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Properties of photochromic retinals

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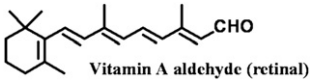
ABSTRACT

In the present review, we summarize our recent studies on the synthesis and spectral–kinetic parameters of photochromic retinals based on spiropyrans, diarylethenes, and a fulgimide and the use of these compounds for the preparation of artificial analogs of natural bacteriorhodopsin.

1. Introduction

Retinoids are referred to as three groups of fat-soluble vitamin A derivatives that differ in the nature of the terminal group.



Vitamin A aldehyde (retinal)

Their molecules consist of the trimethylcyclohexene ring conjugated via four double bonds with the polar terminal group. Retinoids and their complexes with proteins play a key role in light energy transformation processes. They perform their function in the form of complexes with protein receptors: covalent complexes (retinal proteins) and noncovalent complexes (nuclear retinoic acid receptors, RAR and RXR). Retinal proteins contain a number of defined retinal isomers as part of their chromophoric groups bound via the protonated aldimine bond with the ε-amino group of the Lys residue. The selective isomerization of a particular double bond in the polyene chain in retinal proteins determines the type of their physiological response.

Retinal proteins are responsible for important biological functions, such as the light-driven proton transport (bacteriorhodopsin from *Halobacterium salinarum*), vision (rhodopsins) and phototaxis (sensoric and phoborhodopsins). Bacteriorhodopsin (BR) is the focus of our investigation. This compound is a unique natural photochrome acting as a light-driven proton pump. It is located in special areas of the cells, purple membranes, consisting of BR trimers embedded in the lipid bilayer [1–6]. The chromophoric group of this protein is the protonated aldimine of *all-E-* and *13Z-*isomers of vitamin A aldehyde (retinal). Bacteriorhodopsin undergoes cyclic photochemical reactions accompanied by the isomerization of the chromophore polyene chain and the deprotonation and reprotonation of the retinal aldimine moiety (Fig. 1). The B-state ($\lambda_{max} = 570$ nm, $\varepsilon = 63{,}000\ M^{-1}\ cm^{-1}$) and the M-state ($\lambda_{max} = 412$ nm, $\varepsilon = 34{,}000\ M^{-1}\ cm^{-1}$, $\phi = 0.64$) are the key states. This chromoprotein is one of the first successful examples of biological photochromic material designed by the nature.

One promising area of research on the retinal protein structure–function relationship involves the replacement of the natural chromophore by analogs and the comprehensive study of the hybrid products. The photochemical properties of BR analogs can be controlled using the following approaches: 1) the substitution of one or more amino acid residues in certain positions of the BR molecule by genetic engineering methods (using BR mutant strains

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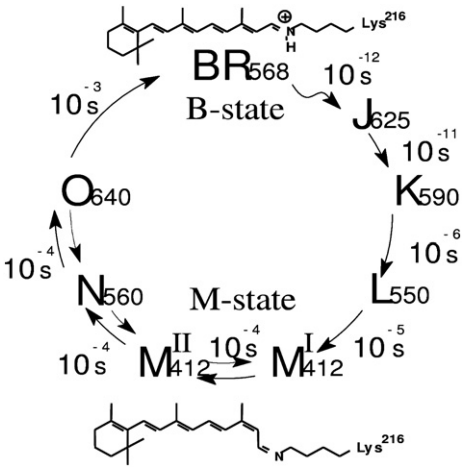


Fig. 1. Photocycle of BR.

with slower photocycles); 2) the use of natural BR incorporated into a polymer matrix, oriented Langmuir–Blodgett films, or oriented layers immobilized on a solid support; 3) the use of environmental conditions (low temperature, electric fields, humidity, pH level); 4) a combination of the above-mentioned approaches. General directions of the BR chromophore structure modification are depicted in Fig. 2. The comparative analysis of our and others researchers data has shown, that by diversification of the chromophore structure, it is possible directly to change λ_{max} in the spectra of the BR analogs in the rather wide interval (from 412 to 830 nm), though not all of these pigments are capable for cyclic photochemical reactions [3–16].

