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Asymmetric *meso*-CF_3-BODIPY dyes based on cycloalkanopyrroles

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Aromatization

ABSTRACT

New *meso*-CF_3-substituted BODIPY derivatives have been synthesized using the methodology that includes as a key step the condensation of pyrroles with trifluoro(2,3-cycloalkanopyrrol-2-yl)ethanols. The further reaction of dipyrromethanes thus obtained with DDQ followed by complexation with BF_3 leads to either benzo[*b*]-fused (in the case of dipyrromethanes obtained from trifluoro(4,5,6,7-tetrahydroindol-2-yl)ethanol) or cycloheptano[*b*]-fused saturated or partially saturated BODIPY dyes. The latter exhibit strong red fluorescence (λ_{em} = 588–634 nm, Φ_f = 0.54–0.68), while benzo[*b*]-fused do not fluoresce at all in either polar or non-polar solvents. The performed quantum-chemical calculations (TD-CAM-B3LYP/SVP) explain the spectroscopic results.

1. Introduction

The discovery of fluorescent 4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacenes, better known as BODIPY dyes, has established a new class of fluorophores with a variety of highly important and useful representatives possessing tunable properties [1]. The most frequent and important applications of these dyes in medicine and related areas comprise photosensitizers for photodynamic therapy [2,3], highly sensitive detectors of specific targets in biological media [4–7], probes, sensors and labelling agents for biochemical research [8–10]. Fluorescent BODIPY dyes are also widely used in OLEDs and laser dyes [11], nonlinear optics [12,13], fluorescent markers and sensors for contamination [14], organic photovoltaics [15], solar batteries [16,17] and so on [1].

Especially promising for practical applications are BODIPY derivatives that exhibit absorption and emission in the deep-red and near infrared (NIR) spectral regions (>650 nm). The search for these fluorophores is progressively growing [18]. This research activity is inspired by the fact that such BODIPYs fit well *in vivo* bioimaging because they lesser photo-damage the biological objects, deeper penetrate in organic tissues, and demonstrate minimum interference from background auto-fluorescence in the living systems [19]. Among the important ways to access NIR BODIPYs are the extension of π-conjugation by introduction of aromatic or heteroaromatic substituents to the boradiazaindacene core or the desymmetrization of their molecules to impart them inner donor-acceptor properties [18,20]. The introduction of strong acceptor - perfluoroalkyl or perfluoroaryl groups at the *meso*-position of the BODIPY molecule also causes a significant red-shift of the absorption and fluorescence spectra [21–24]. Another effective method for the construction of boron dipyrromethene dyes of the above types, i.e. absorbing and emitting in IR or NIR region, is a fusion of saturated or unsaturated cycles with the α,β-positions of the BODIPY core [18,20].

Unlike BODIPY with an extended π-system [25–29], BODIPY dyes with annulated cyclic aliphatic substituents are less studied. There is information [30] that symmetrical *meso*-methyl BODIPYs with fused cycloalkyl substituents exhibit strong fluorescence, high extinction coefficient and show good laser activity. The symmetric fused bis(cyclohexyl)-BODIPYs possess intense chromophore properties comparable to those of alkyl-substituted ones [20,31,32] The quantum chemical calculations also show bathochromic shift for these dyes [20,33]. A representative of the fused cycloalkyl BODIPY was used as fluorescent part of a probe with no dye-induced distortions in lipid membrane research [34]. A lipophilic dye (LD540) derived from cycloalkyl BODIPY is a multicolor probe for microscopic imaging of lipid droplets in living cells [35–37]. The same compound due to its enhanced lipophilicity was successively tested to stain lipids and related biological material within sebaceous fingermarks [38]. The polymer compositions of fused cycloalkyl BODIPYs are incorporated in securing elements to protect the identity documents [39].

Commonly, symmetrically and asymmetrically fused cycloalkyl

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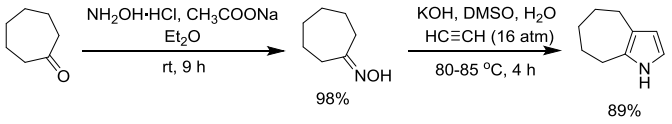


Scheme 1. Synthesis of cycloheptano[*b*]pyrrole by Trofimov reaction.

