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Design, Synthesis and Photophysical Properties of Bodipy-labeled Lupane Triterpenoids †

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Abstract: Novel BODIPY-lupane triterpenoid conjugates bearing a fluorescent marker at the C-2 position of ring A of the triterpene core were obtained via the Sonogashira reaction as a key step. The starting compounds in the cross-coupling reaction were C-2 propynyl derivatives of betulinic or betulonic acids and fluorescent dyes with an iodo-group at C-2 or *meso* position of BODIPY-platform. The newly elaborated coupling procedure might have applicability in the synthesis of fluorescent-labeled triterpenoid conjugates suitable for biological assays.

Keywords: pentacyclic triterpenoids, betulinic acid, BODIPY, fluorescent derivatives, Sonogashira coupling

1. Introduction

Pentacyclic triterpenic acids including the lupane family triterpenoids (betulin, betulinic, betulonic acids) are an important class of plant natural products. The widespread availability in nature, beneficial biological and pharmacological properties (antitumour, antiviral, antiparasitic effects) and easy transformation of native 3-OH and 17-COOH groups make these secondary plant metabolites promising scaffolds for the discovery of new drug candidates [1–3]. To date, the derivatization of the C-3 hydroxyl and C-17 carboxyl functions in natural triterpenic acids has been applied to obtain their numerous semi-synthetic derivatives, which in some cases have surpassed the parent compounds in their biological action and pharmacological parameters [4,5]. Thus, some derivatives of betulinic acid with C-3 and/or C-17 side chains, including 3-O-(3',3'-dimethylsuccinyl)betulinic acid known as beverimate exhibited a high inhibitory effect against the HIV-1 human immunodeficiency virus [6–9]. The addition of lipophilic mitochondria-targeted cationic groups to the triterpene skeleton significantly increased the cytotoxicity of triterpenoids. The resulting cationic derivatives of triterpene acids exhibited antitumour activity at low micromolar or even nanomolar concentrations [10–17]. There are reported works detailing some aspects of the mechanism of antiviral or antitumour action of the identified lead compounds of the triterpene structure [10,14,15,17]. Studies detailing molecular and cellular events involving these compounds have not yet been reported.

Over the last few years, fluorescently labeled probes of bioactive small molecules have provided powerful means for studying biological phenomena and mechanism of action of these molecules. Fluorescent labeling technologies offer a good opportunity to analyze the interaction of drugs with molecular targets at the cellular, subcellular levels, as well as *in vivo* at the level of the whole organism. Meanwhile, among the series of low molecular weight fluorescent compounds used for labeling biologically active molecules and analysis of biological phenomena, BODIPY family fluorophores are in wide demand [18,19]. The fluorophore, boron-dipyrromethene difluoride

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(4,4-difluoro-4-bora-3α,4α-diaza-s-indacene), known under the BODIPY trademark, stand out with its many attractive spectral properties such as high absorption coefficient, high fluorescence (FL) quantum yield, photochemical stability, stability in a physiological environment, good solubility in organic solvents, and great potential for structural derivatization [19,20]. The BODIPY family fluorophores have been covalently linked to numerous classes of biomolecules, including proteins [20,21], carbohydrates [22], fatty acids, and steroids [23–28]. Still, only two research papers on the synthesis and fluorescent biological analysis of BODIPY-labeling of triterpenoid compounds have been reported so far [29,30]. In these works, fluorescent pentacyclic triterpene conjugates have been prepared by covalent binding to the known (BODIPY-FL) BODIPY-propanoic acid fluorophore through the 3-OH and 17-COOH functional groups. Unfortunately, this resulted in a decrease or even a complete loss of the cytotoxic effect of the new compounds compared to the parent compounds. The research results are consistent with the already well-known facts about the key role of the C-3 and C-17 functional groups of triterpenoids as pharmacophores [4,5].