We have previously developed a common procedure for structure–function studies of retinal proteins [10–17]. The preparation of BR analogs and the testing scheme are shown in the Fig. 3. Several approaches to the preparation of BR analogs have been developed earlier based on the addition of polyenals to: 1) growing cells of retinal-deficient *H. salinarum* strains (for example, JW5); 2) to "white" membranes or membrane vesicles obtained from the retinal-deficient strains; 3) to so-called apomembranes containing bacterioopsin (BO) generated from purple membranes by hydroxylaminolysis at pH 7.0 and 0–5 °C under intense illumination. We used the third approach in our investigations with an additional procedure for the removal of retinal oxime based on the treatment of BO with a saturated solution of β-cyclodextrin (see Fig. 3). Then a comprehensive study of the artificial pigments: the kinetic peculiarities of the formation of BR analogs, the spectral properties (λ_{max}, the presence and type of the photochemical cycle, quantum

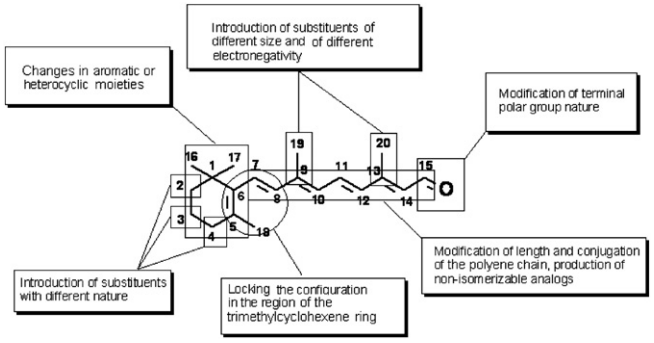


Fig. 2. General directions of the BR chromophore structure modification.

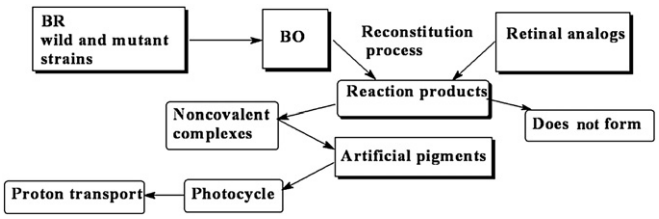


Fig. 3. Scheme of BR analog preparation and photochemistry testing procedure.

yield, the adaptation to the light and darkness) and the efficiency of the proton transport were undertaken.

In this paper we present our results on the synthesis and spectral and photochromic properties of new hybrid retinoid molecules. Two approaches to their modification were used: the replacement of the natural retinal trimethylcyclohexene ring by the photochromic moiety and the replacement of the terminal formyl group by a photochromic *N*-aminofulgimine (**FGM II**). To modify the trimethylcyclohexene ring, we used two classes of photochromic compounds: thermally fast relaxing spiropyrans with (**SPRN I–V**) and without a nitro substituent (**SPR I–V**) in the pyran ring and thermally irreversible diarylethenes (**DTE I–V**).