BODIPYs are synthesized by the treatment of substituted pyrroles with chloroanhydrides [40] or by the $POCl_3$-promoted condensation of 2-acylpyrroles/pyrrole-2-carbaldehydes with other pyrrole molecule having free α-position [20,41,42]. To our knowledge, only one protocol provides BODIPYs with fused substituents and *meso*-CF_3 group, but it is limited to symmetric ones [23]. Evidently, a further progress in this field requires more structural diversity and functional complexity in the BODIPY series. In this context, asymmetric representatives of the *meso*-CF_3-BODIPY, fused with cycloalkyl substituents, could cardinally contribute to potential of these compounds as high effective fluorophores exhibiting absorption and emission in red and near infrared (NIR) spectral regions.

Recently [22], we have reported a new approach to the design of symmetric and asymmetric *meso*-trifluoromethyl-substituted BODIPYs including as a key step condensation of trifluoropyrrolylethanols with pyrroles followed by the conventional procedure, i.e. oxidation with DDQ and complexation with $BF_3{\cdot}Et_2O$.

This approach may open a convenient path to the synthesis of asymmetric *meso*-CF_3 2,3-cycloalkano-fused BODIPY dyes.

In this work, we describe a further unfolding of advantageous features of the above multi-purpose methodology as applied to the synthesis of asymmetric cycloalkano[*b*]-fused *meso*-CF_3 BODIPYs **1** and their major fluorescent characteristics.

2. Results and discussion

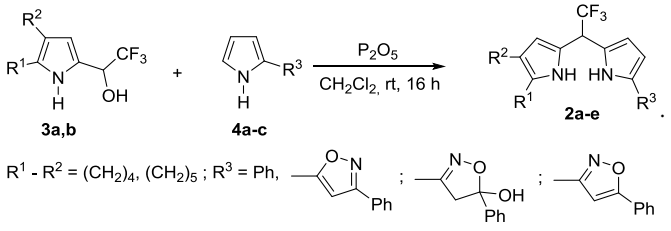
Cyclohexano- and cycloheptano[*b*]-fused BODIPYs were synthesized on the basis of cycloalkanones, i.e. cyclohexanone and cycloheptanone using the modified one-pot Trofimov assembly from oximes and acetylene gas in the system KOH-DMSO (Scheme 1) [43]. The trifluoroacetylation of pyrroles and reduction of trifluoroacetyl derivatives thus prepared were performed accordingly to the improved protocol [22].

The key intermediates of BODIPYs **1** synthesis, *meso*-CF_3-dipyrromethanes **2a-e**, were obtained by the upgraded condensation of trifluoro(pyrrol-2-yl)ethanols **3a,b** with pyrroles **4a-c** in the presence of P_2O_5 (Table 1) [22]. Notably, pyrrolyldihydroisoxazolol **4a** upon condensation with trifluoroethanols **3a,b** undergoes dehydration to afford dipyrromethanes **2a** and **2e** with phenylisoxazolyl substituent (Table 1).

First, we attempted to oxidize dipyrromethane **2a** by equimolar amount of DDQ (CH_2Cl_2, rt, 1 h) followed by chelation with $BF_3{\cdot}Et_2O$ as it was done earlier [22]. Regretfully, in this case, even no traces of the expected BODIPYs were detected in the crude, only mixture of difficult-to-identify compounds being formed.