Here we aimed to work out a new approach for the synthesis of BODIPY-triterpenoid acids conjugates avoiding covalent binding of the triterpene core to the BODIPY-platform at the C-3 and C-17 positions. We have recently developed an efficient method for introducing a propynyl substituent at the C-2 position of the ring A of triterpenic acids, and demonstrated that the terminal acetylene moiety in these compounds can be effectively involved in the CuAAC reaction and in the Sonogashira coupling reaction [31–33]. In this research project, we applied C-2 propynyl derivatives of betulinic and betulonic acids **3-5** as initial substances for conjugation with some BODIPY dyes through the Sonogashira coupling reaction.

2. Materials and Methods

2.1. Chemistry

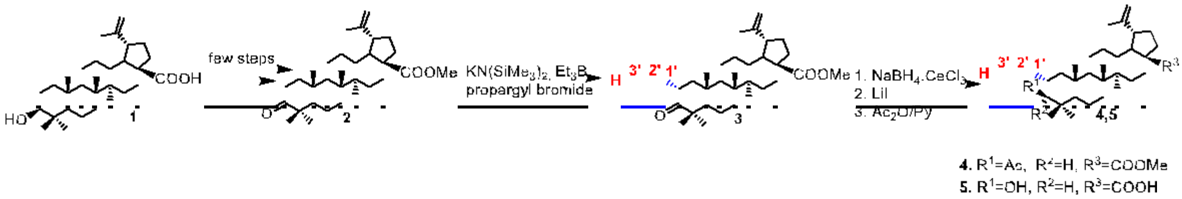
The starting compounds betulin, betulinic acid and reagents: BEt_3 (95%), $KN(SiMe_3)_2$ (1 M solution in THF), $CeCl_3.7H_2O$, $NaBH_4$ were purchased from Aldrich and used without any further purification. Propargyl bromide, LiI, CH_3COCl, CuI, $PdCl_2(PPh_3)_2$, Et_3N, DME (dimethoxyethane) 2,4-dimethylpyrrole, pyrrole, 4-iodobenzaldehyde, boron trifluoride etherate, iodine monochloride, indium(III) chloride, DDQ were purchased from Acros organics and used without any further purification. Betulonic acid was obtained from betulin according to known procedures.[34] The starting compounds **17-20** were prepared according to known procedures. [35–37]

2.1.1. General procedure for the synthesis of methyl betulonate adducts with BODIPY **21-26**.

A mixture of corresponding triterpenoid (0.18 mmol), corresponding BODIPY (0.16 mmol) were dissolved in anhydrous Et_3N/DMF (5 mL, 1.5:1). Then CuI (6.1 mg, 0.03 mmol) and $PdCl_2(PPh_3)_2$ (7.0 mg, 0.01 mmol) were added to the mixture simultaneously and the resulting mixture was stirred at room temperature for 1-3 hours under an argon atmosphere. The completion of reaction was monitored by TLC analysis. The reaction was quenched by addition of water and extracted with EtOAc (3 × 10 mL). The combined organic extracts were dried with $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel with hexane/ EtOAc (from 25:1 to 10:1) as an eluent to afford pure products **21-26**.

