yield of 72%.

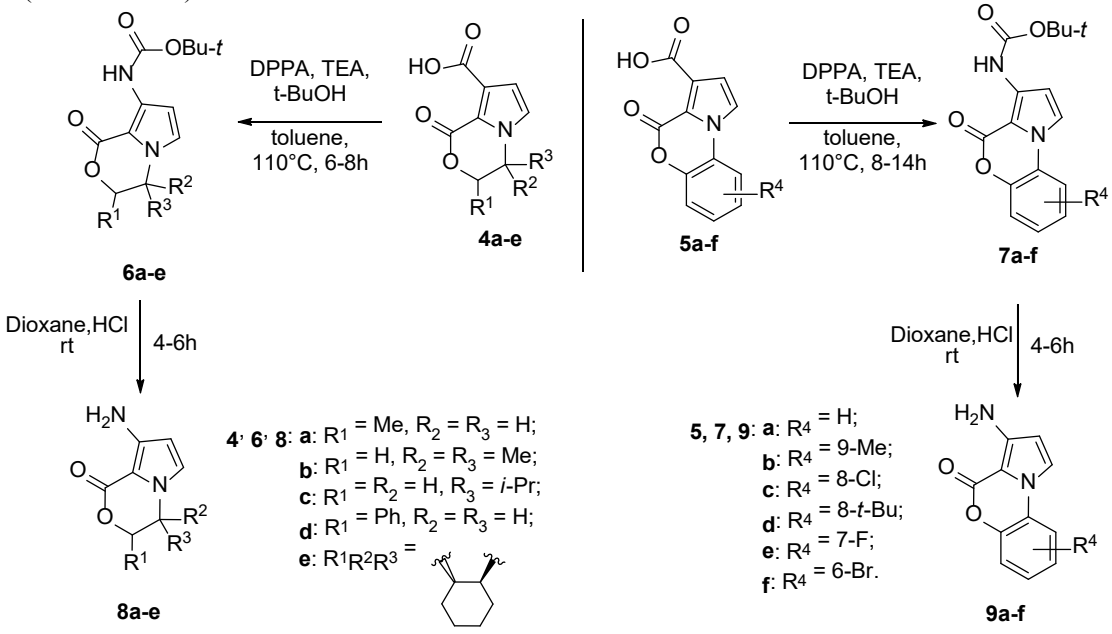


Scheme 1. Synthesis of 1-oxo-3,4-dihydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazine-8-carboxylic acids **4a-e** and 4-oxo-4*H*-pyrrolo[2,1-*c*][1,4]benzoxazine-3-carboxylic acids **5a-f**

The structures of synthesized acids **4a-e** and **5a-f** were confirmed by elemental analysis, HPLC/MS, ^{1}H- and ^{13}C, NMR spectroscopy. The 3,4-dihydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-1-one ring formation is most clearly evidenced by the ^{1}H-NMR doublet signals of the H^6 and H^7 protons for **4a-d** in the range 7.33-7.52 ($^{3}J_{HH}$ = 1.7-2.7 Hz, C^6H), 6.76-6.80 ($^{3}J_{HH}$ = 1.5-2.7 Hz, C^7H) (See Supplemental Materials, **Figs. S5**, **S7**, **S9**, **S11**) and doublet signals of the H^1 and H^2 protons for **4e** 7.42 ($^{3}J_{HH}$ = 2.8 Hz, C^1H), 6.78 ($^{3}J_{HH}$ = 2.8 Hz, C^2H) (Ibid, **Fig. S13**), which agree with the spectral characteristics of structural analogues.[7, 11, 15, 16, 20-25] The 4*H*-pyrrolo[2,1-*c*][1,4]benzoxazin-4-one ring formation is most clearly evidenced by

the ^{1}H-NMR doublet signals of the H^1 and H^2 protons for **5a-f** in the range 8.28-8.58 ($^3J_{HH}$ = 2.9-3.0 Hz, C^1H), 7.11-7.15 ($^3J_{HH}$ = 2.8-2.9 Hz, C^2H) (Ibid, **Figs. S15, S17, S19, S20, S22, S25**), which agree with the spectral characteristics of structural analogues.[10, 27-30, 35, 36, 39]