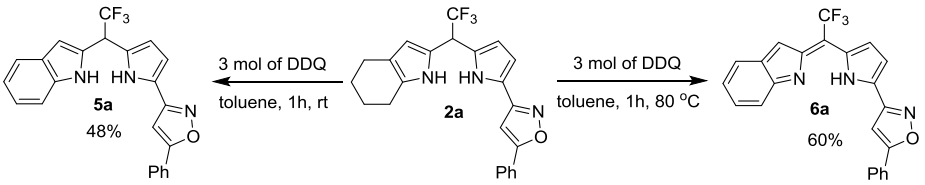
When replacing the solvent (CH_2Cl_2) for toluene (other conditions being the same), in ^1H NMR spectra characteristic indole signals were identified. Surprisingly, the entire aromatization of tetrahydroindole part of the molecule **2a** happened, if threefold molar excess of DDQ (rt, 1 h) was employed: benzo[*b*]-fused dipyrromethane **5a** was obtained in 48% yield, though the expected dipyrromethene was not discernible among the reaction products (Scheme 2). Such ease of dehydrogenation of the cyclohexane ring condensed with the pyrrole moiety draws attention. Usually, the reactions of this type require high temperature and special, often noble metal catalysts [44–46]. For instance, full

Table 1
Synthesis of dipyrromethanes **2a-e** from trifluoro(pyrrolyl)ethanols **3a,b** and pyrroles **4a-c**.

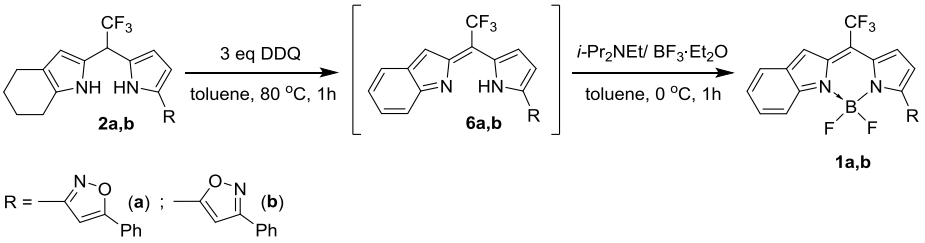


Entry	Trifluoro(pyrrolyl)ethanol	Pyrrole	Dipyrromethane	Yield, %
1	**3a**	**4a**	**2a**	94
2	**3a**	**4b**	**2b**	92
3	**3b**	**4c**	**2c**	94
4	**3b**	**4b**	**2d**	95
5	**3b**	**4a**	**2e**	97

Reaction conditions: trifluoropyrrolylethanols **3a-c** (1 mmol), pyrroles **4a-c** (1 mmol), P_2O_5 (1 mmol), CH_2Cl_2, rt, 16 h.



Scheme 2. Aromatization of dipyrromethane **2a** with DDQ.



Scheme 3. Formation of BODIPY dyes **1a,b**.

aromatization of 4,5,6,7-tetrahydroindole is realized in the presence of Ni_2S/Al_2O_3 catalyst [45,47,48]. Eventually, when the reaction of **2a** with DDQ was carried out at a higher temperature (80 °C), the desired benzo[*b*]-dipyrromethene **6a** was isolated in 60% yield (Scheme 2). This compound turned out to be highly reactive, decomposing in a freezer after a few days.

Consequently, benzo[*b*]-fused BODIPYs **1a,b** were assembled from dipyrromethanes **2a,b** by one-pot manner (without isolation of unstable dipyrromethenes **6**), employing 3 mol excess of DDQ (toluene, 80 °C, 1 h) and $BF_3{\cdot}Et_2O$ (*i*-Pr_2NEt, toluene, 0 °C, 1 h). However, the isolated yields of the target products (Scheme 3, Table 2) were 7–8%, obviously due to the above-mentioned instability of the intermediate dipyrromethene **6**.

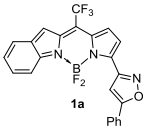
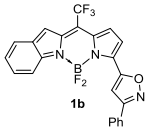
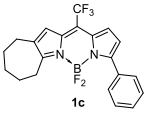
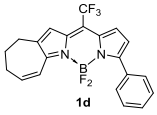
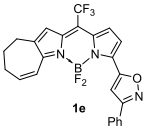
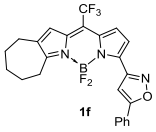
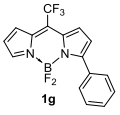
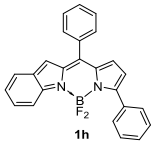
Thus, as shown above, the aromatization of a cyclohexano[*b*]pyrrole moiety precedes the formation of dipyrromethene and, hence, it prevents receiving the BODIPY with cyclohexano[*b*]pyrrole counterpart via this route.

