Journal Pre-proof

Synthesis and study of new photochromic unsymmetrical bis-spiropyrans with nonequivalent heteroarene fragments conjugated through the common 2H, 8H-pyrano[2,3-f]chromene moiety

Ilya V. Ozhogin, Eugene L. Mukhanov, Anatoly V. Chernyshev, Artem D. Pugachev, Boris S. Lukyanov, Anatoly V. Metelitsa
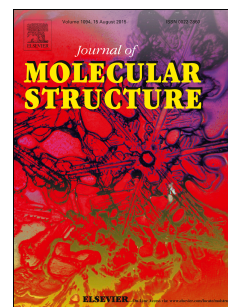
Please cite this article as: I.V. Ozhogin, E.L. Mukhanov, A.V. Chernyshev, A.D. Pugachev, B.S. Lukyanov, A.V. Metelitsa, Synthesis and study of new photochromic unsymmetrical bis-spiropyrans with nonequivalent heteroarene fragments conjugated through the common 2H, 8H-pyrano[2,3-f]chromene moiety, *Journal of Molecular Structure* (2020), doi: https://doi.org/10.1016/j.molstruc.2020.128808.

This is a PDF file of an article that has undergone enhancements after acceptance, such as the addition of a cover page and metadata, and formatting for readability, but it is not yet the definitive version of record. This version will undergo additional copyediting, typesetting and review before it is published in its final form, but we are providing this version to give early visibility of the article. Please note that, during the production process, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Credit Author Statement.

All the authors contributed equally to this manuscript.
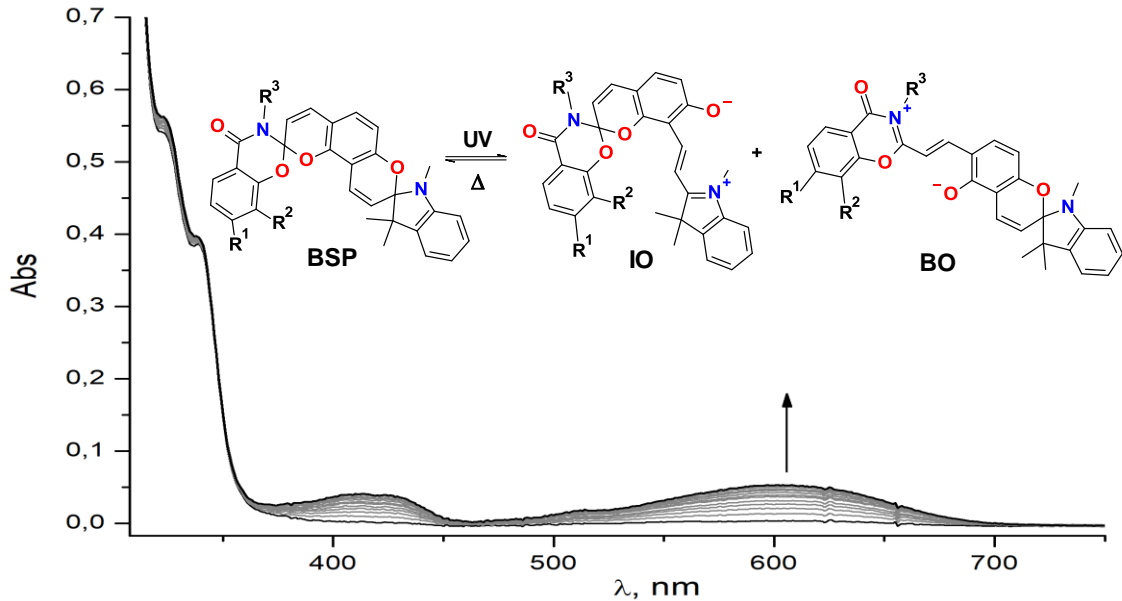
Synthesis and study of new photochromic unsymmetrical bis-spiropyrans with nonequivalent heteroarene fragments conjugated through the common 2*H*,8*H*-pyrano[2,3-*f*]chromene moiety

Ilya V. Ozhogin [a,*], Eugene L. Mukhanov [a], Anatoly V. Chernyshev [a], Artem D. Pugachev [a], Boris S. Lukyanov[a], Anatoly V. Metelitsa[a]

[a] *Institute of Physical and Organic Chemistry, Southern Federal University, 194/2 Stachka ave., 344090, Rostov-on-Don, Russian Federation*

Abstract: Four novel bis-spiropyrans possessing two different photochromic units based on indoline and 1,3-benzoxazine heterocycles which are connected through the common 2H,8H-pyrano[2,3-f]chromene moiety and modified with electron donating substituents were obtained by multistep synthesis starting with 2,4-dihydroxy-iso-phthalic aldehyde. The structure of the compounds was confirmed by ^{1}H and ^{13}C NMR, FTIR and HRMS. All bis-spirocompounds exhibited photochromic activity at room temperature. Investigation of photochromic properties of bis-spiropyrans revealed that their once-opened merocyanine isomers were more stable than the double-opened ones under experimental conditions. It was also found that modification of the benzoxazine moiety of the molecule with electron donating substituents along with introduction of bulky benzyl group close to the oxazine spiro-center leads to an increase of the merocyanine lifetime up to 148 s.

---

[*] Corresponding author. E-mail: iozhogin@sfedu.ru

Spiropyrans (SP) represent one of the most interesting and well-studied classes of the organic photochromic compounds [1-3], which can undergo reversible isomerization between spirocyclic and merocyanine forms under the activating irradiation. One of the main advantages of SPs over the other organic photochromes is that their photoisomerization is accompanied by the significant changes in the molecular structure, which lead not only to a redshift of the absorption maxima, but also to the changes in other physical and chemical characteristics, such as the dipole moment, fluorescent properties, the basicity, the affinity to metal ions and other chemical species, etc. Applications of spiropyrans include but are not limited by such areas as molecular electronics and photonics [4-6], chemosensing [7-9], fluorescent microscopy and bio-imaging [10-13], targeted drug delivery [14-17] and photopharmacology [18-19]. There are a lot of recognized reviews devoted to spiropyrans in which one may get acquainted with the main trends of their potential use [20-26].

In recent years, much attention has been paid to various multiphotochromes [27-30], including bis-spiropyrans (BSP) – the compounds possessing two potentially photochromic spiropyran fragments. The theoretically possible consecutive or simultaneous opening of their pyran rings can lead to the formation of different merocyanine isomers. Each of them should be characterized by specific long-wavelength absorption maximum that allows us to consider these compounds as potential components of multistable molecular switches. However, the chemistry of BSP is a much less explored area compared to their mono-spirocyclic analogues.

All the known bis- and poly-spirocompounds may be divided into several structural groups differing by the manner in which photochromic centres are connected in the molecule. The first group, more or less fully described in the literature, consists of the molecules, in which there is no electronic conjugation between two photoactive units. So, the spiropyran fragments are linked by the simple σ-bond or other σ-linker [31-41]. In most of these cases, the absorption

spectra of the BSPs' open forms differ a little from their mono-spiroanalogues, indicating the opening of only one spirocycle.

Much more interest is aroused by the BSP, whose photoactive centers are connected through the common π-electronic systems of their heteroarene [42-47] or 2*H*-chromene moieties [48-52]. In this case, the opening of one of the pyran rings leading to serious structural and electronic transformations of the molecule must have a critical impact on the photodynamic characteristics of the second photochromic fragment. In modern literature there are several references related to the observation of the photochemically induced double opening of conjugated BSP [46, 51], but these observations are not fully confirmed by experimental and theoretical data. At the same time a critical factor determining the prospects of using multiphotochromic compounds as multistate molecular switches is to have the possibility of selective switching between the spectrally distinguishable photoisomers.