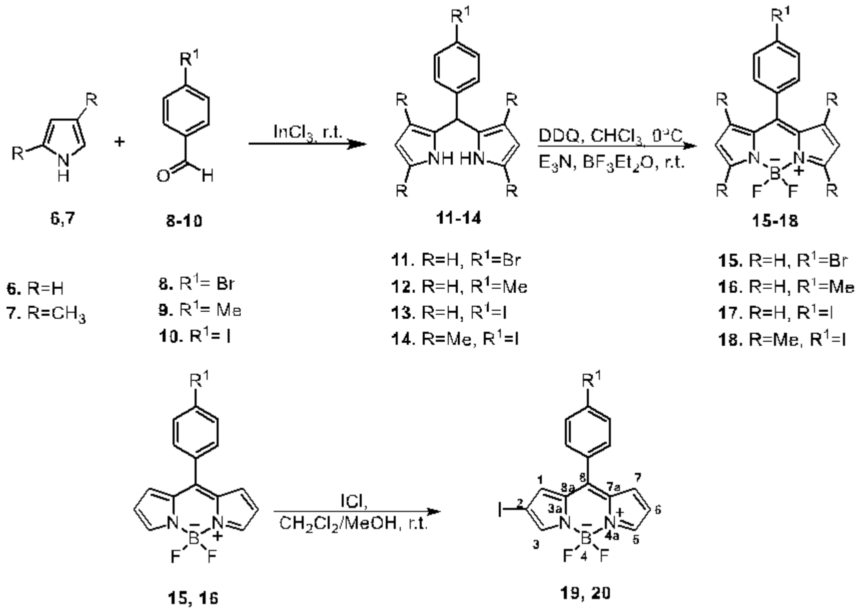
3. Results and Discussion

Compounds **3-5** were synthesized through α-alkylation with propargyl bromide of potassium enoxytriethylborates, generated by treating betulonic acid methyl ester **2** with the $KN(SiMe_3)_2$-Et_3B reagent. Methyl betulonate **2** was obtained by oxidation of commercially available betulin **1** (Scheme 1). The derived triterpenoids **3-5** were linked to the BODIPY-core by a chemically stable carbon-carbon bond through propynyl or phenylpropynyl linkers. To accomplish this, we synthesized photostable *meso*-arylsubstituted BODIPY **15-20** as starting compounds from commercially available pyrrole, 2,4-dimethylpyrrole, and 4-Br, 4-Me and 4-I benzaldehydes.



Scheme 1. Synthesis of C-2 propynyl derivatives of betulonic and betulinic acids **3-5** [31].

BODIPY iodine derivatives containing an iodine atom in the phenyl ring **17, 18** were linked directly to triterpenoids **3–5**, while *meso*-arylsubstituted BODIPY **15, 16** containing an electron-donor (Me) or electron-withdrawing (Br) substituent in the aryl group were subjected to iodination to obtain the target monoiodo-BODIPY derivatives at 2-position **19, 20** (Scheme 2).



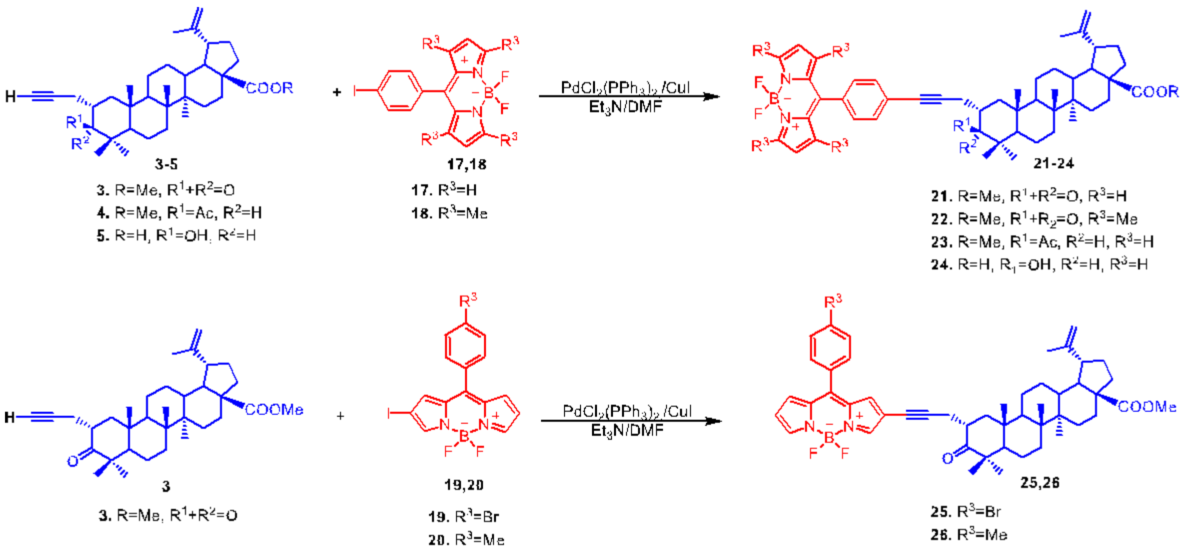
Scheme 2. Synthesis of meso-arylsubstituted derivatives BODIPY 15-20.