Since the carboxyl group is synthetically attractive for various structural transformations, it seemed advisable to study the obtained acids **4a-e** and **5a-f** as new synthetic subunits in some reactions with its participation. Given that the modified Curtius rearrangement is a convenient one-reactor method for the direct conversion of carboxylic acids under the action of diphenylphosphoryl azide (DPPA) into the corresponding carbamates,[49] pyrrolo[2,1-*c*][1,4]oxazine-8-carboxylic acids **4a-e** and 4-oxo-4*H*-pyrrolo[2,1-*c*][1,4]benzoxazine-3-carboxylic acids **5a-f** were investigated in this process. It was determined that they interact with DPPA in the presence of triethylamine (TEA) and *t*-butanol in toluene at 110 °C for 6-14 h with the formation of *t*-butyl (1-oxo-3,4-dihydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-8-yl)carbamates **6a-e** and *t*-butyl (4-oxo-4*H*-pyrrolo[2,1-*c*][1,4]benzoxazine-3-yl)carbamates **7a-f**, which can be considered as a kind of *N*-Boc-protected amines. Under the influence of hydrogen chloride in dioxane at room temperature for 4-6 hours, they were transformed into 8-amino-3,4-dihydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-1-ones **8a-e** and 3-amino-4*H*-pyrrolo[2,1-*c*][1,4]benzoxazin-4-ones **9a-f** with yields of 53-84% (See **Scheme 2**).

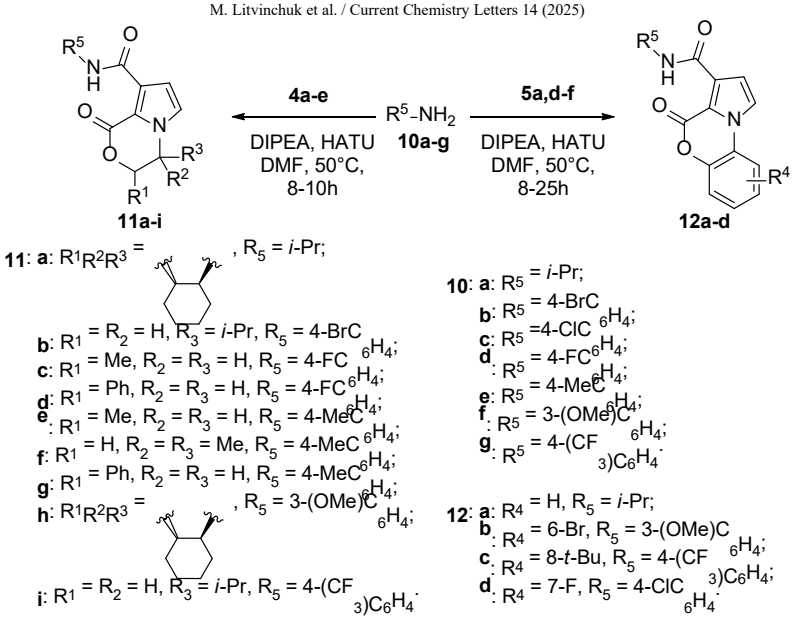


Scheme 2. Synthesis of *t*-butyl carbamates **6a-e**, **7a-f** and amines **8a-e, 9a-f**

The structures of *tert*-butyl carbamates **6a-e**, **7a-f** and amines **8a-e**, **9a-f** were confirmed by elemental analysis, HPLC/MS, ^{1}H- and ^{13}C, NMR spectroscopy. The 3,4-dihydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-1-one ring formation is most clearly evidenced by the ^{1}H-NMR signals of the H^6 and H^7 protons for **6a-d** in the range 8.13-8.23 (C^6H), 6.57-6.93 (C^7H) (See Supplemental Materials**, Figs. S27**, **S29**, **S31**, **S33**), doublet signals of the H^6 and H^7 for **8a-d** in the range 6.57-6.67 ($^3J_{HH}$ = 2.2-2.9 Hz, C^6H), 5.67-5.72 ($^3J_{HH}$ = 2.1-2.9 Hz, C^7H) (Ibid, **Figs. S50**, **S52**, **S54**, **S56**) and signals of the H^1 and H^2 protons for **6e** 8.13 (C^1H), 7.20 (C^2H) (Ibid, **Fig. S35**) and doublet signals of the H^1 and H^2 protons for **8e** 6.65 ($^3J_{HH}$ = 2.8 Hz, C^1H), 5.68 ($^3J_{HH}$ = 2.8 Hz, C^2H) (Ibid, **Fig. S58**), which agree with the spectral characteristics of structural analogues.[7, 11, 15, 16, 20-25] The 4*H*-pyrrolo[2,1-*c*][1,4]benzoxazin-4-one ring formation is most clearly evidenced by the ^{1}H-NMR signals of the H^1 and H^2 protons for **7a-f** in the range 7.80-8.33 (C^1H), 6.96-7.22 (C^2H) (Ibid, **Figs. S37**, **S39**, **S41**, **S43**, **S45**, **S48**), doublet signals of the H^1 and H^2 protons for **9a-f** in the range 7.60-8.04 ($^3J_{HH}$ = 2.9-3.1 Hz, C^1H), 6.02-6.09 ($^3J_{HH}$ = 2.9-3.1 Hz, C^2H) (Ibid, **Figs. S60**, **S62**, **S64**, **S66**, **S68**, **S71**), which agree with the spectral characteristics of structural analogues.[10, 27-30, 35, 36, 39]