In our previous studies we have reported and theoretically substantiated the photoinduced opening of both pyran rings in a series of unsymmetrical indoline-benzoxazine BSPs [53-56]. In these compounds the nonequivalent hetarene moieties of the molecule are connected through a common conjugated 2*H*,8*H*-pyrano[2,3-*f*]chromene fragment. The presence of unsymmetrical conjugated system combined with seriously differing properties of the hetarene fragments makes possible the existence of the several merocyanine isomers with different conjugation chain length and different positions of the absorption bands in the electronic spectra accordingly (**Scheme 1**).
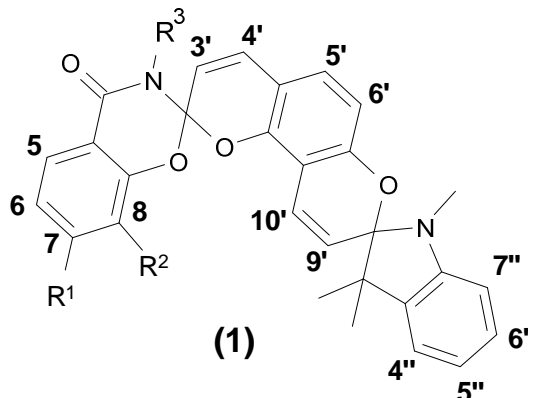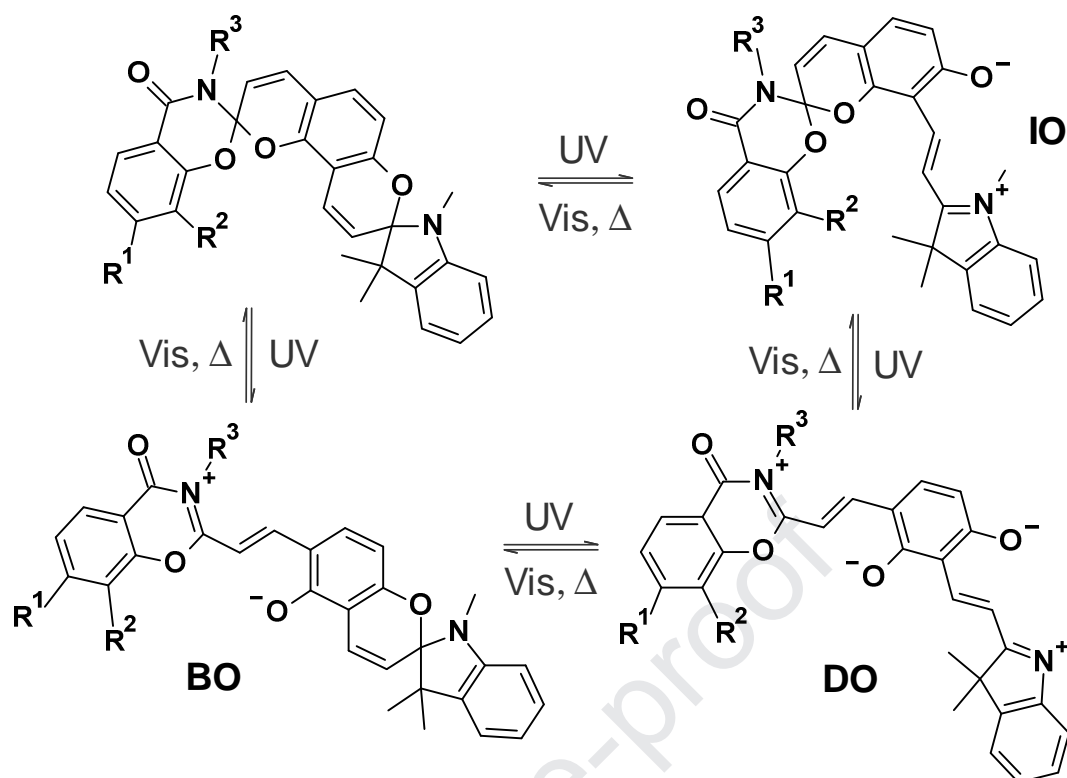
Scheme 1. Possible photoisomerization transformations of asymmetric BSPs

In the present study, we decided to synthesize BSPs with improved photochromic properties resulted in the increased stability of their merocyanine forms and therefore increased lifetimes. One of the well-known methods to increase stability of merocyanine isomers of SP is an introduction of donor substituents into the hetarene fragment. This fact may be explained due to the delocalization of the positive charge, appearing in the corresponding fragment of the molecule after the reaction of the pyran ring opening. The other way to stabilize merocyanine which was realized by us is an introduction of bulky substituent at the closest position to the benzoxazine spiro-centre. This modification should create steric hindrance for the thermal recyclization reaction.

Thus, this work was aimed at synthesis and investigation of new BSPs (**1**), containing methyl or methoxy groups at different positions of the benzoxazine moiety and methyl or benzyl group linked to the nitrogen atom of the oxazine cycle (**Table 1**).

Table 1. Structure and numbering of target bis-spiropyrans (**1**)

		R^1	R^2	R^3
	a	Me	H	Me
	b	H	Me	Me
	c	H	OMe	Me
	d	H	OMe	CH$_2$Ph

The structure diagram labeled **(1)** appears in the leftmost column spanning all rows, showing atom numbering: R^3, 3', 4', 5', 6', O, N, 5, 6, 7, 8, 10', 9', O, O, R^2, R^1, N, 7", 6", 5", 4".

2. Experimental

2.1. Materials and spectroscopic methods

All reagents were purchased from Alfa Aesar or Merck and used as received. Organic solvents used were purified and dried according to standard methods. NMR ^{1}H and ^{13}C spectra were recorded on a Bruker DPX-250 (250 MHz) spectrometer at the Scientific and Educational Laboratory of Resonance Spectroscopy, Department of Natural and High Molecular Compounds Chemistry of Southern Federal University. The signals were assigned relatively to the signals of residual protons of the deuterated solvent (CDCl$_3$, δ = 7.26 ppm). IR spectra of compounds were recorded on a Varian Excalibur 3100 FT-IR by the partial internal reflection method. High-resolution mass spectra were obtained from a TOF mass spectrometer Bruker micrOTOF with an ESI source. Melting points were determined on a Fisher-Jones apparatus (Fisher Scientific Co). Elemental analysis was carried out by a conventional method [57].

2.1.1 Spectral and photokinetic studies

The electronic absorption spectra and kinetic curves of thermal reactions of the studied compounds were recorded on an "Agilent 8453" spectrophotometer equipped with a temperature-controlled cell holder. Irradiation light was brought

into the thermostatic cell compartment at 90° from a 200W high-pressure mercury lamp "Newport" equipped with glass filters for the allocation of mercury lines.

The values of the rate constants of the reverse thermal reactions were determined from the dependence of the optical densities at the maxima of the long-wavelength absorption bands of merocyanine isomers on the time of bleaching of the solution according to the equation corresponding to the monoexponential nature of the attenuation:

$$D = D_\infty + D_1 e^{-t/\tau_1},$$

where D is current optical density value; D_∞ is the equilibrium optical density in the absence of irradiation; D_0 is the maximum optical density; t is time, s; τ_1 is the lifetime of the merocyanine form.

2.2. Synthetic methods

2,3,7-Trimethyl-1,3-benzoxazin-4-onium perchlorate (5a), 2,3,8-Trimethyl-1,3-benzoxazin-4-onium perchlorate (5b), 2,3-Dimethyl-8-methoxy-1,3-benzoxazine-4-onium perchlorate (5c) and 3-Benzyl-8-methoxy-2-methyl-1,3-benzoxazine-4-onium perchlorate (5d) were obtained from 4-methyl-, 3-methyl- or 3-methoxysalicylic acid as white crystalline solids according to the previously described procedure [58] and used further without characterization. Yields: 5.50 g (95%) for (**5a**); 5.21 g (90%) for (**5b**); 5.38 g (88%) for (**5c**); 6.87 g (90%) for (**5d**).

3,7-Dimethyl-8'-formyl-7'-hydroxy-4-oxo-spiro[1,3-benzoxazine-2,2'-chromene] (7a). 2.90 g (0.01 mol) of perchlorate (**5a**) was added to a hot solution of 1.83 g (0.011 mol) of aldehyde (**2**) in 10 mL of glacial acetic acid. The reaction mixture was heated at reflux for 7–10 min, then sealed and left overnight. The precipitated bright yellow styryl salt (**6a**) was filtered and washed with dry diethyl ether (3 x 15 mL). Dry salt was placed in absolute diethyl ether (50 mL) and an equimolar amount of triethylamine was added dropwise. After a day of staying in the dark, the ether was decanted, the solvent was distilled off and the residue was

6

chromatographed on SiO_2 with chloroform as the eluent. Yield 1.010 g (30%). mp 176–178 °C. IR spectrum, ν, cm^{-1}: 1683 (C=O); 1636, 1608 (C=C); 949, 929 (C_{spiro}–O). NMR ^{1}H (CDCl$_3$) δ, ppm (*J*, Hz): 2.32 (3H, s, 7- CH$_3$), 3.15 (3H, s, N-CH$_3$), 5.95 (1H, d, *J* = 9.8, 3′-H), 6.60 (1H, d, *J* = 8.6, 6′-H), 6.67 (1H, s, 8-H), 6.9 (1H, d, *J* = 9.8, 4′-H), 6.98 (1H, d, *J* = 7.9, 6-H), 7.36 (1H, d, *J* = 8.6, 5′-H), 7.91 (1H, d, *J* = 7.9, 5-H), 9.84 (1H, s, 8′-CHO), 11.69 (1H, s, 7′-OH). Anal. calc. for $C_{19}H_{15}NO_5$: C 67.65; H 4.48; N 4.15. Found: C 67.56; H 4.50; N 4.12.