2. Results

2.1. Objects

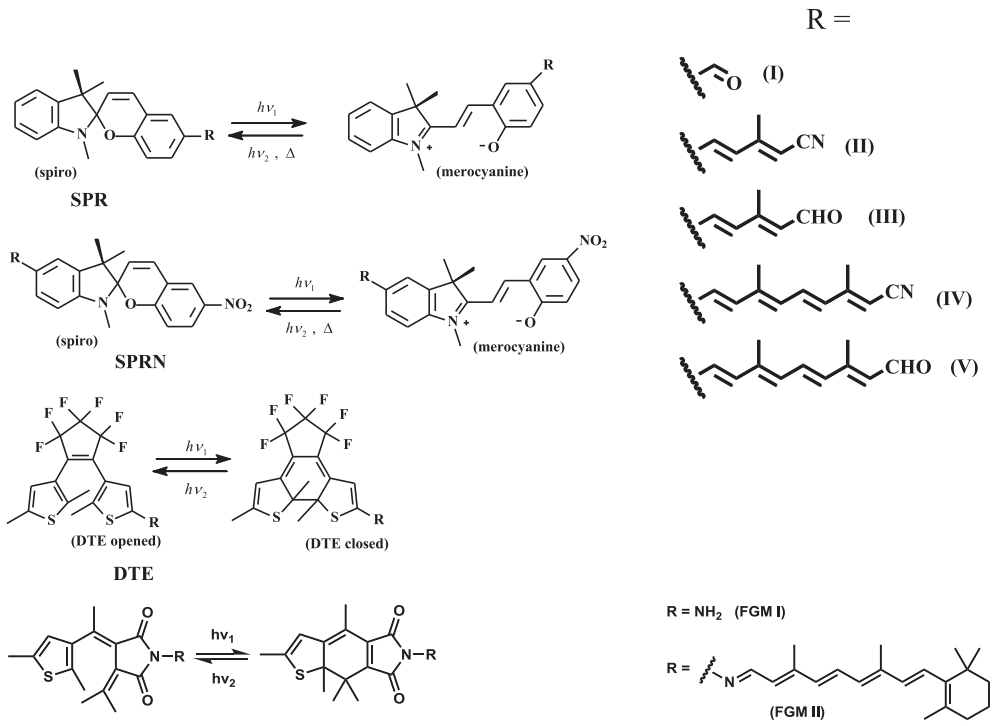
Three series of compounds based on hybrids of retinoids and spiropyran and dithienylethene photochromes as new model photosensitive systems were produced. The final design of target retinal analogs was made based on the topographic analysis and computer simulation of the chromophore cavity of BR (PDB 1C3W) using the HyperChem v. 8.03, the analysis of ligand–protein contacts (LPC), and the comparison of selected polyenal structures shape and size of (**SPR V**, **SPRN V, DTE V**) with that of the chromophore cavity [17,18].

Two new series of photochromic compounds belonging to spiropyrans (**SPR I–V** and **SPRN I–V**) that differ by the introduction site of the polyene moiety into the photochromic moiety were synthesized. The method for the synthesis of the corresponding derivatives containing the polyene chain of different length either at 6′-position of the pyran ring (**SPR I–V**) or at the C_5 atom of the indoline moiety (**SPRN I–V**) was developed and enabled the synthesis of these compounds [22–24,29–36]. In addition, the procedure for the preparation of another series of photochromic retinoids based on dithienylethenes derivatives (**DTE I–V**) has been developed [25–36] (Scheme 1).

2.2. Synthesis

The main strategies and methods for the design of different retinal analogs and their synthesis have been described in detail in our reviews [3–5] and in more recent publications [19–21].

In present work a universal synthesis procedure for the construction of the retinoid molecule and its analogs (Scheme 2) was employed, which has been successfully used in the synthesis of another retinal analogs [19–36]. This procedure involves the Horner–Emmons olefination of the carbonyl precursor **(I)** with anion of the C_5-phosphonate reagent, the reduction of intermediate nitrile **(II)** with DIBAH to aldehyde **(III)**, the subsequent olefination of aldehyde **(III)** with anion of C_5-phosphonate, and the reduction of the resulting nitrile **(IV)** to target aldehyde **(V)**. C_5-Phosphonate was used as a 60:40 mixture of *E* and *Z* isomers (^{1}H NMR data).



Scheme 1.

Hydrazone of all-*E*-retinal (**FGM II**) and photochromic *N*-aminofulgimine (**FGM I**) were synthesized according to Scheme 3.