Obviously, less prone to dehydrogenation would be cycloheptano[*b*] pyrrole, because of its inability to be aromatized. Therefore, this pyrrole was involved, for the first time, in a BODIPY dye assembly via the same sequence: the trifluoroacetylation, reduction ($NaBH_4$) to the corresponding trifluoromethyl alcohol and further condensation with pyrroles.

Transformation of dipyrromethanes **2c-e** to dipyrromethenes and their following complexation with $BF_3{\cdot}OEt_2$ (*i*-Pr_2NEt, 2 h) into fluorophores BODIPYs **1c-f** were carried out according to the methodology [22].

It appeared that despite the lesser tendency of the cycloheptane ring to be dehydrogenated, dipyrromethane **2c** after 1.5 h of contact with one equivalent of DDQ followed by the treatment $BF_3{\cdot}OEt_2$ (*i*-Pr_2NEt, 2 h) at room temperature was transformed into a mixture of cycloheptane- and cycloheptene-fused boradiazaindacenes **1c** and **1d**, their isolated yields being 2 and 16% correspondingly. Under the same conditions, from dipyrromethane **2d**, only partially dehydrogenated BODIPY **1e** was

Table 2
Synthesis of BODIPY dyes **1a-f** from dipyrromethanes **2a-e**.

Dipyrromethane	BODIPY	Yield, %	Dipyrromethane	BODIPY	Yield, %
2a	 **1a**	7[a]	**2b**	 **1b**	8[a]
2c	 **1c**	12[b]	**2c**	 **1d**	16[b]
2d	 **1e**	10[b]	**2e**	 **1f**	12[b]
Reference compd	 **1g**		Reference compd	 **1h**	

Reaction conditions.
[a] dipyrromethanes **2a,b** (1 mmol), DDQ (3 mmol), *i*-Pr_2NEt (10 mmol), $BF_3{\cdot}Et_2O$ (11 mmol), toluene, 0 °C, 1 h.
[b] dipyrromethanes **2c-e** (1 mmol), DDQ (1 mmol), *i*-Pr_2NEt (10 mmol), $BF_3{\cdot}Et_2O$ (11 mmol), CH_2Cl_2, 20–25 °C, 2 h.

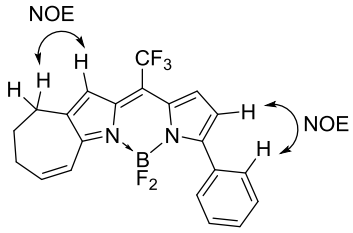


Fig. 1. Cross-peaks in compound **1d**.

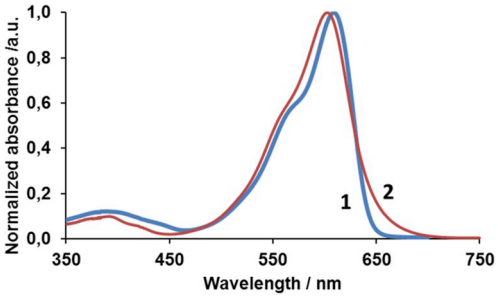


Fig. 2. Normalized absorption spectra of **1e** (1) and **1b** (2) in MeCN.

isolated in 10% yield. When the contact time of dipyrromethane **2c** with DDQ was reduced to 0.5 h, fluorophores **1c** and **1d** were isolated in 12 and 10% yields, respectively. Likewise, from dipyrromethane **2e** only saturated cycloheptano[*b*]-fused boradiazaindacene **1f** was isolated in 12% yield.