3,8-Dimethyl-8'-formyl-7'-hydroxy-4-oxo-spiro[1,3-benzoxazine-2,2'-chromene] (7b) was obtained by the method used for the synthesis of (**7a**) starting with 2.90 g (0.01 mol) of compound (**5b**). Yield 977 mg (29%). mp 168–170 °C. IR spectrum, ν, cm^{-1}: 1677 (C=O); 1647, 1600 (C=C); 949, 921 (C_{spiro}–O). NMR ^{1}H (CDCl$_3$) δ, ppm (*J*, Hz): 2.01 (3H, s, 8- CH$_3$), 3.17 (3H, s, N-CH$_3$), 5.98 (1H, d, *J* = 9.8, 3′-H), 6.60 (1H, d, *J* = 8.6, 6′-H), 6.92 (1H, d, *J* = 9.8, 4′-H), 7.07 (1H, t, 6-H), 7.30 (1H, d, 7-H), 7.37 (1H, d, *J* = 8.6, 5′-H), 7.88 (1H, d, 5-H), 9.78 (1H, s, 8′-CHO), 11.68 (1H, *b*s, 7′-OH). Anal. calc. for $C_{19}H_{15}NO_5$: C 67.65; H 4.48; N 4.15. Found: C 67.54; H 4.49; N 4.11.

8'-Formyl-7'-hydroxy-8-methoxy-3-methyl-4-oxo-spiro[1,3-benzoxazine-2,2'-chromene] (7c) was obtained by the method used for the synthesis of (**7a**) starting with 3.06 g (0.01 mol) of compound (**5c**). Yield 777 mg (22%). mp 157–159 °C. IR spectrum, ν, cm^{-1}: 1679 (C=O); 1641, 1594 (C=C); 946, 921 (C_{spiro}–O). NMR ^{1}H (CDCl$_3$) δ, ppm (*J*, Hz): 3.14 (3H, s, N-CH$_3$), 3.74 (3H, s, 8-OCH$_3$), 5.97 (1H, d, *J* = 9.8, 3′-H), 6.59 (1H, d, *J* = 8.6, 6′-H), 6.94 (1H, d, *J* = 9.8, 4′-H), 7.03-7.13 (2H, m, 6-H, 7-H), 7.36 (1H, d, *J* = 8.6, 5′-H), 7.63 (1H, d, 5-H), 9.85 (1H, s, 8′-CHO), 11.69 (1H, s, 7′-OH). Anal. calc. for $C_{19}H_{15}NO_6$: C 64.58; H 4.28; N 3.96. Found: C 64.48; H 4.30; N 3.92.

3-Benzyl-8'-formyl-7'-hydroxy-8-methoxy-4-oxo-spiro[1,3-benzoxazine-2,2'- chromene] (7d) was obtained by the method used for the synthesis of (**7a**) starting with 3.82 g (0.01 mol) of compound (**5d**). Yield 858 mg (20%). mp 148–150 °C. IR spectrum, ν, cm^{-1}: 1678 (C=O); 1635, 1597 (C=C); 930 (C_{spiro}–O).

NMR ^{1}H (CDCl$_3$) δ, ppm (J, Hz): 3.80 (3H, s, 8-OCH$_3$), 4.81 (1H, d, J = 15.8, N–CH$_2$), 5.06 (1H, d, J = 15.8, N–CH$_2$), 5.89 (1H, d, J = 9.9, 3′-H), 6.58 (1H, d, J = 8.6, 6′-H), 6.89 (1H, d, J = 9.9, 4′-H), 7.12 – 7.25 (7H, m, arom. H), 7.33 (1H, d, J = 8.6, 5′-H), 7.73 (1H, dd, J = 7.5, 1.7, 5-H), 9.73 (1H, s, 8′-CHO), 11.67 (1H, s, 7′-OH). Anal. calc. for C$_{25}$H$_{19}$NO$_6$: C 69.92; H 4.46; N 3.26. Found: C 69.80; H 4.51; N 3.22.

1′′,3,3′′,3′′,7-Pentamethyl-4-oxo-dispiro(1,3-benzoxazine-2,2′-pyrano[2,3-*f*]chromene-8′,2′′-indoline) (1a). 355 mg (1 mmol) of spiropyran (**7a**) and 274 mg (1 mmol) of 3*H*-indolium perchlorate were dissolved in 10 mL of *i*-propanol. 0.1 mL (1.1 mmol) of piperidine was added dropwise to the resulting mixture under heating. After 10 minutes of refluxing the mixture was left in a dark place for the night. The formed precipitate was filtered off, washed with hexane and chromatographed on silica gel with chloroform as an eluent. Yield 393 mg (80%). mp 229–232 °C. IR spectrum, ν, cm^{-1}: 1681 (C=O); 1644, 1606 (C=C); 933 (C$_{spiro}$–O). NMR ^{1}H (CDCl$_3$) δ, ppm (J, Hz): 1.08 (3H, s, 3′′-CH$_3$), 1.24 (3H, s, 3′′-CH$_3$), 2.34 (3H, s, 7-CH$_3$), 2.65 (3H, s, 1′′-CH$_3$), 3.14 (3H, s, 3-CH$_3$), 5.51 (1H, dd, J = 10.4, 8.4 Hz, 9′-H), 5.84 (1H, d, J = 9.8, 3′-H), 6.39 (1H, d, J = 8.3, 6′-H), 6.46 (1H, dd, J = 2.4, 7.7, 7′′-H), 6.71 (1H, s, 8-H), 6.73 (1H, dd, J = 10.3, 18.2, 10′-H), 6.77 – 6.91 (2H, m, 5′′-H (t, J = 7.8), 4′-H (d, J = 9.8)), 6.91 – 7.07 (3H, m, 5′-H, 6-H, 4′′-H), 7.12 (1H, t, J = 7.6, 6′′-H), 7.95 (1H, d, J = 7.9, 5-H). NMR ^{13}C (CDCl$_3$) δ, ppm: 20.0 (3′′-CH$_3$), 21.9 (7-CH$_3$), 25.8 (3′′-CH$_3$), 28.8 (N(3)-CH$_3$), 30.0 (N(1′′)-CH$_3$), 51.8 (C-3′′), 104.7, 106.8 (C-7′′), 107.0, 107.6, 109.2 (C-6′), 110.9, 113.8, 115.5 (C-3′), 116.9 (C-7), 118.5 (C-9′), 119.2 (C-5′′), 121.5 (C-4′′), 122.5 (C-10′), 124.0 (C-6), 127.5 (C-5), 127.6 (C-6′′), 127.9 (C-5′), 129.6 (C-4′), 136.6, 145.7, 146.8, 148.0, 152.7, 156.2, 161.8 (C=O). HRMS (ESI-TOF) m/z [M+H]$^+$ calcd for C$_{31}$H$_{28}$N$_2$O$_4$ 493.2122, found 493.2102.