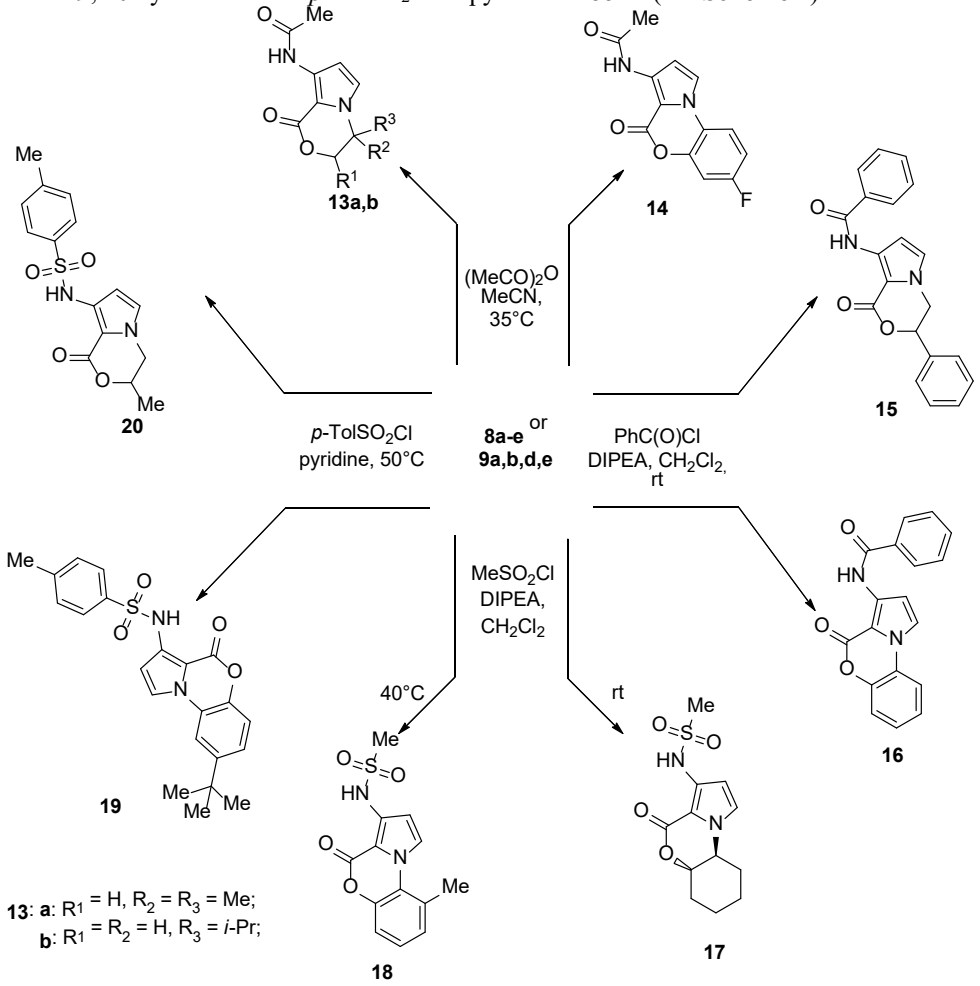
Taking into account the fact that the amide bond is an important element of the structure of peptides, natural and synthetic products,[50-53] as well as potential drugs, it seemed advisable to use acids **4a-e**, **5a-f** and amines **8a-e**, **9a-f** with pharmacophoric pyrrole[2,1-*c*][1,4](benz)oxazine scaffold for obtaining small libraries of various types of amides for further biological screening.