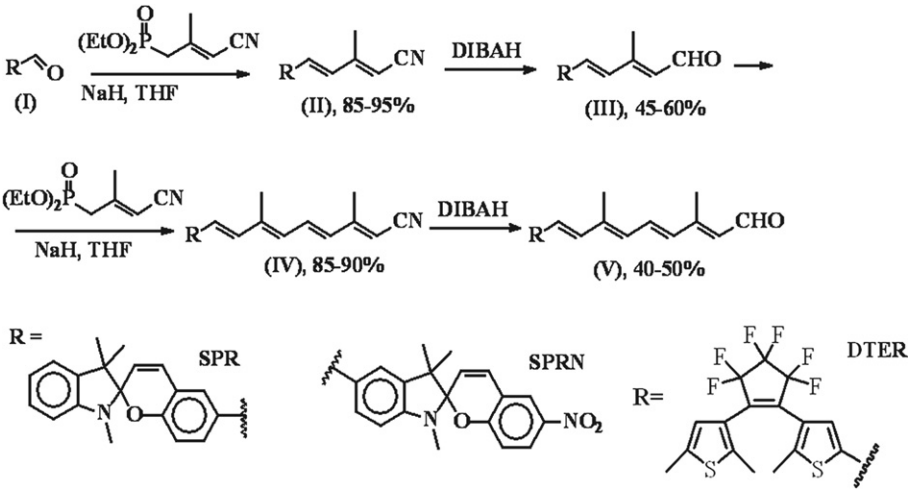
The reaction of the starting fulgide with *N*-Boc hydrazine under reflux in benzene afforded a mixture of isomeric *E*- and *Z*-hydrazide acids. The cyclization of these acids in the presence of *N*,*N*′-carbonyldiimidazole under mild conditions gave *N*-Boc-aminofulgimide. The further elimination of the Boc protecting group in the presence of an ethanolic solution of HCl gave *N*-aminofulgimide **(FGM I)** and then the final product **(FGM II)**.

Investigation of the photochromic behavior and spectral–kinetic properties of these retinoid hybrids was the main direction of the next stage of the study.

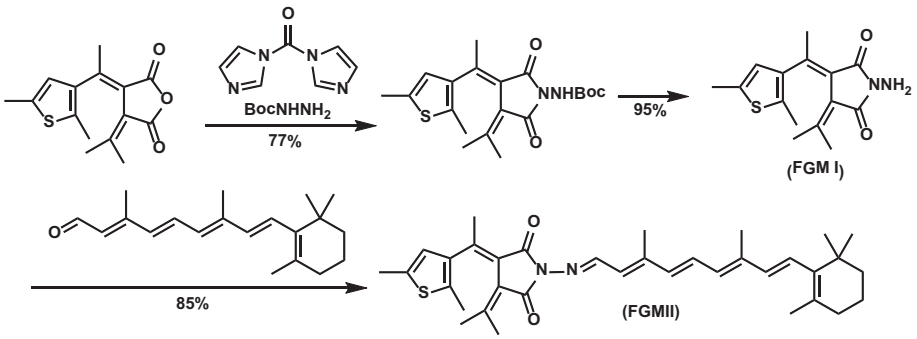
2.3. Spectral–kinetic study

The photochromic reactions in the spiropyran and dithienylethene series are shown in Scheme 1.

Thermally relaxing spiropyrans undergo not only reversible photoniduced transformations between the cyclic colorless form A and the open colored form B but also the spontaneous bleaching of the B form to give the initial form A. The photochromism of these compounds is due to the reversible C–O bond photodissociation followed by the *cis–trans* isomerization. As this takes place, only nitro-substituted spiro compounds exhibit photochromic properties at ambient temperatures. Unlike spyropyrans, diarylethenes and fulgimides undergo the reversible valence isomerization between the colorless open form A and the colored cyclic form B



Scheme 2.



Scheme 3.

only under UV and visible light. Hence, these compounds are thermally irreversible because these compounds are most promising candidates for the development of different technical device prototypes, such as a high-density 3D-optical memory.

The results of the spectral–kinetic study of the synthesized compounds **(SPR I–V** and **SPRN I–V)** and their photochromic transformations in nonpolar (toluene) and polar (ethanol) solvents are presented in Table 1 and in Figs. 4–7. The analysis of the absorption spectra of the cyclic form of spiropyrans without (Fig. 4) and with the 6′-nitro substituent in the pyran moiety (Fig. 5) shows that the elongation of the polyene chain leads to the bathochromic shift of the absorption maxima. This is attributed to the involvement of unsaturated retinal moieties in the conjugation with the π systems of the pyran ring. It can be seen that the observed spectral shift is determined by the number of conjugated double bonds and the nature of the terminal polar group.

The experiments showed that the spiropyran series (**SPR I–V**) containing the polyene chain at position 6′ of the pyran ring demonstrated a very fast dark thermorelaxation process with elongation of polyene chain and their photochromism can be observed only by time-resolved spectroscopy in the microsecond range. At this time, series (**SPRN I–V**) having a strong electron-acceptor substituent – the nitro group at the 6′-position in the pyran cycle is characterized by large lifetime of the photoinduced merocyanine forms. In this case registration of electronic spectra, kinetic data for photocoloration and spontaneous decoloration processes were performed using the fiber–optic spectrophotometric set – model HR-2000+ (Ocean Optics, USA) and irradiation of the Hamamatsu Lightincure - LC8 lamp (Hamamatsu, Japan). As result of the spectral–kinetic study of phototransformations of new polyenic 6′-nitro-substituted indolinespiropyrans (**SPRN II–V**), a number of their differences in spectral properties and photochromism as compared with the initial 5-formyl-spiropyran derivative (**SPRN I**) has been revealed. The possibility of regulation of the spiropyran form spectral characteristics by modification of polyenic substituents nature and length has been shown.

It was found that spectral characteristics of the spiropyran form may be regulated by changing the length of the polyene chain. Nitro-substututed spiropyrans exhibit the sharp spectral difference for photoinduced merocyanine form B in nonpolar toluene and polar ethanol (Fig. 6 and 7, Table 1). It is seen that absorption spectra of the photoinduced form are characterized by two maxima in toluene and one maximum in ethanol solution. The short-wavelength shoulder of the photoinduced absorption band in toluene practically coincides with the maximum of the same

Table 1
Spectral–kinetic characteristics photochromic retinals based on nitro-substituted spiropyrans **(SPRN I–V)**.

Compound	Solvent	λ_{max}^{A}, nm	λ_{max}^{B}, nm	ΔD_B^{phot}	k_{BA}, s^{-1}	$t_{1/2}^{pd}$, s
SPRN I	Ethanol	328	567	0.77	0.069	44
	Toluene	320	590 sh, 625	1.19	0.139	31
SPRN II	Ethanol	365	567	0.27	0.006	**
	Toluene	365	590 sh, 630	0.55	0.035	38
SPRN III	Ethanol	385	563	0.30	0.004	**
	Toluene	377	590 sh, 630	0.45	0.039	35
SPRN IV	Ethanol	405	567	0.10	0.002	**
	Toluene	407	590 sh, 630	0.16	0.033	70
SPRN V	Ethanol	330, 433	563	0.10	0.002	**
	Toluene	425	590 sh, 630	0.08	0.031	90

Note: λ_{max}^{A} and λ_{max}^{B} – maxima of absorption bands of the initial spiropyran cyclic A and photoinduced merocyanine open B forms, consequently; ΔD_B^{phot} – a photoinduced change of optical density at the maximum of the photoinduced form in the photoequilibrium state; k_{BA} – a constant of dark bleaching the B form; $t_{1/2}^{pd}$ – a time of irreversible decreasing a value of photoinduced optical density at the absorption band maximum in two times under non-filter irradiation; ** not observed during more 10 min.

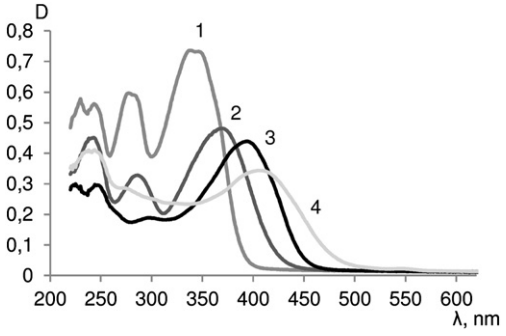


Fig. 4. Absorption spectra of photochromic retinals (**SPR II–V**) in methanol: 1- **SPR II**, 2- **SPR III**, 3- **SPR IV**, 4- **SPR V**.

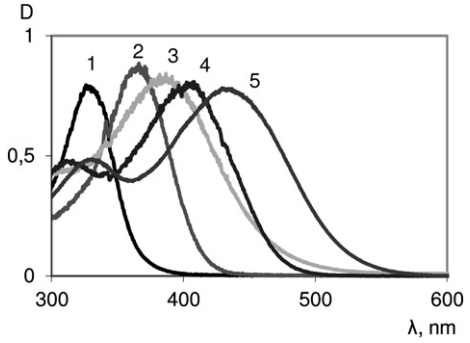


Fig. 5. Absorption spectra of the initial cyclic form for photochromic retinals (**SPRN I–V**) in ethanol: 1- **SPRN I**, 2- **SPRN II**, 3- **SPRN III**, 4- **SPRN IV**, 5- **SPRN V**.

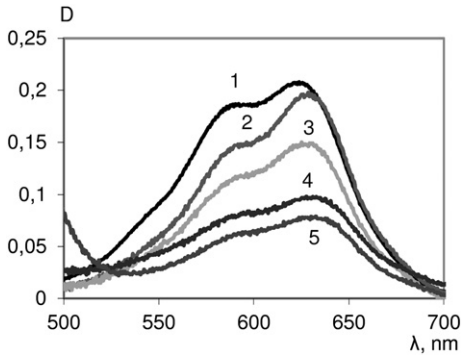


Fig. 6. Absorption spectra of photoinduced merocyanine form for photochromic retinals (**SPRN I**–**V**) in toluene: 1- **SPRN I**, 2- **SPRN II**, 3- **SPRN III**, 4- **SPRN IV**, 5- **SPRN V**.

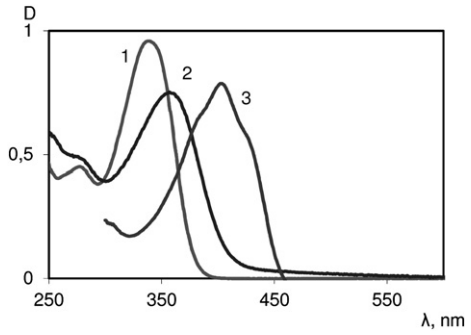


Fig. 8. Absorption spectra of photochromic retinals **DTER II**,**III**,**V** in ethanol: 1- **DTER II**, 2- **DTER III**, 3- **DTER V**.

absorption band in ethanol. We assume that the short-wavelength band is due to appearance of monomeric form, but the long-wavelength band is due to the J-aggregated merocyanine form [37].

In contrast to the spectral characteristics of the closed form, the location of maxima for absorption bands of monomeric as well as aggregated photoinduced forms of photochromic retinoids weakly depends on the nature and the length of polyenic substituents (Table 1). This can be explained by a lack of conjugation between the polyene chain and the merocyanine form of the spiropyran.

The analysis data presented in Table 1 shows that the efficiency of photoinduced coloration which is estimated by the value of photoinduced change of optical density (ΔD_B^{phot}) decreases with increasing length of the polyene substituent in ethanol and toluene. The same dependence was observed for the value of the constants of dark bleaching of the photoinduced colored form. These experimental data may be due to isomerization of retinal chains. The photoresistance of photochromic nitro-substituted spiropyrans drastically increases in ethanol compared to toluene. This fact can be explained by stabilization of the photoinduced merocyanine forms by hydrogen bonds between molecules of the merocyanine form and the solvent.

Photochromic retinals based on thermally irreversible diarylethenes exhibit long-wavelength spectral shifts in their spectrafor the initial open form with increasing a length of the retinal chain, similar to the cyclic form of spiropyrans (Figs. 8 and 9, Table 2).

Typical absorption spectra of the photoinduced cyclic form for photochromic retinals based on diarylethenes are presented on Fig. 9.

The analysis of spectral–kinetic data for photochromic retinals based on diarylethenes shows that all synthesized retinals exhibit photochromic properties and their photochromic transformations are thermally irreversible. It is established that, as in the case of spiropyrans, the introduction of the polyene chain conjugated with the thiophene moiety into diarylethene molecules leads to the bathochromic spectral shift of the absorption maximum of the open form compared to the starting aldehyde **DTER I**.The longer the retinal chain the larger the shift. As in spyropyrans, the absorption maximum for the photoinduced cyclic form is virtually independent of the presence of the retinal chain. A decrease in the light-sensitivity is less evident than for spiropyrans. A comparison of the relationship of the constants of photocoloration and photobleaching processes shows that, as opposite to diarylethene **DTER I**, all compounds containing the polyene moiety are characterized by the more effective photocoloration rate but it decreases with increasing chain length. The analysis of data on photodegradation (Table 2) shows that the compound **DTER II** containing the electron-withdrawing CN-group exhibits the best tolerance for irreversible phototransformations. Unlike spiropyrans, an increase in the length of the polyene chain leads to an increase in the photodegradation efficiency.

Retinal hydrazone **FGM II** significantly differs from the aforementioned photochromic retinals containing spiropyran and diarylethene moieties due to substitution of the terminal formyl group to photochromic fulgimide fragment. It was found that this compound manifests photochromic properties similar to the precursor **FGM I** (Table 3). As compared to the precursor, the compound **FGM II** is characterized by bathochromic spectral shifts for the initial open and photoinduced forms. It is due to elongation of the π-system of the fulgimide. Unfortunately, the efficiency of the photocoloration process of **FGM II** decreases and photodegradation grows as compared to the precursor.

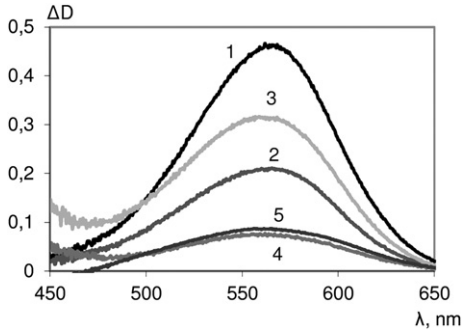


Fig. 7. Absorption spectra of photoinduced merocyanine form for photochromic retinals (**SPRN I**–**V**) in ethanol: 1- **SPRN I**, 2- **SPRN II**, 3- **SPRN III**, 4- **SPRN IV**, 5- **SPRN V**.

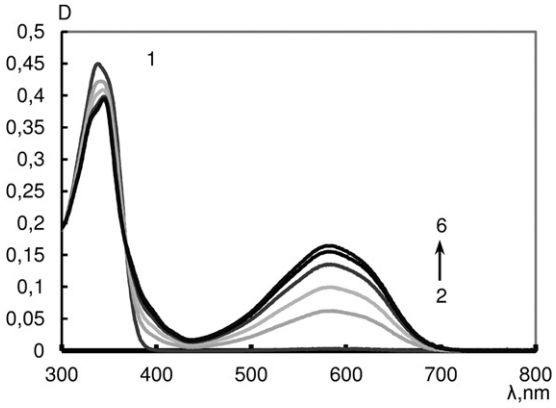


Fig. 9. Absorption spectra of the compound **DTER III** in toluene before (1) and after successive UV irradiation (2–7).

Table 2
Spectral–kinetic characteristics photochromic retinals based on diarylethenes (**DTER I**–**V**).

Compound	λ_{max}^{A}, nm		λ_{max}^{B}, nm		ΔD_B^{phot} in toluene	k_{AB}/k_{BA} in toluene	$t_{1/2}^{pd}$, s in toluene
	Toluene	Ethanol	Toluene	Ethanol			
DTER I	295	–	580	–	0.4	1.4	340
DTER II	340	276, 338	585	576	0.2	7.8	660
DTER III	353	355	585	580	0.2	5.9	275
DTER V	390, 400	390, 402	553	579	0.5	2.6	240

k_{AB}/k_{BA} – a ratio of constants of photocoloration and photobleaching, consequently, at the relative conditions.

Table 3
Spectral–kinetic characteristics photochromic fulgimides **(FGM I,II)** in toluene.

Compound	λ_{max}^{A}, nm	λ_{max}^{B}, nm	ΔD_B^{phot}	k_{AB}/k_{BA}	$t_{1/2}^{pd}$, s
FGM I	325	520	0.9	1.00	70
FGM II	395	535	0.6	0.13	60

2.4. Properties of artificial BR analogs

The synthesized retinal analogs (**SPR V**, **SPRN V, DTE V**) and their short-chain derivatives (**SPR III**, **SPRN III, DTE III**) were tested further in recombination with bacterioopsin (BO), from apomembranes *H. salinarum* (strain ET1001). Apomembranes were obtained from purple membranes by hydroxylaminolysis at pH 7.0 and 0–5 °C under an intensive illumination. The resynthesis of pigments is conducted by addition of methanol solution of the analog to a suspension of apomembranes in a buffer (protein concentration – 2 mg/ml, 21 °C, pH 6.0, 5 mM MES). It was found that the formation of pigments takes place during 1–2 h and is finished after 1–7 days. Spectral parameters of these pigments **ABR** are presented in the Table 4 and in Fig. 10. Fig. 10 shows the spectral pattern for the **ABR** formation process from polyenal **DTER V** and apomembranes. It should be noted that a position of λ_{max} for the **ABR** located within the wavelength range which is typical for the pigments, in which trimethylcyclohexene ring of the retinal is replaced by the various aromatic rings (460–530 nm) [3,5–8]

From Table 4 it is seen that all compounds with long polyene and short polyene chains and formyl terminal groups form pigments. The change of formyl function in the retinoid molecule to a nitrile group completely blocks the **ABR** reconstitution process. It was shown that ABR based on spiropyran derivative **SPRN III** has the unexpectedly large bathochromic shift (165 nm).

Table 4
Spectral characteristics of photochromic retinals interaction products with bacterioopsin in apomembranes from *H. salinarum*.

Compound	λ_{max}, nm		
	In MeOH	Noncovalent complex	Pigment
DTER II	338	–	–
DTER III	355	–	430
DTER IV	381	–	–
DTER V	402	–	510
SPR II	340	–	–
SPR III	365	–	440
SPR IV	390	400	–
SPR V	411	455	495
SPRN II	367	–	–
SPRN III	385	–	605
SPRN IV	405	–	–
SPRN V	400	–	500

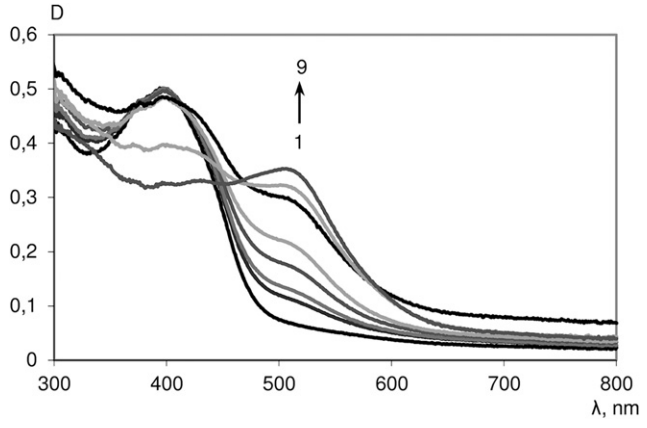


Fig. 10. Spectral changes during the **ABR** formation process from polyenal **DTER V** and apomembranes prepared from *Halobacterium salinarum* strain ET1001 (C_{BO} = 2 mg/ml, 21 °C, pH 6.0, 5 mM MES): 1- 1 min, 2- 3 min, 3- 5 min, 4- 12 min, 5- 25 min, 6- 1 h, 7- 24 h, 8-48 h, 9- 8 days.

3. Conclusion

New retinoid analogs based on a photochromic spiropyran, a diarylethene and a fulgimide were synthesized. Their spectral–kinetic characteristics and peculiarities of photochromic behavior were studied. The structure–property relationship was revealed. The possibility of controlling the spiropyran and diarylethene spectral characteristics by varying the nature and the length of polyene substituents was demonstrated. It was found that certain retinal analogs were able to form artificial pigments (**ABR**) with BO in apomembranes from *H. salinarum*. Thus, in principle the possibility for the preparation of hybrid **ABR** containing photochromic moieties in chromophoric groups is demonstrated. These hybrids exhibit the ability to undergo reversible photochemical transformations which can be used for the photocontrolled design of biostructures.

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