1′′,3,3′′,3′′,8-Pentamethyl-4-oxo-dispiro(1,3-benzoxazine-2,2′-pyrano[2,3-*f*]chromene-8′,2′′-indoline) (1b) was obtained by the method used for the synthesis of (**1a**) from spiropyran (**7b**). Yield 363 mg (74%). mp 156–158 °C. IR

8

spectrum, ν, cm^{-1}: 1675 (C=O); 1604 (C=C); 950, 925 (C$_{spiro}$–O). NMR ^{1}H (CDCl$_3$) δ, ppm (*J*, Hz): 1.07 (3H, s, 3″-CH$_3$), 1.23 (3H, s, 3″-CH$_3$), 2.0 (3H, s, 8-CH$_3$), 2.63 (3H, s, 1″-CH$_3$), 3.17 (3H, s, 3-CH$_3$), 5.5 (1H, dd, *J* = 10.4, 9′-H), 5.9 (1H, d, *J* = 9.7, 3′-H), 6.39 (1H, d, *J* = 8.4, 6′-H), 6.48 (1H, d, *J* = 7.7, 7″-H), 6.6-6.7 (1H, dd, *J* = 10.4, 10′-H), 6.8 (1H, t, *J* = 7.6, 6-H), 6.9 (1H, d, *J* = 9.7, 4′-H), 6.95 (1H, d, *J* = 8.4, 5′-H), 7.02 – 7.17 (3H, m, 4″-H, 5″-H, 6″-H), 7.31 (1H, d, *J* = 7.3, 7-H), 7.91 (1H, d, *J* = 7.6, 5-H). NMR ^{13}C (CDCl$_3$) δ, ppm (*J*, Hz): 14.8, 20.0, 25.8, 28.8, 30.1, 51.7, 104.7, 106.8, 107.7, 109.2, 111.3, 115.8, 116.3, 118.7, 119.0, 119.2, 121.5, 122.3, 122.4, 125.2, 126.2, 127.6, 127.8, 129.8, 135.4, 136.6, 146.7, 147.99), 150.7, 156.2, 162.0. HRMS (ESI-TOF) *m/z* [M+H]$^{+}$ calcd for C$_{31}$H$_{28}$N$_2$O$_4$ 493.2122, found 493.2116.

8-Methoxy-1″,3,3″,3″-tetramethyl-4-oxo-dispiro(1,3-benzoxazine-2,2′-pyrano[2,3-*f*]chromene-8′,2″-indoline) (**1c**) was obtained by the method used for the synthesis of (**1a**) from spiropyran (**7c**). Yield 183 mg (36%). mp 149–151 ^{o}C. IR spectrum, ν, cm^{-1}: 1681 (C=O); 1605 (C=C); 941, 925 (C$_{spiro}$–O). NMR ^{1}H (CDCl$_3$) δ, ppm (*J*, Hz): 1.07 (3H, s, 3″-CH$_3$), 1.22 (3H, s, 3″-CH$_3$), 2.64 (3H, s, 1″-CH$_3$), 3.15 (3H, s, 3-CH$_3$), 3.74 (3H, s, 8-OCH$_3$), 5.51 (1H, dd, *J* = 10.45, 9′-H), 5.88 (1H, d, *J* = 9.8, 3′-H), 6.38 (1H, d, *J* = 8.4, 6′-H), 6.48 (1H, d, *J* = 7.7, 7″-H), 6.70 (1H, dd, *J* = 10.45, 10′-H), 6.81 (1H, t, *J* = 7.4, 5″-H), 6.90 (1H, d, *J* = 9.8, 4′-H), 6.95 (1H, d, *J* = 8.4, 5′-H), 7.02 (1H, d, *J* = 7.4, 4″-H), 7.07 – 7.17 (3H, m, 7-H, 6-H, 6″-H), 7.91 (1H, d, 5-H). NMR ^{13}C (CDCl$_3$) δ, ppm: 20.4 (3″-CH$_3$), 26.2 (3″-CH$_3$), 29.2 (N(1″)-CH$_3$), 30.3(N(3)-CH$_3$), 52.1 (C-3″), 56.9(O-CH$_3$), 105.1, 107.2 (C-7″), 107.4, 107.9, 109.6 (C-6′), 111.2, 115.4 (C-3′), 117.4, 117.7, 119.0 (9′-C), 119.4, 119.5 (C-5″), 119.6 (C-5), 121.9 (C-4″), 122.9 (C-10′), 128.0 (C-6″), 128.4 (C-5′), 130.5 (C-4′), 137.0, 142.8, 147.2, 148.4, 148.6, 156.6, 162.0 (C=O). HRMS (ESI-TOF) *m/z* [M+H]$^{+}$ calcd for C$_{31}$H$_{28}$N$_2$O$_5$ 509.2071, found 509.2051.

3-Benzyl-8-methoxy-1″,3″,3″-trimethyl-4-oxo-dispiro(1,3-benzoxazine-2,2′-pyrano[2,3-*f*]chromene-8′,2″-indoline) (**1d**) was obtained by the method used for the synthesis of (**1a**) from spiropyran (**7d**). Yield 175 mg (30%). mp 188–

191 ^{o}C. IR spectrum, ν, cm^{-1}: (C=O); (C=C); (C$_{spiro}$–O). NMR ^{1}H (CDCl$_3$) δ, ppm (*J*, Hz): 1.10 (3H, d, *J* = 6.4, 3″-CH$_3$), 1.25 (3H, d, *J* = 8.8, 3″-CH$_3$), 2.66 (3H, d, *J* = 5.3, N″-CH$_3$), 3.76 (3H, d, *J* = 1.8, 8-OCH$_3$), 4.63 (1H, dd, *J* = 15.9, 3.5, N-CH$_2$), 5.19 (1H, dd, *J* = 16.0, 6.3, N-CH$_2$), 5.50 (1H, dd, *J* = 10.4, 4.9, 9′-H), 5.77 (1H, d, *J* = 9.7, 3′-H), 6.37 (1H, d, *J* = 8.3, 6′-H), 6.50 (1H, d, *J* = 7.6, 7″-H), 6.65 (1H, dd, *J* = 10.2, 10′-H), 6.82 (2H, m, 4′-H+5″-H), 6.91 (1H, d, *J* = 8.4, 5′-H), 7.00 – 7.32 (m, 9H, arom. H), 7.76 (1H, dd, *J* = 7.2, 1.5, 5-H). NMR ^{13}C (CDCl$_3$) δ, ppm: 20.0, 25.9, 28.8, 47.0, 51.8, 56.5, 104.7, 106.8, 107.3, 107.4, 109.2, 110.7, 114.6, 117.1, 117.5, 118.5, 119.0, 119.3, 121.5, 122.5, 122.6, 127.1, 127.4 (2C), 127.7, 128.0, 128.5 (2C), 130.2, 136.6, 137.8, 142.6, 146.5, 148.0, 148.3, 156.3, 161.7. HRMS (ESI-TOF) *m/z* [M+H]$^+$ calcd for C$_{37}$H$_{32}$N$_2$O$_5$ 585.2384, found 585.2353.

3. Results and discussion

3.1. Synthesis

Preparation of all target unsymmetrical BSP has been succeeded due to the use of 2,4-dihydroxy-*iso*-phthalic aldehyde (**2**) synthesized from resorcinol by Reimer – Thiemann excess formylation as it was described previously [59]. To obtain the desired products (**1a-d**) a five-step synthesis has been carried out (**Scheme 2**). N-substituted amides (**4**) were prepared from chloranhydrides of the corresponding salicylic acids (**3**) by treatment of latter with the excess of methylamine or benzylamine. Synthesis of cyclic 1,3-benzoxazin-4-onium perchlorates (**5**) was carried out on the basis of methylamides (**4**) in acetic anhydride by the action of perchloric acid [58], after which they were involved into the condensation reaction with 2,4-dihydroxy-*iso*-phthalic aldehyde (**2**) to finally isolate bright-colored styryl salts (**6**). Spiropyrans (**7a-d**) were obtained by the action of triethylamine on the salts (**6**) in diethyl ether. With *ortho*-located formyl and hydroxyl functions, compounds (**7a-d**) were found to be the derivatives of salicylaldehyde and the precursors of bis-spirocompounds. Cyclocondensation of