Syntheses of meso-arylsubstituted BODIPY were carried out by classical three-step method, starting with condensation of pyrrole rings with aryl aldehydes. In these reactions, trifluoroacetic acid or BF_3·OEt_2 is traditionally involved as acid catalysts protonating or chelating the carbonyl oxygen atom, and the reactions are carried out in CH_2Cl_2 [19]. We synthesized dipyrromethanes **11-14** by the method [35] with $InCl_3$ as an acid catalyst. The reactions were carried out at a large (20 molar) excess of the pyrrole or dimethylpyrrole, serving as a reagent and solvent at once. These conditions offered significant reduction of the formation of pyrrole oligomerization by-products and preparation of the target dipyrromethanes **11-14** in high yields (67-87%). Oxidation of dipyrromethanes by 2,3-dichloro-5,6-dicyano-p-benzoquinone (DDQ) gave dipyrromethenes which were reacted with a 16-fold excess of BF_3·OEt_2 without isolation and purification under typical conditions involving Et_3N [36]. Two-step one-pot synthesis helped to achieve target BODIPY derivatives **15-18** in 28-67% yields (Scheme 2). The oxidation and complexation reactions of dipyrromethane **14** were considerably complicated by the formation of oligomerization products; thorough chromatographic purification of the reaction mixture on silica gel gave fluorophore **18** in a relatively low yield (28%).

The record shows, that introduction of halogens, usually Br or I atoms, at positions 2 and 6 or 3 and 5 of the BODIPY platform brings about a bathochromic shift in the absorption and emission spectra and FL quenching as compared to parent dyes [37]. The products of halogenation of pyrrole fragments at these positions are usually further applied to implement Pd-catalyzed coupling reactions, including the Sonogashira coupling [37–42]. The analysis of the mesomeric structures of

BODIPY revealed that the 2- and 6-positions have a small positive charge compared to other carbon atoms of the pyrrol fragments. Therefore, these positions can be most susceptible to electrophilic attacks. The study [37] illustrated that iodination of a BODIPY dye with unsubstituted pyrrole rings using ICl in an equimolar ratio gives the C-2 monoiodo derivative of BODIPY in a relatively high yield and selectivity. In our study, iodination of *meso*-substituted derivatives of BODIPY **15, 16** according to the method [37] at an equimolar ratio of fluorophores and ICl in a mixture of solvents CH_2Cl_2/MeOH produced the target iodides **19, 20** after their purification by column chromatography on silica gel in 76 and 77% yields, respectively.

The synthesis of BODIPY-triterpenoid **21-26** conjugates linked through propynyl or phenylpropynyl bridges at the *meso* position of the dye or at the C-2 position of the BODIPY platform was carried out by cross-coupling according to the Sonogashira reaction. The reaction proceeded for 1-3 hours at room temperature in Et_3N/DMF (1.5:1) medium under the action of $PdCl_2(PPh_3)_2$ and CuI catalysts. The yields of target products **21-26** were 53-88% after a silica gel column chromatography (Scheme 3). It should be pointed out that the propynyl derivative of betulonic acid **3** was not involved in the cross-coupling reaction with the *meso*-(4-bromophenyl) substituted derivative BODIPY **15**. Under the above conditions, dimerization of the methyl ester of betulonic acid was registered; the target product could not be observed even in trace amounts (Scheme 3).



Scheme 3. Synthesis of BODIPY-triterpenoid conjugates **21-26** via the Sonogashira coupling.