It was found that easy direct amido-functionalization of acids **4a-e**, **5a,d-f** with amines **10a-g** involves the use of HATU (*N*-[(dimethylamino)(3*H*-[1,2,3]triazolo[4,5-*b*]pyridin-3-yloxy)methylidene]-*N*-methylmethanaminium hexafluorophosphate)[54, 55] as a condensing agent and DIPEA as a base in DMF at 50 °C. Under these conditions, exposure of acids **4a-e** for 8-10 h and acids **5a,d-f** for 8-25 h leads to the target carboxamides **11a-i** and **12a-d** in 66-93% and 89-94% yields, respectively (See **Scheme 3**).



Scheme 3 Synthesis of *N*-alkyl(aryl) carboxamides **11a-i** and **12a-d**

The reactions of 8-amino-3,4-dihydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-1-ones **8a-e** and their benzoannelated analogues **9a**,**b**,**d**,**e**,**f** with a series of acylating and sulfonylating reagents were investigated to obtain new pyrrolooxazinone derivatives exofunctionalized with biorelevant amide or sulfamide groups. It was shown that they are easily acylated by acetic anhydride in acetonitrile at 35 °C, benzoyl chloride in dichloromethane in the presence of DIPEA at room temperature with the formation of the corresponding *N*-acetamides **13a**,**b**, **14** and *N*-benzamides **15**, **16**. In turn, *N*-methanesulfonamides **17**, **18** were obtained by reaction with methanesulfonyl chloride in dichloromethane using DIPEA as a base, and *N*-*p*-toluenesulfonamides **19**, **20** by the action of *p*-TolSO$_2$Cl in pyridine at 55°C (see **Scheme 4**).



Scheme 4. Synthesis of *N*-acetamides **13a**,**b**, **14**, *N*-benzamides **15**, **16**, *N*-methanesulfonamides **17**, **18** and *N*-*p*-toluenesulfonamides **19**, **20**

Physico-chemical parameters of the synthesized compounds **11a-i**, **12a-d**, **13a,b**, **14**, **17**, **18**, **19**, **20** are given in the Experimental section and confirm their structure. In addition, the results of X-ray diffraction of amide **11b** showed the presence of the *S*-configuration of the stereogenic center C-4 of the biheterocyclic system, which indicates the absence of cycle inversion during synthetic transformations (see **Fig. 3**).

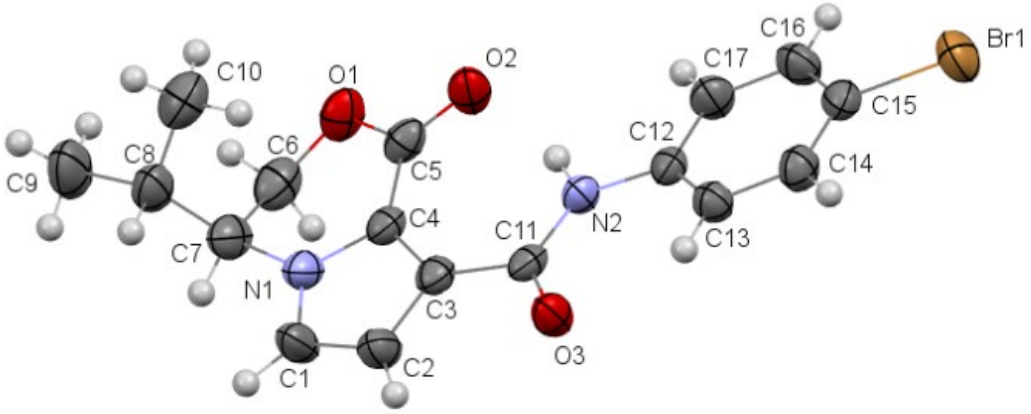


Fig. 3. Molecular structure of compound **11b** according to X-ray diffraction data. Thermal ellipsoids are shown at **5**0% probability level.