these SPs with 1,2,3,3-tetramethyl-3*H*-indolium perchlorates in presence of piperidine afforded the final BSPs (**1a-d**) with moderate to good yields.
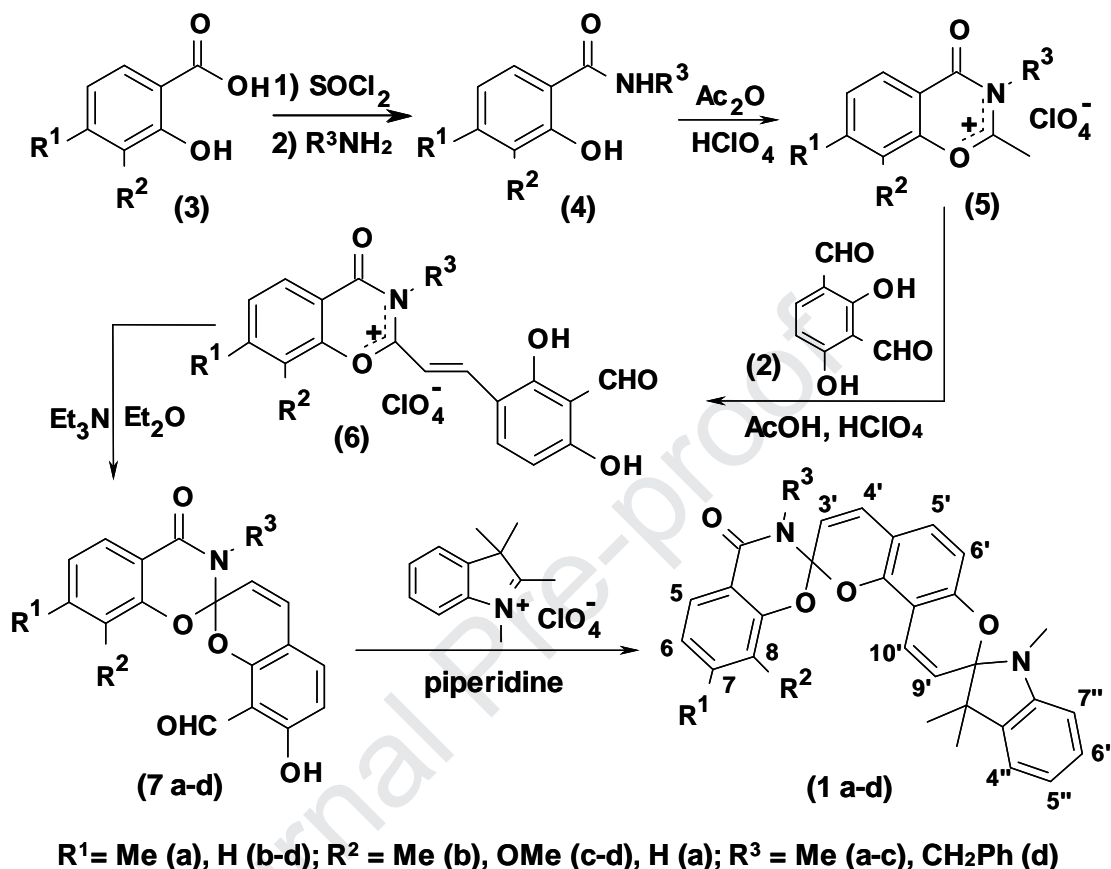
Scheme 2. Synthesis of the target bis-spiropyrans (**1**)

3.2 FT-IR and NMR studies.

The structure of the obtained bis-spirocompounds was proved by IR, NMR ^{1}H and ^{13}C spectroscopy. FT-IR spectra of the compounds demonstrate the presence of strong absorption bands corresponding to the stretching vibrations of the carbonyl group of the oxazinone fragment in the range of 1671-1686 cm^{-1}, as well as the stretching vibrations of the double bonds of -C=C- vinyl fragments of the pyranochromene ring in the region of 1604-1647 cm^{-1}. Absorption of the C(2')–N(3) bond of the oxazine ring occurs in the 1351-1364 cm^{-1} range, while the vibrations of the analogous C(8')–N(1") bonds of the indoline part are located in the range of 1275-1286 cm^{-1}. Characteristic vibrational frequencies of C$_{spiro}$–O

bonds are observed at 923-958 cm^{-1}. It should be noted that passing from oxazine SPs (**7**) to BSPs (**1**), intensification of this band is observed, as well as its splitting or appearance of the shoulder, which is associated with the appearance of the second spirocycle in the molecule.

In the NMR ^{1}H spectra of the obtained BSP, the characteristic signals of all the proton-containing groups are present, which in accordance with the values of the integrated absorption intensities, chemical shifts, and *J*-constants completely correspond to the proposed structures. In the "strong" field of the spectra of BSP in the range of 1.0 – 1.2 ppm, there are characteristic signals of *hem*-dimethyl groups appearing in the form of two 3H singlet signals, which confirm the proximity to the asymmetric carbon spiro-atom. The proton signals of the methyl groups bound to the nitrogen atoms of the indoline and oxazine moieties are at about 2.6 and 3.1 ppm, respectively. The characteristic signals of the 3' and 9' protons of the pyranochromene fragment appear as doublets near 5.8 – 6.0 and 5.5 ppm and form AB-systems with protons 4' and 10' respectively. The values of the coupling constants of these AB-systems lie in the ranges of 9.7 – 9.8 Hz for $J_{3',4'}$ and 10.4 Hz for $J_{9',10'}$ which are characteristic for *cis*-configuration of corresponding protons.

In the spectrum of the compound (**1d**) the signals of the methylene protons of benzyl fragment are manifested as nonequivalent split doublets in the 4.6 – 5.3 ppm region, which is due to the proximity of these fragments to asymmetric carbon atoms and is also the evidence of the cyclic structure of the BSP molecules.

In order to correctly assign the signals of the aromatic protons, compounds (**1a**) and (**1c**) were investigated using two-dimensional NMR techniques, namely COSY ^{1}H-^{1}H (**Fig. 1**), NOESY ^{1}H-^{1}H (**Fig. 2**) and HMQC ^{1}H-^{13}C. The combination of these methods made it possible to unambiguously identify the signal of each aromatic proton in spectra.
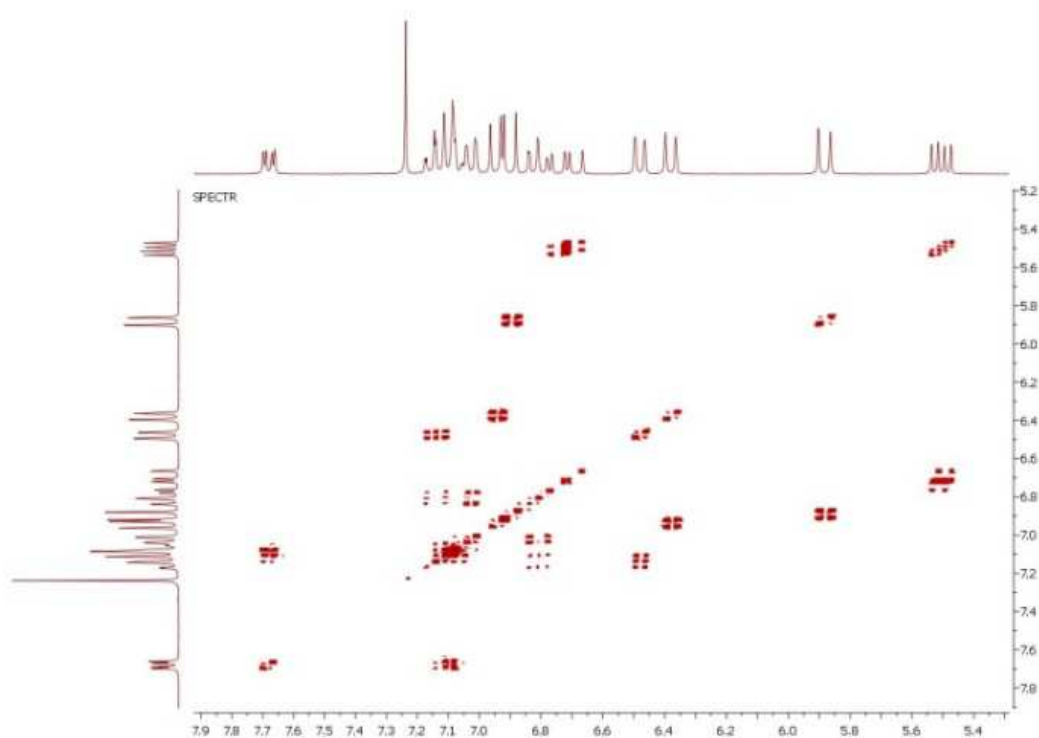
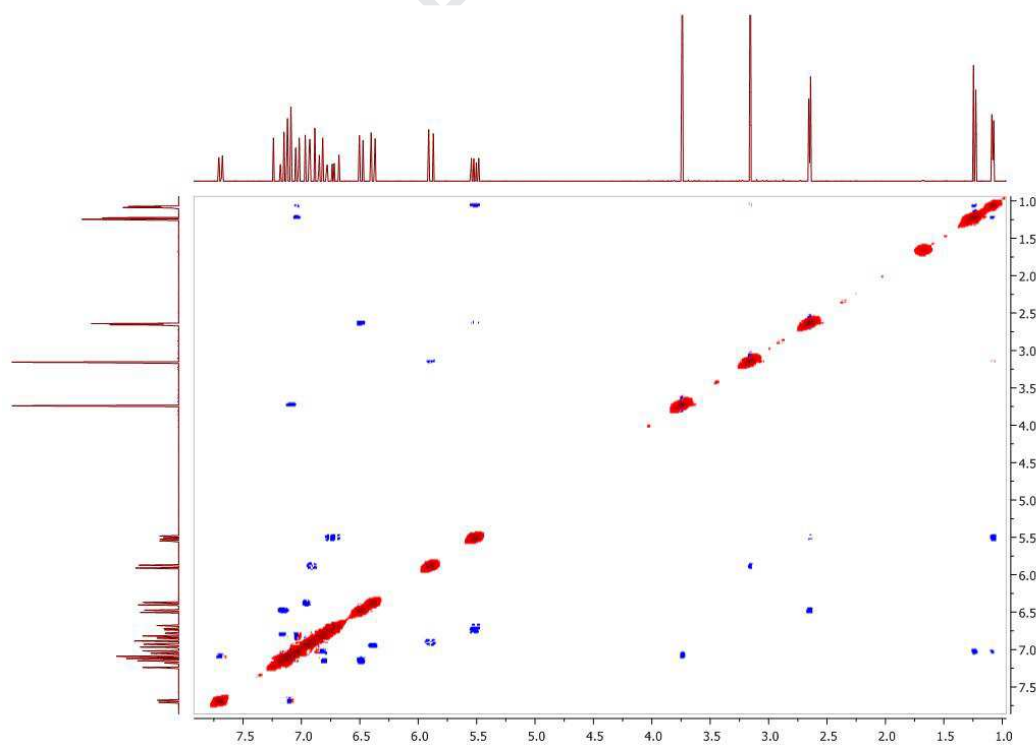**Fig. 1.** NMR spectrum COSY [1]H–[1]H of the compound **(1c)**, aromatic protons area.