The compounds **21-26** were studied by various spectroscopic techniques. The molecular ion peak in mass spectra and matching elemental analysis with the expected composition of compounds confirmed the identity of the compounds **21-26**. The NMR spectra data of compounds **21-26** slightly differed. As such, an extensive analysis of the NMR spectrum for compound **21** is presented here. Thus, the signals of the carbon atoms of the acetylene bond C-2' and C-3' were observed to shift downfield (to 92.1 and 80.9 ppm, respectively) in the ^{13}C NMR spectrum of compound **21**, compared to the original propynyl derivative **3** (82.8 and 69.1 ppm, respectively). Moreover, a signal of a quaternary carbon atom in the region of 126.9 ppm was registered in the ^{13}C NMR spectrum, which we identified as the carbon atom bonded to the acetylene fragment. The ^{1}H NMR spectrum of compound **21** revealed the presence of a new multiplet signal in the region of 7.54 ppm, belonging to the signals of the phenyl substituent, as well as the presence of signals of pyrrole protons in the region of 6.94 (H-1''), 6.56 (H-2''), 7.96 (H-3'') ppm. The collected spectral data conclude that there is a covalent bond in the structure of compound **21** between the carbon of the phenyl substituent BODIPY and the carbon of the acetylene fragment of the triterpene framework, and consequently, the involvement of functional groups in the Sonogashira cross-coupling reaction.

In fact, the aryl substituent in the *meso* position of the BODIPY fluorophores is located almost perpendicular to the BODIPY nucleus. Therefore, it participates little in electronic conjugation and does not have a significant impact on the change in the absorption and emission wavelengths of the dye. At the same time, the introduction of π-electron donors such as phenylethynyl or ethynyl groups in the 2,6- or 3,5-position of the BODIPY skeleton can noticeably increase the absorption and emission wavelengths compared to the unsubstituted BODIPY molecule [41,42]. In this regard, we decided to investigate the spectroscopic properties of the fluorescent conjugates of tritepenoid-BODIPY **21-24** in comparison with conjugates **25, 26**.

Table 1. Spectral and luminescent properties of compounds **17-26** at T=297 K in MeOH.

Entry	Solvent	Abs λ_{max}, nm	ε×10$_4$ $M^{-1}\cdot cm^{-1}$	FL λ_{max}, nm	φ	Stokes shift nm
17	MeOH	500	6.8	518	0,01	18
18	MeOH	500	9.3	509	0,41	9
19	MeOH	503	4.2	522	0,01	19
		519	4.1	548		29
20	MeOH	517	5.9	544	0,01	27
21	MeOH	499	4.2	519	0,01	20
22	MeOH	498	6.5	509	0,38	11
23	MeOH	500	3.6	517	0,01	17
24	MeOH	500	4.6	518	0,01	18
25	MeOH	539	4.7	582	0,06	43
26	MeOH	534	2.4	571	0,14	37

[1] Absorption (λ_{max}, nm) and FL (λ_{max}, nm) wavelength of the maximum; molar absorption (ε×10^4 $M^{-1}\cdot cm^{-1}$) at the maximum wavelength; and FL quantum yield (φ).

The spectroscopic properties of BODIPY-fluorophores **17-20** and conjugates **21-26** were studied in MeOH. The findings of this study are summarized in Table 1 and Figure 1 (absorption and photoluminescence (PL) spectra of compounds **17-26** in MeOH). The form of the absorption and emission spectra of BODIPY-derivatives **17-20** corresponds to the previously reported similar compounds [37,38,41]. Characteristic maxima with rather high molar extinction coefficients and small Stokes shifts are recorded in the absorption and PL spectra of these compounds. The iodine substituent at the C-2 atom of the BODIPY core causes a significant red-shift of the absorption and emission maxima, while quenching of the quantum yield is observed.

Conjugation of the triterpenoid core to BODIPY at the C-8 atom of the dye through the phenylethynyl spacer in compounds **21-24** did not change the position of the absorption and PL maxima in comparison with the initial fluorophores (for example, compounds **17** and **21**).