The six-membered cycle of the compound **11b** (See **Fig. 3**) adopts a sofa conformation. The O1, C5, C4, N1, C7 atoms lie in the plane with an accuracy of 0.033 Å and the C6 atom deviates from this plane by 1.654(6) Å. The carbamide fragment is coplanar to the planar five-membered cycle (the C2–C3–C11–O3 torsion angle is -3.6(7)°), which is additionally stabilized by the N2–H…O intramolecular hydrogen bond (the H…O distance is 1.94 Å, the N–H…O angle is 164°). The *para*-bromophenyl ring is also coplanar to the carbamide fragment (the C11–N2–C12–C13 torsion angle is -5.1(8)°) due to conjugation between their π-systems and formation of the C13–H…O3 intramolecular hydrogen bond (the H…O distance is 2.24 Å, the C–H…O angle is 121°). The isopropyl substituent is located in an axial position (the C1–N1–C7–C8 torsion angle is 72.9(7)°) and is turned in such a way that the N1–C7–C8–H8 torsion angle is -54.5°.

3. Conclusions

We showed that the interaction of methyl (2-oxomorpholin-3-ylidene)ethanoates and methyl (2-oxo-2*H*-1,4-benzoxazine-3(4*H*)-ylidene)ethanoates with 2-bromo-1,1-diethoxyethane is a convenient method for the synthesis of new derivatives of 1-oxo-3,4-dihydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazine-8-carboxylic acids and 4-oxo-4*H*-pyrrolo[2,1-*c*][1,4]benzoxazine-3-carboxylic acids. The resulting acids undergo a Curtius rearrangement in the presence of DPPA, TEA and *t*-butanol in toluene to form *t*-butyl (1-oxo-3,4-dihydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazine-8-yl)carbamates and *t*-butyl (4-oxo-4*H*-pyrrolo[2,1-*c*][1,4]benzoxazin-3-yl)carbamates which were converted to the corresponding amines by hydrogen chloride in dioxane. A method for the direct amidation of 1-oxo-3,4-dihydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-8-carboxylic acids and 4-oxo-4*H*-pyrrolo[2,1-*c*][1,4]benzoxazin-3-carboxylic acids with alkyl and aryl amines in the presence of NATU and DIPEA in DMF was developed, which led to the preparation of a series of 1-oxo-*N*-phenyl-3,4-dihydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-8-carboxamides and 4-oxo-*N*-phenyl-4*H*-pyrrolo[2,1-*c*][1,4]benzoxazin-3-carboxamides. Reactions of 8-amino-3,4-dihydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-1-ones and 3-amino-4*H*-pyrrolo[2,1-*c*][1,4]benzoxazin-4-ones with acetic anhydride, benzoyl chloride, methanesulfonyl chloride, and *p*-toluenesulfonyl chloride were successfully used for the synthesis of *N*-acetamides, *N*-benzamides, *N*-methanesulfonamides, and 4-methyl-*N*-*p*-toluenesulfonamides. In total, 30 new derivatives of 1-oxo-3,4-dihydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazinones and 27 new 4-oxo-4*H*-pyrrolo[2,1-*c*][1,4]benzoxazinones were obtained. A reliable structural determination of all the synthesized compounds has been performed by elemental analysis and a number of spectroscopic methods (^{1}H and ^{13}C NMR, and HPLC/MS) as well as by X-ray diffraction analysis.

4. Experimental

4.1. Materials and Methods

All commercially available chemicals were purchased from Sigma-Aldrich Chemicals (Steinheim, Germany), Merck Chemicals (Darmstadt, Germany), Enamine Ltd (Kyiv, Ukraine). Melting points were determined on a Kofler bench and are uncorrected. ^{1}H-NMR spectra were acquired on a Varian UNITY INOVA 400 spectrometer (400 MHz) in $CDCl_3$ solution (for compounds **1b**, **1c**, **6b**, **6c**, **6d**, **8a-e**, **13a**, **13b**, **17**) and in DMSO-d_6 solution (for compounds **4a-e**, **5b**, **5d**, **6e**,