Fig. 2. NMR spectrum NOESY [1]H–[1]H of the compound **(1c).**

NMR ^{13}C spectra of BSP (**1a-d**) showed the presence of signals from all the carbon atoms of their molecules. In all of the spectra the signal of the C=O carbon atom of benzoxazine moiety appears in the region of 161.7 – 162.0 ppm.

3.3 Photochemical investigation

Photochemical studies of BSPs (**1**) containing electron donating substituents were carried out in acetonitrile solutions under irradiation with UV light ($\lambda = 313$ nm). The solutions of all the compounds at ambient temperature were colorless, which indicates a complete shift of the thermal equilibrium towards the bis-spirocyclic form under these conditions. This fact is consistent with our previous studies [12]. Under the influence of activating irradiation, an appearance of the long-wavelength maxima in the regions of 413–420 nm and 600–607 nm was observed in the absorption spectra of BSP (**Figs. 3** and **S24**). In previous works, these absorption bands were assigned to the once opened merocyanine isomers (**IO** and **BO**, **Scheme 1**) with help of DFT quantum chemical calculations.
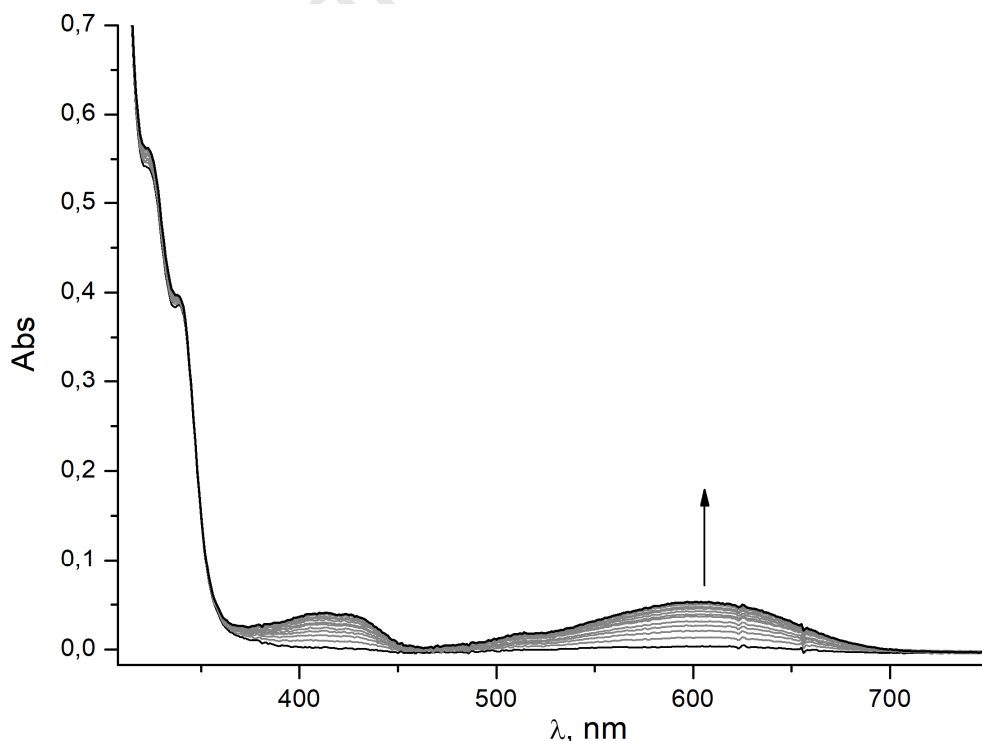

Fig. 3. Absorption spectra changes of BSP (**1a**) under UV irradiation ($\lambda_{irr} = 313$ nm, dt = 10 s) in acetonitrile, $T = 288$ K.

14

The absence of a pronounced maximum at 505 nm, which is characteristic for double opened (**DO**) isomers [53-55], can be associated with an increase in the relative stability of the once opened isomers in polar acetonitrile due to the solvation effects, which leads to an increase in the absorption maximum at 600 nm and possible superposition with a less pronounced peak at about 505 nm. In some cases, a maximum near 500 nm can be detected as a shoulder in the electron absorption spectrum of BSP under conditions of photo-stationary equilibrium.

After irradiation of BSP solutions had been stopped, a thermal discoloration reaction proceeded with a complete return of the spectra to their initial form (**Fig. 4**). **Table 2** shows the spectral and kinetic characteristics of new BSPs modified with EDG (**1a-d**), and synthesized earlier but not investigated under these conditions BSPs (**1e**) and (**1f**) that do not contain EDG in their hetarene parts ($R_1 = R_2 = H$; $R_3 = Me$ (**1e**), CH_2Ph (**1f**)).
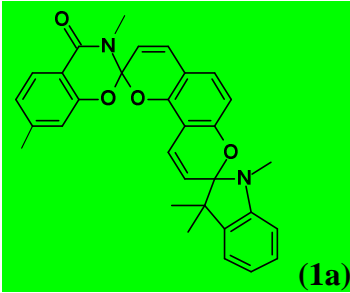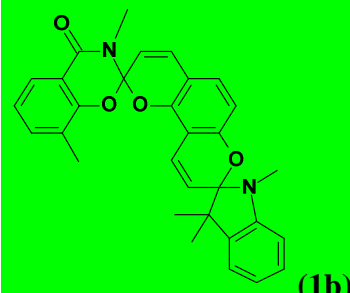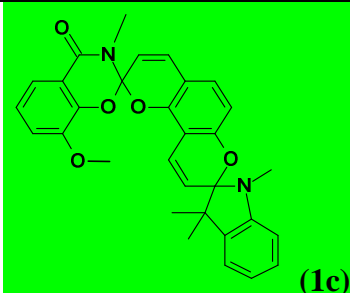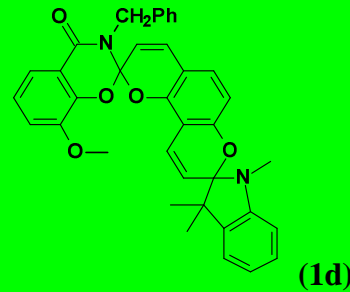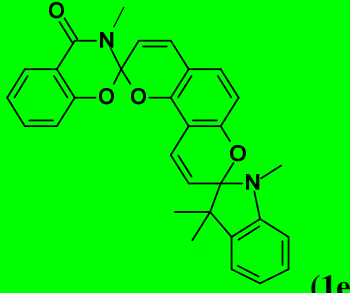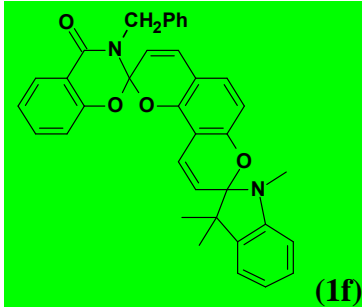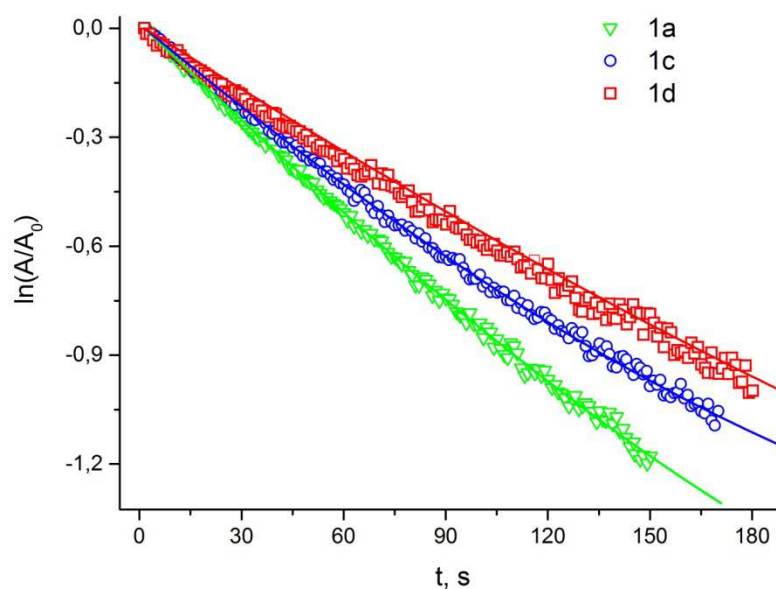