The structure of the synthesized fluorophores, in particular, with respect to the position of the double bond in the cycloheptene moiety of BODIPY dyes **1d** and **1e**, was proved by ^{1}H and ^{13}C spectroscopy using 2D HMBC and HSQC methods. For instance, the ^{1}H NMR spectrum of compound **1d** contains a doublet at 7.11 ppm (J = 12.4 Hz) and a doublet of triplets at 6.47 ppm (J = 12.4, 5.0 Hz) of the olefin fragment. In the high-field part of the spectrum, characteristic multiplets of 3 CH_2 groups were preserved. The presence of cross peaks in the 2D NOESY spectrum between proton signals at 7.04 ppm (H-3 pyrrole) and 2.77 (CH_2 group) indicated the position of the olefin fragment (See Fig. 1).

Spectroscopic and photophysical data [the positions of the maxima of the absorption, emission, and fluorescence excitation bands, Stokes shifts ($\Delta\nu_{St}$), fluorescence lifetimes (τ_f), and fluorescence quantum yields (Φ_f)] for the fused asymmetric BODIPY dyes **1a-f** are summarized in Table 3, while individual spectra (absorption, emission and excitation) are placed in the ESI (Figs. S1–S5). Additionally, for the comparison, Table 3 shows data for their unfused asymmetric analog 8-CF_3-5-Ph-BODIPY (**1g**) [22].

As compared to the reference molecule, the presence of a cycloheptane[*b*]-fused moiety in **1c** and a cycloheptene[*b*]-fused moiety in **1d** leads to a red shift of the main absorption bands by 16 nm and 50 nm, respectively (for reference BODIPY **1g** and BODIPY **1c** and **1d** dissolved in *n*-hexane). This bathochromic displacement is in accordance with a stronger inductive electron-donating effect of alkyl groups and the expansion of the π-system of *b*-annulated cyclic substituents relative to the reference BODIPY **1g** having no substituents in the positions 2 and 3.

Replacement of the phenyl ring in the position 5 in compound **1d** for the isoxazole moiety (cycloheptene[*b*]-fused BODIPY **1e**) and further replacement of cycloheptene moiety for an indole in BODIPY **1b** do not considerably change the length and character of the conjugation chain in these molecules, and, therefore, maxima of the main absorption bands for **1d**, **e** and **1b** almost coincide (Table 3). The main absorption bands of BODIPY **1b** relative to isomeric **1a** are red-shifted by 24 nm, in accordance with reference [50]. The absorption wavelength of the main band of BODIPY **1f** with the shortest conjugate system, in turn, is slightly less than that of the reference molecule.

Compounds **1c-f** exhibit strong red fluorescence (λ_{em} = 588–634 nm). The fluorescence excitation spectra perfectly match the absorption spectra (Figs. S1–S4) and fluorescence lifetimes are in the normal range. The Φ_f values of **1c-f** are higher than 0.50 (Table 3). As follows from the comparison with the reference molecule, the fusion with cycloheptyl moiety does not decrease Φ_f. Unexpectedly, benzo[*b*]-fused (indole-derived) BODIPYs **1a** and **1b** do not fluoresce at all in both polar and non-polar solvents.

The reasons for the low fluorescence quantum yield of a series of the asymmetric indole-derived BODIPYs (**1h** is typical example) have been already mentioned in literature [51,52]. However, due to the fact that all these dyes in the *meso*-position contain a phenyl substituent (sp^2-bonded type), which is an effective quencher of BODIPY fluorescence [53,54], their weak emission properties were attributed to the free rotation of the *meso*-phenyl group [51,52]. On the other hand, in our case the *meso*-position is bonded to sp^3 carbon. Such BODIPY dyes usually strongly fluoresce relative to their sp^2-bonded congeners [54].

Table 4
Calculated electronic excitation energies and oscillator strengths (f) in the gas phase for BODIPY **1b** and **1e** molecules computed at the TD-CAM-B3LYP/SVP level of theory.

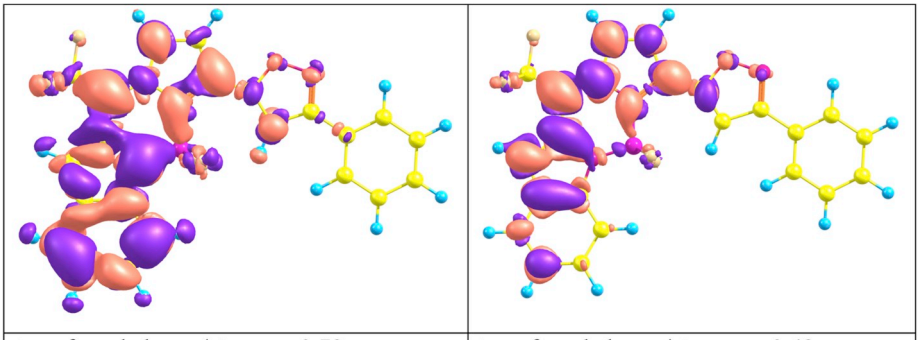
Transition	BODIPY	Energy, eV	f	Main configuration	Contribute, %
$S_0 \rightarrow S_1$	**1e**	2.48	0.74	H[a]-L[b]	98
	1b	2.49	0.16	H-L	37
				H-1-L	60
$\rightarrow S_2$	**1e**	3.67	0.07	H-4-L	92
	1b	2.55	0.69	H-L	63
				H-1-L	35
$\rightarrow S_3$	**1e**	3.93	0.00_1	H-5-L	82
				H-3-L	13
	1b	3.73	0.00_1	H-2-L	95

[a] designation for HOMO.
[b] designation for LUMO.

Table 3
Photophysical properties of BODIPY dyes **1a-f** in MeCN at 293K

BODIPY	λ_{abs}(max), nm	ε(max), $M^{-1}cm^{-1}$	λ_{ex}(max), nm	λ_{em}(max), nm	$\Delta\nu_{St}$, cm^{-1}	τ_f, ns	Φ_f[a]
1a	580	50,000	N.F.[c]	N.F.	N.F.	N.F.	N.F.
1b	604	47,500	N.F.	N.F.	N.F.	N.F.	N.F.
1c	572; 577[b]	31,000	572	600	820	6.09	0.57
1d	605; 611[b]	39,500	605	632	700	5.91	0.63
1e	609	47,000	608	634	670	5.57	0.68
1f	555	36,000	553	588	1010	5.04	0.54
Reference BODIPY **1g** in *n*-hexane [22]							
1g	561	36,000	561	578	520	4.5	0.56

[a] Relative to 4,4-difluoro-3-[(4-methyl)phenyl]-5-phenyl-8-trifluoromethyl-4-bora-3a, 4a-diaza-s-indacene (Φ_f = 0.87 in MeCN [49]).
[b] Measured in *n*-hexane. Given to show similarity with spectra in MeCN and for comparison with reference compound **1g**.
[c] N.F. – non fluorescence.



transferred charge/e⁻ : 0.73	transferred charge/e⁻ : 0.42
distance charge transfer/Å: 1.92	distance charge transfer/Å: 0.97
$\mu(S_0)$/ D: 1.82	$\mu(S_0)$/ D: 1.82
$\mu(S_1)$/ D: 8.11	$\mu(S_2)$/ D: 3.15

Fig. 3. The electron density difference plot between the S_i (i = 1, 2) and S_0 state of the benzo[*b*]-fused derivative **1b** (plotted for the isosurface value of 0.001 a.u.). Red and blue correspond to positive ($\rho > 0$) and negative ($\rho < 0$) regions, respectively, and thus represent increase and decrease in electron density due to the excitation. $\mu(S_1)$ and $\mu(S_2)$ - dipole moment S_1 and S_2 states, respectively. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

As far as many known *meso*-CF_3-BODIPY dyes [21–24,49,50,55–58], as well as some here synthesized CF_3-BODIPY exhibit excellent fluorescent properties, it seems that the lack of fluorescence in derivatives **1a** and **1b** should be caused by other reasons than in the case of *meso*-Ph-BODIPY [51,52], probably by the presence of fused indole substituent. Aggregation-caused emission quenching effect for BODIPYs **1a,b** could be excluded because of their high solubility in *n*-hexane/MeCN and low concentration of solutions used.

In order to better understand the quenching mechanism, we compared the photophysical properties of benzo[*b*]-fused (indole-derived) derivatives **1b** (and **1a**) with those of cycloheptene[*b*]-fused derivative **1e**, which intensively fluoresces unlike benzo[*b*]-fused derivatives. Other substituents (in the positions 3 and 8) were the same for pair **1b** and **1e**. The maxima of the absorption bands of these derivatives almost coincide (Table 3), that is very convenient for the comparison.

Fig. 2 displays the absorption spectra of compounds **1b** and **1e**. It is seen that the main absorption band of the benzo[*b*]-fused dye **1b** is much wider and extends up to 700 nm, while the absorption of dye **1e** ends at ≈ 650 nm.

Taking into account these differences, we assume that in the case of benzo[*b*]-fused dyes, another one weak transition is located on the red side of the main transition. Due to the strong overlap of bands, the maximum of this second band cannot be determined accurately. Therefore, only the red tail of this absorption band is observed.

To test this hypothesis, TD-CAM-B3LYP/SVP calculations (Gaussian 09, Revision B.01 [59]) for the first five electronic transitions of dyes **1a, 1b** and **1e** have been performed and their results are presented in Table S1 (ESI). The molecular orbitals involved into these transitions are shown in Fig. S6. Results for the first three transitions for **1b** and **1e** are shown in Table 4.

TD-DFT calculations reveal that the longest absorption bands in **1e** is the envelope of a single and intense (f = 0.74) $S_0 \rightarrow S_1$ transition, which is due to the one electron excitation from the HOMO to the LUMO (98%) (Table 4). The weaker $S_0 \rightarrow S_2$ and $S_0 \rightarrow S_3$ transitions, which are far enough from the transition $S_0 \rightarrow S_1$ located in the high-energy spectral region form the second absorption band in the spectrum of **1e**.

A completely different picture is observed for benzo[*b*]-fused derivatives **1a** and **1b**. Here, the long-wavelength part of the spectra is formed by two closely spaced transitions, the main contribution to which are done by HOMO-LUMO and HOMO-1-LUMO single-electron excitations (Table 4 for **1b** as example and Table S1). The first of them, the $S_0 \rightarrow S_1$ transition, is relatively low-intense and has a moderate charge transfer (CT) character, and the second, intense $S_0 \rightarrow S_2$ transition, is a local excited type (LE) transition. This is obvious from the electron density difference plot (Fig. 3) and the picture of the molecular orbitals of derivatives **1a** and **1b** involved in these transitions (Fig. S6).

As a result, the absence of fluorescence of the derivatives **1a** and **1b** may be due to the competition of the radiative transition from the ^{1}LE fluorescent state and the additional nonradiative transition from the ^{1}LE state to the ^{1}CT non-fluorescent state, as shown schematically in Fig. S7.

3. Conclusions

In conclusion, an expedient strategy for the synthesis of highly efficient BODIPY fluorophores of novel family of *meso*-CF_3-cycloheptane- and cycloheptene[*b*]-fused BODIPY dyes fluorescing in a 588–634 nm region with good quantum yields ($\Phi_f = 0.54$–0.68) has been developed. The key step of this strategy is the P_2O_5-promoted condensation of readily accessible trifluoro-1-(2,3-cycloalkanopyrrol-2-yl)ethanols with diverse pyrroles. The strategy proved to be a general easy route to previously inaccessible asymmetric BODIPY fluorophores.

Declaration of competing 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.

CRediT authorship contribution statement

Denis N. Tomilin: Investigation. **Elena F. Sagitova:** Investigation. **Konstantin B. Petrushenko:** Software, Validation. **Lyubov N. Sobenina:** Project administration, Writing - original draft. **Igor A. Ushakov:** Visualization, Validation, Software. **Guoqiang Yang:** Investigation, Validation. **Rui Hu:** Investigation, Validation. **Boris A. Trofimov:** Conceptualization, Methodology.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.dyepig.2020.108228.

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