7a, **7c-7f**, **9a**, **9e**, **9f**, **11e**, **11g**, **12b**, **12d**, **16**) and a Varian Mercury 300 spectrometer (300 MHz) in $CDCl_3$ solution (for compounds **6a**, **7b**, **9b**, **11b**, **11c**, **11d**, **15**, **18**, **19**, **20**) and in DMSO-d_6 solution (for compounds **5a**, **5c**, **5e**, **5f**, **9c**, **9d**, **11a**, **11f**, **11h**, **11i**, **12a**, **12c**, **14**) with TMS as an internal standard. ^{13}C, NMR spectra were acquired on a Varian Mercury 300 spectrometer (76 MHz) in $CDCl_3$ solution (for compounds **9b**), in DMSO-d_6 solution (for compounds **9c**) and in CF_3COOD solution (for compounds **14**), Bruker AVANCE DRX 500 spectrometer (125 MHz) in $CDCl_3$ solution (for compounds **1b**, **7a-f**, **8b**, **8c**, **8d**, **8e**, **9d**, **9e**, **11b**, **12a**, **12c**, **13a**, **13b**, **15**, **17**, **19**, **20**) and in DMSO-d_6 solution (for compounds **4a**, **4c-4e**, **5a**, **9f**, **11a**, **11c**, **11f**, **11g**, **11i**, 18) and a Agilent 600MHz spectrometer (150 MHz) in $CDCl_3$ solution (for compounds **6b-6e**, **8a**, **9a**) and in DMSO-d_6 solution (for compounds **1c**, **4b**, **5b**, **5d**, **5e**, **5f**, **11d**, **11e**, **11h**), Bruker AVANCE III 400 (101 MHz) in CF_3COOD solution (for compounds **12b**), with TMS as an internal standard. ^{19}F, NMR spectra were acquired on a Varian Mercury-400 spectrometer (376 MHz) in $CDCl_3$ solution (for compounds **11c**, **11d**, **12c**) and in DMSO-d_6 solution (for compounds **5e**, **7e**, **9e**, **11i**, **12d**). Mass spectra were recorded on an Agilent LC/MSD SL instrument; column Zorbax SB-C18, 4.6 × 15 mm, 1.8 μm (PN 82(c) 75-932); solvent DMSO, at atmospheric pressure, electrospray ionization. Merck 60 (40–63 μ) silica gel was used for column chromatography. X-ray difraction study of (4*S*)-*N*-(4-bromophenyl)-4-(1-methylethyl)-1-oxo-3,4-dihydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazine-8-carboxamide **11b** was solved by direct method using SHELXTL package.[56] All reactions were monitored using thin layer chromatography TLC on TLC-sheets ALUGRAM Xtra SIL G/UV_{254} (MACHEREY-NAGEL) (eluent CH_2Cl_2–MeOH, 50:1).

*4.2.1. General procedure for the synthesis of 1-oxo-3,4-dihydro-1H-pyrrolo[2,1-c][1,4]oxazine-8-carboxylic acid **4a-e** and 4-oxo-4H-pyrrolo[2,1-c][1,4]benzoxazine-3-carboxylic acid **5a-f**.* To a solution of (32.5 mmol) methyl (2-oxomorpholin-3-ylidene)ethanoate **1a-e** or methyl (2-oxo-2*H*-1,4-benzoxazin-3(4*H*)-ylidene)ethanoate **2a-f** in 60 cm^3 AcOH, 6.41 g bromoacetaldehyde diethyl acetal (32.5 mmol) was added. The resulting mixture was stirred at 80 °C for 6–12 h. After the reaction was completed, the mixture was cooled and the insoluble materials were filtered off, washed with AcOH (2 × 5 cm^3), MTBE (2 × 2 cm^3), hexane (2 × 4 cm^3) and dried under reduced pressure.

*4.2.2. General procedure for the synthesis of tert-butyl (1-oxo-3,4-dihydro-1H-pyrrolo[2,1-c][1,4]oxazin-8-yl)carbamate **6a-e** and tert-butyl (4-oxo-4H-pyrrolo[2,1-c][1,4]benzoxazin-3-yl)carbamate **7a-f**.* To a suspension of (7.2 mmol) 1-oxo-3,4-dihydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazine-8-carboxylic acid **4a-e** or 4-oxo-4*H*-pyrrolo[2,1-*c*][1,4]benzoxazine-3-carboxylic acid **5a-f** in 50 cm^3 toluene, 0.95 g of TEA (1.3 mmol) and 2.14 g of *tert*-butyl alcohol (28.9 mmol) were added. To the resulting mixture was added 2.59 g of DPPA (9.4 mmol) dropwise. The resulting mixture was stirred at 110°C for 6–14 h. After the reaction was completed, the reaction mixture was cooled and washed with H_2O (2 × 10 cm^3) and brine (2 × 10 cm^3), the organic phase was dried over Na_2SO_4 and evaporated under reduced pressure. For the compounds **6a-e**, **7a**,**b**,**d**, formed precipitate was purified by column chromatography on silica gel, eluent CH_2Cl_2–MeOH, 100:1. For the compounds **7c**,**e**,**f**, formed precipitate was washed with boiling hexane (2 × 5 cm^3) and dried under reduced pressure.

*4.2.3. General procedure for the synthesis of 8-amino-3,4-dihydro-1H-pyrrolo[2,1-c][1,4]oxazin-1-one **8a-e** and 3-amino-4H-pyrrolo[2,1-c][1,4]benzoxazin-4-one **9a-f**.* To a (2.8 mmol) *tert*-butyl (1-oxo-3,4-dihydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-8-yl)carbamate **6a-e** or *tert*-butyl (4-oxo-4*H*-pyrrolo[2,1-*c*][1,4]benzoxazin-3-yl)carbamate **7a-f** 10 cm^3 of hydrogen chloride in dioxane, was added. The resulting mixture was stirred at room temperature for 4–6 h. After the reaction was completed, the obtained mixture was evaporated under reduced pressure. The formed precipitate was purified by column chromatography on silica gel, eluent CH_2Cl_2–MeOH, 50:1.

*4.2.4. General procedure for the synthesis of N-alkyl(aryl)-1-oxo-3,4-dihydro-1H-pyrrolo[2,1-c][1,4]oxazine-8-carboxamide **11a-i** and N-alkyl(aryl)-4-oxo-4H-pyrrolo[2,1-c][1,4]benzoxazine-3-carboxamide **12a-d**.* To a solution of (1.17 mmol) 1-oxo-3,4-dihydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazine-8-carboxylic acid **4a-e** or 4-oxo-4*H*-pyrrolo[2,1-*c*][1,4]benzoxazine-3-carboxylic acid **5a,d-f** in 5 cm^3 DMF, 1.17 mmol of corresponding amines **10a-g**, 0.23 g DIPEA (1.75 mmol), and 0.53 g HATU (1.40 mmol) were added. The resulting mixture was stirred at 50°C for 8–25 h. After the reaction was completed, the reaction mixture was cooled and water (5 ml) added, the insoluble materials were filtered off, washed with H_2O (2 × 5 cm^3), hexane (2 × 4 cm^3) and dried under reduced pressure.

*4.2.5. General procedure for the synthesis of N-(4,4-dimethyl-1-oxo-3,4-dihydro-1H-pyrrolo[2,1-c][1,4]oxazin-8-yl)acetamide **13a** and N-[(4S)-1-oxo-4-(propan-2-yl)-3,4-dihydro-1H-pyrrolo[2,1-c][1,4]oxazin-8-yl]acetamide **13b**.* To a solution of (1.02 mmol) 8-amino-4,4-dimethyl-3,4-dihydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-1-one **8b** or (4*S*)-8-amino-4-(propan-2-yl)-3,4-dihydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-1-one **8c** in 5 cm^3 acetonitrile, 0.10 g acetic anhydride (1.02 mmol) was added. The resulting mixture was stirred at 35°C for 3 h. After the reaction was completed, the obtained mixture was evaporated under reduced pressure. The formed precipitate washed with hexane (2 × 4 cm^3), MTBE (1 × 1 cm^3) and dried under reduced pressure.

*4.2.6. General procedure for the synthesis of N-(7-fluoro-4-oxo-4H-pyrrolo[2,1-c][1,4]benzoxazin-3-yl)acetamide **14**.* To a solution of (1.02 mmol) 3-amino-7-fluoro-4*H*-pyrrolo[2,1-*c*][1,4]benzoxazin-4-one **8b** in 20 cm^3 acetonitrile, 0.10 g acetic anhydride (1.02 mmol), and 0.13 g DIPEA (1.02 mmol) were added. The resulting mixture was stirred at 35°C for 8 h. After the reaction was completed, the obtained mixture was evaporated under reduced pressure. The formed precipitate washed with H_2O (2 × 2 cm^3), MTBE (1 × 1 cm^3), hexane (2 × 4 cm^3) and dried under reduced pressure.

*4.2.7. General procedure for the synthesis of N-(1-oxo-3-phenyl-3,4-dihydro-1H-pyrrolo[2,1-c][1,4]oxazin-8-yl)benzamide **15** and N-(4-oxo-4H-pyrrolo[2,1-c][1,4]benzoxazin-3-yl)benzamide **16**.* To a solution of (1.31 mmol) 8-amino-3-phenyl-3,4-dihydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-1-one **8d** or 3-amino-4*H*-pyrrolo[2,1-*c*][1,4]benzoxazin-4-one **9a** in 20 cm^3 CH_2Cl_2, 0.20 g DIPEA (1.58 mmol), 1.45 mmol of benzoyl chloride were added. The resulting mixture was stirred at room temperature for 6–8 h. After the reaction was completed, for the compound **15**, the reaction mixture washed with H_2O (2 × 5 cm^3) and brine (2 × 5 cm^3), the organic phase was dried over Na_2SO_4 and evaporated under reduced pressure. The formed precipitate washed with hexane (2 × 4 cm^3), MTBE (1 × 1 cm^3) and dried under reduced pressure. For the compound **16**, the insoluble materials were filtered off, washed with H_2O (2 × 5 cm^3), hexane (2 × 4 cm^3), and dried under reduced pressure.

*4.2.8. General procedure for the synthesis of N-[(5aS,9aS)-4-oxo-5a,6,7,8,9,9a-hexahydro-4H-pyrrolo[2,1-c][1,4]benzoxazin-3-yl]methanesulfonamide **17** and N-(9-methyl-4-oxo-4H-pyrrolo[2,1-c][1,4]benzoxazin-3-yl)methanesulfonamide **18**.* To a solution of (1.07 mmol) (5*aS*,9*aS*)-3-amino-5*a*,6,7,8,9,9*a*-hexahydro-4*H*-pyrrolo[2,1-*c*][1,4]benzoxazin-4-one **8e** or 3-amino-9-methyl-4*H*-pyrrolo[2,1-*c*][1,4]benzoxazin-4-one **9b** in 25 cm^3 CH_2Cl_2, 0.17 g DIPEA (1.28 mmol), 1.17 mmol of methanesulfonyl chloride were added. The resulting mixture was stirred at room temperature for 6 h for the compound **17** or at 40°C for 8 h for the compound **18**. After the reaction was completed, the reaction mixture washed with H_2O (2 × 5 cm^3) and brine (2 × 5 cm^3), the organic phase was dried over Na_2SO_4 and evaporated under reduced pressure. The formed precipitate washed with hexane (2 × 4 cm^3), MTBE (1 × 1 cm^3) and dried under reduced pressure. The formed precipitate was purified by column chromatography on silica gel, eluent $CHCl_3$–MeOH, 100:1 (for compound **17**), $CHCl_3$–MeOH, 50:1 (for compounds **18**).

*4.2.9. General procedure for the synthesis of N-(8-tert-butyl-4-oxo-4H-pyrrolo[2,1-c][1,4]benzoxazin-3-yl)-4-methylbenzenesulfonamide **19** and 4-methyl-N-(3-methyl-1-oxo-3,4-dihydro-1H-pyrrolo[2,1-c][1,4]oxazin-8-yl)benzenesulfonamide **20**.* To a solution of (1.08 mmol) 3-amino-8-*tert*-butyl-4*H*-pyrrolo[2,1-*c*][1,4]benzoxazin-4-one **9d** or 8-amino-3-methyl-3,4-dihydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-1-one **8a** in 35 cm^3 pyridine, 1.14 mmol of 4-methylbenzenesulfonyl chloride was added. The resulting mixture was stirred at 55°C for 10-12 h. After the reaction was completed, the reaction mixture washed with H_2O (2 × 5 cm^3) and brine (2 × 5 cm^3), the organic phase was dried over Na_2SO_4 and evaporated under reduced pressure. The formed precipitate was purified by column chromatography on silica gel, $CHCl_3$–MeOH, 50:1.

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For details, please see Supporting Information available.

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