The presence of methyl substituents in the pyrrolic fragments of BODIPY **18** and its conjugate with triterpenoid **22** considerably increased the quantum yield and caused about a slight hypsochromic shift of the PL maximum in comparison to unsubstituted analogues **17** and **21**. Attachment of the triterpenoid **2** to BODIPY moiety at C-2 position via propynyl spacer produced a noticeable bathochromic shift in the absorption maximum in conjugates **25** and **26** (Table 1 and Figure 1c, d). The luminescence of conjugates **25** and **26** (570-580 nm) also shifted to the long-wavelength region of the spectrum relative to unsubstituted BODIPY (518 nm). Furthermore, compared to the initial iodine derivatives BODIPY **19** and **20**, a noticeable increase in the quantum yield and Stokes shifts was observed in conjugates **25** and **26**.

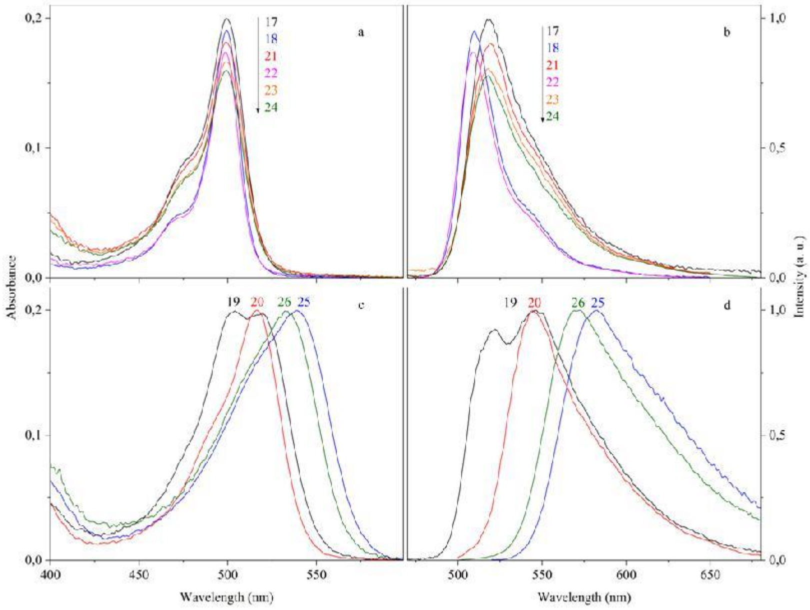


Figure 1. Absorption spectra (a, c) and PL (b, d) of the target BODIPY derivatives **17-20** and BODIPY triterpenoid conjugates **21-26**. T = 298 K, C = 10^{-6} mol·l^{-1} in MeOH, λexc = 350 nm, Fluorolog-3, $\Delta\lambda$ = 1 nm.

4. Conclusions

Thus, an efficient synthesis has been developed and six new fluorescent conjugates of lupane triterpenoids have been synthesized, with the triterpene core linked to the BODIPY fluorophore at the C-8 or C-2 positions of the dye through propynyl or phenylpropynyl spacers. The study of the fluorescent properties of the resulting conjugates revealed that the conjugates (compounds **21-24**) retain the fluorescent properties of the initial chromophores upon covalent binding of terpenoids to the BODIPY nucleus at the *meso* position. Meanwhile, the acetylene fragment in the propynyl bridge at the C-2 atom of the pyrrole ring increases the π-electronic delocalization of BODIPY-backbone in compounds **25** and **26**. Consequently, conjugates **25** and **26** demonstrated a significant bathochromic shift of the absorption maximum (**25**, λ_{abs} 551 nm,) and the luminescence maximum (λ_{em} 578 nm) relative to BODIPY (λ_{em} 518 nm). Moreover, compared to the initial substances, iodine derivatives of BODIPY **19** and **20**, conjugates **25** and **26** exhibited an increase in quantum yields and Stokes shifts. We believe that the novel approach developed by our research group can find application in the synthesis of BODIPY-triterpenoid conjugates as potential fluorescent probes for biological studies of triterpene compounds.

Supplementary Materials: The following are available online at http://www.xxxxx.

Author Contributions: Validation and writing—review and editing, A.S.; performing the chemistry experiments, R.G. and E.D.; performing the photoluminescent (PL) experiments, A.T. The manuscript was prepared through the contributions of A.S., R.G., and D.N. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest: The authors declare no conflict of interest.

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