Fig. 4. Logarithm of the relative change in optical density at the maximum of the colored form of BSPs during thermal relaxation

15

Table 2. Spectral and kinetic characteristics of target BSPs (**1**) in acetonitrile at 293 K.

Structure	λ_{max}^{SP} , nm	$\varepsilon(\lambda_{max}^{SP})$, $M^{-1}cm^{-1}$	λ_{max}^{MC} , nm	τ^{MC} , s
(1a)	205 248 275 *sh* 281 *sh* 328 *sh* 340 *sh*	72200 44040 25800 21300 2800 2200	600 413 510 *sh*	97
(1b)	206 249 275 *sh* 339 *sh*	73400 44300 26500 2300	600 415	98
(1c)	206 249 277 292 339	78400 45300 26700 22600 2400	600 420	106
(1d)	206 249 276 289 341	65300 35800 21000 18400 2100	~605	148
(1e)	326 *sh* 341	3270 2310	600 415	99

16

	246 274 *sh* 290 *sh* 325 *sh* 340	37500 25930 22600 3460 2370	601 412	136.4

Analysis of the obtained data (**Table 2, Figs. 3-4**) showed that the introduction of donor substituents in the benzoxazine fragment of the molecule, as well as the replacement of the methyl substituent at the nitrogen atom of this fragment with a more bulky benzyl group, leads to a decrease in the rate constant of the reaction of thermal discoloration, and, accordingly, to an increase in the lifetime of photoinduced isomers. Comparing the obtained results with the photodynamic characteristics of the previously obtained compounds (**1e, f**), we can conclude that the introduction of such a donor substituent as a methoxy group leads to an increase of the lifetime τ of the once-opened isomers (**IO** and **BO**) in about 1.1 times. The introduction of a methyl group into the benzene ring of the benzoxazine fragment does not lead to any increase in the lifetime of merocyanines due to the weak $+I$ donor effect of this substituent. At the same time, the replacement of the methyl group by the benzyl substituent at the nitrogen atom of the oxazine ring allowed us to increase the lifetime of merocyanine isomers by 40%. This fact can be explained by steric hindrance that arises during the thermal recyclization reaction due to the presence of a bulky substituent in the immediate vicinity to the spiro-atom. The longest lifetime in the series of BSP under the study, equal to 148 s, was shown by compound (**1d**) equipped with a methoxy group at position 8 and a benzyl substituent at the oxazine nitrogen atom. BSP (**1a, b**) and (**1e**) differing only by presence or absence of an additional methyl group have the same values of τ within the experimental error.

4. Conclusions

17

In summary, four novel spiropyrans of 1,3-benzoxazine series and four novel unsymmetrical bis-spiropyrans with nonequivalent heteroarene fragments modified with methyl, methoxy and benzyl groups were synthesized *via* multi-step technique. The structure of the bis-spirocompounds was thoroughly studied and confirmed by NMR ^{1}H and ^{13}C, FT-IR and high-resolved mass-spectroscopy or elemental analysis. Photochemical studies revealed photochromic properties of target bis-spiropyrans at room temperature in their acetonitrile solutions. It was found out that the once opened merocyanine isomers of the compounds are more stable and can be better identified in such a polar solvent after irradiation with UV-light. Also, it can be concluded that the introduction of electron donating substituents in the benzoxazine moiety of the molecule, as well as the replacement of the methyl substituent at the nitrogen atom of this fragment with a more bulky benzyl group, leads to an increase in the lifetimes of the photoinduced isomers up to 146 s.

We envisage that the unsymmetrical bis-spiropyrans and their derivatives can be used in future as multistable chromogenic systems for different biomedical applications, while the data obtained will be useful for the development of new polyfunctional materials with predetermined properties. Our future research will be aimed at the study of the selective switching possibilities of bis-spiropyrans of this series.

References

[1]   L. Kortekaas, W. R. Browne, *Chem. Soc. Rev.*, **2019**, *48*, 3406–3424.

[2]   R. Guglielmetti in *Photochromism molecules and systems, revised edition* (Eds.: H. Dürr, H. Bouas-Laurent), Elsevier, Amsterdam, **2003**, pp. 314–466

[3]   R. C. Bertelson in *Organic photochromic and thermochromic compounds. Topics in applied chemistry*, *Vol. 1* (Eds.: J. C. Crano, R. J. Guglielmetti), Springer US, Kluwer Academic Publishers, **2002**, pp. 11-83.

[4]   M. Suda, R. Kato, H. M. Yamamoto, *Science*, **2015**, *347*, 743–746.

[5]   N. Darwish, A. C. Aragonès, T. Darwish, S. Ciampi, I. Díez-Pérez, *Nano Lett.*, **2014**, *14*, 7064–7070.

[6]   F. M. Raymo, S. Giordani, *Proc. Natl. Acad. Sci.*, **2002**, *99*, 4941–4944.

[7]   M. S. A. Abdel-Mottaleb, M. Saif, M. S. Attia, M. M. Abo-Aly, S. N. Mobarez, *Photochem. Photobiol. Sci.*, **2018**, *17*, 221–230.

[8]   A. V. Chernyshev, N. A. Voloshin, I. A. Rostovtseva, E. V. Solov'eva, E. B. Gaeva, A. V. Metelitsa, *Dye. Pigment.*, **2018**, *158*, 506–516.

[9]   M. Natali, S. Giordani, *Chem. Soc. Rev.*, **2012**, *41*, 4010–4029.

[10] Z. Tian, A. D. Q. Li, *Acc. Chem. Res.*, **2013**, *46*, 269–279.

[11] Y. Xiong, P. Rivera-Fuentes, E. Sezgin, A. Vargas Jentzsch, C. Eggeling and H. L. Anderson, *Org. Lett.*, **2016**, *18*, 3666–3669.

[12] H. Zhang, C. Wang, T. Jiang, H. Guo, G. Wang, X. Cai, L. Yang, Y. Zhang, H. Yu, H. Wang, K. Jiang, *Anal. Chem.*, **2015**, *87*, 5216–5222.

[13] S. Doddi, K. Narayanaswamy, B. Ramakrishna, S. P. Singh, P. R. Bangal, *J. Fluoresc.*, **2016**, *26*, 1939–1949.

[14] N. Aibani, P. F. da Costa, J. Masterson, N. Marino, F. M. Raymo, J. Callan, B. Callan, *J. Control. Release*, **2017**, *264*, 136–144.

[15] . Olejniczak, C. J. Carling, A. Almutairi, *J. Control. Release*, **2015**, *219*, 18–30.

[16] N. Fomina, J. Sankaranarayanan, A. Almutairi, *Adv. Drug Delivery Rev.*, **2012**, *64*, 1005-1020.

[17] F. Cardano, E. Del Canto, S. Giordani. *Dalton Trans.*, **2019**, *48*, 15537–15544.

[18] M. M. Lerch, M. J. Hansen, G. M. van Dam, W. Szymanski, B. L. Feringa, *Angew. Chemie - Int. Ed.*, **2016**, *55*, 10978–10999.

[19] W. Szymański, D. Yilmaz, A. Koçer, B. L. Feringa, *Acc. Chem. Res.*, **2013**, *46*, 2910–2923.

[20] R. Klajn, *Chem. Soc. Rev.*, **2014**, *43*, 148–184.

[21] V. I. Minkin in *Molecular Switches* (Eds: B. L. Feringa, W. R. Browne), Wiley-VCH, Weinheim, **2011**, p. 37.

[22] V. I. Minkin, *Russ. Chem. Rev.*, **2013**, *82*, 1–26.

[23] B. S. Lukyanov, M. B. Lukyanova, *Chem. Heterocycl. Compd.*, **2005**, *41*, 281–311.

[24] V. I. Minkin, *Chem. Rev.*, **2004**, *104*, 2751–2776.

[25] G. Berkovic, V. Krongauz, V. Weiss, *Chem. Rev.* **2000,** *100,* 1741–1753.

[26] V. A. Barachevsky, J. Photochem. Photobiol. A: Chem., **2018**, *354*, 61–69.

[27] A. Fihey, A. Perrier, W.R. Browne, D. Jacquemin, *Chem. Soc. Rev.*, **2015**, *44*, 3719–3759.

[28] J. Andreasson, U. Pischel, *Isr. J. Chem.,* **2013**, *53*, 236–246.

[29] G. Szalöki, G. Sevez, J. Berthet, J.-L. Pozzo, S. Delbaere, *J. Am. Chem. Soc.*, **2014**, *136*, 13510–13513.

[30] D. Jacquemin, E. A. Perpète, F. Maurel, A. Perrier, *J. Phys. Chem. Lett.*, **2010**, *1*, 2104–2108.

[31] S. R. Keum, Y. K. Choi, S. H. Kim, C. M. Yoon, *Dyes and Pigments*, **1999**, *41*, 41-47.

[32] A. A. Shimkin, V. Z. Shirinian, A. K. Mailyan, M. M. Krayushkin, *Russ. Chem. Bull.*, **2009**, *58*, 380–386.

[33] P. K. Kundu, A. Lerner, K. Kucanda, G. Leitus, R. Klajn, *J. Am. Chem. Soc.*, **2014**, *136*, 11276–11279.

[34] Y. Zhou, D. Zhang, Y. Zhang, Y. Tang, D. Zhu, *J. Org. Chem.*, **2005**, *7*, 6164–6170.

[35] S. Lee, S. Ji, Y. Kang, *Bull. Korean Chem. Soc.*, **2012**, *33*, 3740–3744.

[36] S. R. Keum, Y. K. Choi, M. I. Lee, S. H. Kim, *Dyes and Pigments*, **2001**, *50*, 171-176.

[37] Y. J. Cho, K. Y. Rho, S. H. Kim, S. R. Keum, C. M.Yoon, *Dyes and Pigments*, **1999**, *44*, 19-25.

[38] Y. Strokach, M. Alfimov, V. Barachevsky, V. Arsenov, A. Gorelik, *Mol. Cryst. Lic. Cryst.*, **1997**, *298*, 97-103.

[39] J. Filley, M. A. Ibrahim, M. R. Nimlos, A. S. Watt, D. M. Blake, *J. Photochem. Photobiol. A: Chem.*, **1998**, 117, 193-198.

[40] B. F. Zhang, M. Frigoli, F. Vetrone, J. A. Capobianco, *Chem. Comm.*, **2012**, *48*, 7244–7246.

[41] K. Sadakane, M. Takaichi, S. Maruta, *J. Biochem.*, **2018**, *164*, 239–246.

[42] Y. N. Malkin, V. A. Kuz'min, G. G. Dyadyusha, A. N. Boguslavskaya, F. A. Mikhailenko, *Russ. Chem. Bull.*, **1976**, *25*, 536–540.

[43] Y. N. Malkin, V. A. Kuz'min, F. A. Mikhailenko, *Russ. Chem. Bull.*, **1977**, *26*, 70–74.

[44] Sh. A. Samsoniya, M. V. Trapaidze, N. N. Nikoleishvili, K. G. Japaridze, J. P. Maisuradze, U. Kazmaier, *Chem. Heterocycl. Compd.*, **2010**, *46*, 1016–1019.

[45] Sh. A. Samsoniya, M. V. Trapaidze, N. N. Nikoleishvili, K. G. Japaridze, J. P. Maisuradze, U. Kazmaier, *Chem. Heterocycl. Compd.*, **2011**, *47*, 1098–1104.

[46] S. Samsoniya, M. Trapaidze, N. Nikoleishvili, K. Japaridze, J. Maisuradze, *Bull. Georg. Nat. Acad. Sci.*, **2013**, *7*, 51–56.

[47] I. R. Mardaleishvili, G. V. Lyubimova, A. V. Lyubimov, L. S. Kol'tsova, A. I. Shienok, P. P. Levin, A. S. Tatikolov, N. L. Zaichenko, *High Energy Chem.*, **2019**, *53*, 13–21.

[48] E. R. Zakhs, R. P. Polyakova, L. S. Efros, *Chem. Heterocycl. Compd.*, **1976**, *12*, 273–279.

[49] N. A. Voloshin, E. V. Solov'eva, S. O. Bezugliy, A. V. Metelitsa, V. I. Minkin, *Chem. Heterocycl. Compd.*, **2012**, *48*, 1361-1370.

[50] O. G. Nikolaeva, O. Y. Karlutova, A. S. Cheprasov, A. V. Metelitsa, I. V. Dorogan, A. D. Dubonosov, V. A. Bren', *Chem. Heterocycl. Compd.*, **2015**, *51*, 229–233.

[51] F. Nourmohammadian, A. A. Abdi, *Bull. Korean Chem. Soc.*, **2013**, *34*, 1727–1734.

[52] F. Nourmohammadian, A. A. Abdi, Spectrochim. Acta A, **2016**, 153, 53–62.

[53] E. L. Mukhanov, Y. S. Alekseenko, B. S. Luk'yanov, I. V. Dorogan, S. O. Bezuglyi, *High Energy Chem.*, **2010**, *3*, 220–223.

[54] E. L. Mukhanov, Yu. S. Alekseenko, I. V. Dorogan, V. V. Tkachev, B. S. Lukyanov, *Chem. Heterocycl. Compd.*, **2010**, *46*, 279–290.

[55] E. L. Mukhanov, I. V. Dorogan, A. V. Chernyshev, S.O. Bezuglyi, I. V. Ozhogin, M. B. Lukyanova, B. S. Lukyanov, *Int. J. Photoenergy*, **2013**, *2013*, doi:10.1155/2013/752949.

[56] I. V. Ozhogin, V. V. Tkachev, B. S. Luk'yanov, E. L. Mukhanov, A. V. Chernyshev, O. A. Komissarova, V. I. Minkin, S. M. Aldoshin, *Dokl. Chem.*, **2016**, *471*, 378–383.

[57] N. E. Gel´man, E.A. Terent´eva, T.M. Shanina, L.M. Kiparenko, Metody kolichestvennogo organicheskogo elementnogo analiza [Methods of Quantitative Organic Elemental Analysis], Khimiya, Moscow, **1987**, 296 pp. (in Russian).

[58] B. S. Luk'yanov, Y. I. Ryabukhin, G. N. Dorofeenko, L. E. Nivorozhkin, V. I. Minkin, *Chem. Heterocycl. Compd.,* **1978**, *14*, 122–127.

[59] Yu. S. Alekseenko, E. L. Mukhanov, O. N. Ryashin, M. B. Lukyanova, B. S. Lukyanov, Scientific Thought of the Caucasus, **2004**, Appendix No. 11, p. 135-140 (in Russian).

- New unsymmetrical bis-spiropyrans with indoline and 1,3-benzoxazine photochromic units were synthesized

- Once-opened merocyanine isomers were found to be more stable than the double-opened ones

- Introduction of bulky substituent close to benzoxazine spiro-atom increases merocyanine lifetime

Declaration of interests

✓ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: