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CARBORANE–BODIPY CONJUGATES: SYNTHESIS AND CHARACTERIZATION

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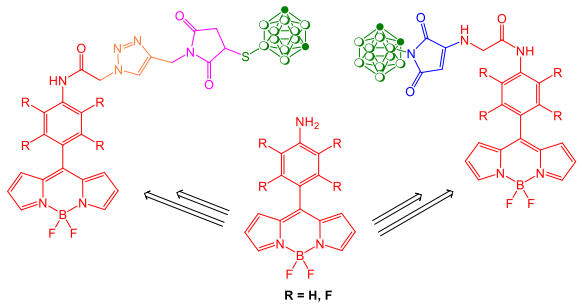
Abstract

A series of new carborane–BODIPY conjugates bearing succinimide–triazole or maleimide functional groups are prepared from synthetically available amino-substituted BODIPYs. The resulting compounds are characterized by UV–vis, IR, and NMR spectroscopy as well as mass spectrometry.



Key words: BODIPY, carborane, maleimide, succinimide, triazole.

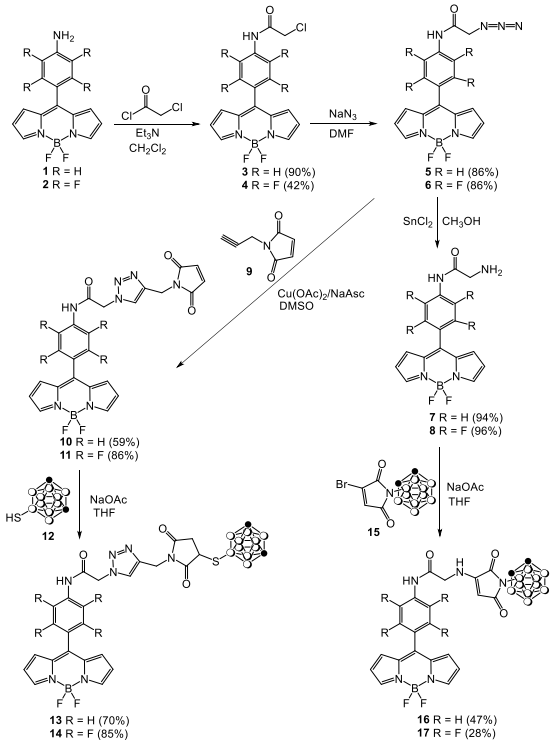
Introduction

4,4-Difluoro-4-bora-3a,4a-diaza-*s*-indacenes (BODIPYs) are important compounds that find application in various fields, including biology, medicine, and materials science [1–5]. They display valuable photophysical and optoelectronic properties, such as high quantum yields of fluorescence, small absorption and emission bandwidths, high stability at physiological pH values, and chemical inertness along with ample opportunities to modify a structure of the chromophoric BODIPY ligand and thus impart new properties to the system [6]. The BODIPY fluorescent dyes, being structural analogs of porphyrins, are widely used in biochemistry, biophysics, and biotechnology as fluorescent markers, and in medicine for imaging living cells and animals in preclinical research [7, 8]. A number of reports are devoted to the structural modification of the BODIPY compounds aiming at improving and extending their application scope [9]. Recently, the BODIPY dyes have been proposed as photosensitizers (PSs) for photodynamic therapy (PDT). Today, PDT is one of the efficient binary methods for the treatment of cancer diseases. PDT is based on the selective destruction of pathological cells by the action of cytotoxic reactive oxygen species (ROS) ($^1O_2$, HO_2^-, $HO^{\cdot}$), which are locally generated upon excitation with monochromatic light selectively accumulated in tumor PS, thus limiting undesired effects on healthy tissues [10]. At the same time, the BODIPY derivatives are not only efficient PSs for PDT but have remarkable fluorescence properties, which make them useful compounds for diagnosis by fluorescence bioimaging [11]. Furthermore, owing to their unique spectroscopic features, the BODIPY dyes are of interest for the modification with carborane clusters. Carboranes have unique structural and electronic properties, such as high chemical and thermal stability [12], three-dimensional aromaticity [13, 14], high hydrophobicity and electron-withdrawing character [15], as well as high biocompatibility [16]. The high synthetic potential of carboranes and their derivatives provides the basis for the preparation of promising compounds for practical application in different areas, such as catalysis [17], creation of luminescent materials and materials for nonlinear optics [18], thermally stable polymers [19], dendrimers and precursors for nanostructured systems [20]. Moreover, carborane derivatives are attractive building blocks for the design of new pharmaceuticals [21]. Owing to their synthetic flexibility, high thermal and hydrolytic stability, general robustness, remarkable biostability, as well as high boron content, carboranes are useful as potential components of drugs for boron neutron capture therapy (BNCT). BNCT is a binary method for the treatment of cancer that is based on the selective absorption of the non-radioactive ^{10}B isotope in the tumor tissue followed by irradiation with low energy thermal neutrons. The $^{10}B(n,\alpha)^7Li$ reaction produces the energetic α particles and residual ^7Li nuclei (with the energies of 200 and 350 keV μm^{-1}, respectively) that have a cell killing effect within a 10 μm range (about one cell diameter) causing the lethal damage of the ^{10}B enriched tumor cells. Therefore, BNCT selectively destroys cancer cells without damaging the surrounding healthy tissue. In this context, the modification of the BODIPY dyes with carboranes opens up a possibility to use them both as photosensitizers for PDT and as potential drugs for BNCT [22–28]. In this article, different ways of the targeted modification of a BODIPY core with carborane polyhedra were developed in order to create multifunctional drug candidates for PDT, BNCT, and other applications. Herein, we report on the synthesis and characterization of new maleimide-containing BODIPY dyes as efficient compounds for selective introduction of carborane clusters *via* the Michael addition followed by the formation of the corresponding succinimide-substituted BODIPYs. These conjugates were prepared by the copper(I)-

catalyzed 1,3-dipolar cycloaddition of the azido-substituted BODIPYs with *N*-propargyl maleimide. The carborane BODIPY-substituted maleimides were also synthesized by the reaction of carborane bromomaleimide with amino-substituted BODIPYs. The novel conjugates are promising building blocks for the synthesis of biologically active molecules suitable for PDT and BNCT of cancer and perhaps for other diseases in which this modality is currently used [29–31]. The incorporation of the maleimide fragment into organic scaffolds can significantly affect the biological activity. The maleimide group reacts specifically with sulfhydryl groups in biomolecules, allowing for conjugation with peptides *via* the formation of biologically active succinimide derivatives [32]. Therefore, along with the known modifications for BNCT and PDT (*e. g.*, boronation), this study offers an opportunity of a specific peptide targeting compounds *via* the interaction of the sulfhydryl residues with the exogenous maleimide moiety. The new conjugates can emerge as versatile biochemical tools.

Results and discussion

For the synthesis of the BODIPY derivatives containing carborane clusters, readily available 8-(4-aminophenyl)-4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene (**1**) and 8-(4-amino-2,3,5,6-pentafluorophenyl)-4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene (**2**) were chosen as the key precursors. They were smoothly obtained according to the published procedures in 90–95% yields [33, 34]. The acylation of the amino groups in compounds **1** and **2** with chloroacetyl chloride in CH_2Cl_2 in the presence of Et_3N for 1–6 h led to the formation of chloroacetylamido derivatives **3** and **4** in 91% and 42% yields, respectively (Scheme 1).



Scheme 1. Synthesis of the BODIPY–carborane conjugates.

Compounds **3** and **4** easily formed the corresponding azides in 86% yields under the action of NaN_3 in DMF at the ambient temperature. The azide groups in **5**, **6** were then reduced with $SnCl_2$ in MeOH at the ambient temperature, affording amines **7**, **8** as red crystalline solids in 94–96% yields. BODIPY derivatives **5**, **6** were conjugated to *N*-propargyl maleimide **9** [35] *via* the click reaction [36] in the presence of $Cu(OAc)_2$ and sodium ascorbate in dry DMSO for 15–60 min to give corresponding BODIPYs **10**, **11** containing triazole linkers modified with maleimides in 59–86% yields. Owing to the presence of the activated double bond, the maleimide substituents in **10**, **11** can act as the Michael acceptors in the reactions with *S*-, *N*-, and *O*-nucleophiles [37]. The selective reactivity of the maleimide substituents in compounds **10**, **11** towards *S*-nucleophiles was demonstrated by the example of 9-mercapto-*m*-carborane **12** [38]. It was shown that the reactions of mercaptocarborane **12** readily proceed at the maleimide double bonds of compounds **10**, **11** in THF in the presence of NaOAc to generate thiosuccinimide products **13**, **14** in 70–85% yields as red crystalline solids (Scheme 1). Furthermore, the alkylation of the amino groups in compounds **7**, **8** with 3-bromo-1-(*N*-(*o*-carborane-3'-yl)maleimide (**15**) [39] in THF in the presence of NaOAc resulted in the formation of carborane maleimide BODIPYs **16**, **17** in 28–47% yields.

The structures of all the new compounds were confirmed by UV–vis, IR, ^1H, ^{11}B, and ^{19}F NMR spectroscopy as well as mass spectrometry. In the IR spectra, the characteristic absorption bands of the amino groups were observed at 3272–3465 cm^{-1}. The absorption bands at *ca.* 1700 cm^{-1} correspond to the stretching vibrations of the C=O group for all the compounds obtained. Compounds **13**, **14**, **16**, and **17** showed an intense absorption band in the infrared spectrum at 2597–2606 cm^{-1} that was assigned to the stretching vibrations of the BH groups in the *closo*-carborane polyhedron. The azide absorption bands for compounds **5**, **6** were detected at 2106 cm^{-1} and 2114 cm^{-1}, respectively. All the compounds showed the absorption bands at 1260 cm^{-1} attributed to the BODIPYs BF_2 groups.

For all the new compounds, the six protons of the pyrrole rings appeared as singlet signals at 8.14–7.91 ppm, as doublets in the regions of 6.87–8.03 ppm and 6.53–7.26 ppm. The four protons of phenyl ring appeared as doublet signals at 7.94–7.72 ppm and 8.56–7.51 ppm. The spacer methylene protons were observed as singlets at δ_H = 4.09–5.32 ppm. The methylene protons in the succinimide ring (compounds **13**, **14**) showed the doublet of doublet signals at δ_H = 3.25–3.90 ppm, the maleimide CH=CH protons in compounds **10**, **11** were found as singlets at δ_H = 6.72–6.94 ppm. The maleimide CH protons in compounds **16**, **17** appeared as singlets at 5.14 and 5.07 ppm, respectively. The protons of the carborane CH groups in compounds **13**, **14**, **16**, and **17** were found as broaden singlets in the range of 3.02–4.41 ppm. The $^{11}B\{^1H\}$ NMR spectra of compounds **13**, **14**, **16**, and **17** exhibited the signals at 0.2 ppm (**13**, **14**, **17**) or 0.3 ppm (**16**), which can be attributed to the BF_2 units, along with the signals of the carborane BH units in the region from −1.1 to −17.8 ppm, confirming the *closo*-structure of the carborane clusters. The detailed spectroscopic data of all the compounds obtained can be found in the Electronic Supplementary Information.

Experimental

General remarks

All reactions were performed in an atmosphere of dry argon. All solvents were dried according to the standard protocols. Unless otherwise specified, the reagents were purchased from Sigma-Aldrich. The ^{1}H, ^{11}B, and ^{19}F NMR spectra were recorded on a Bruker Avance-400 spectrometer operating at 400 MHz for ^{1}H NMR, 128 MHz for ^{11}B NMR, and 376 MHz for ^{19}F NMR or a Bruker Avance-300 spectrometer operating at 282 MHz for ^{19}F NMR. The chemical shifts (δ) were referenced internally to the residual solvent peak ($CDCl_3$, ^{1}H: 7.26 ppm; $(CD_3)_2CO$, ^{1}H: 2.05 ppm) for ^{1}H or externally relative to $BF_3{\cdot}OEt_2$ for ^{11}B and $CFCl_3$ for ^{19}F. The IR spectra were recorded on a Bruker Tensor 37 FTIR spectrometer in KBr tablets. The UV–vis spectra were measured on a Carl Zeiss Specord M 40 spectrophotometer in CH_2Cl_2 or acetone. The MALDI mass spectra were recorded on a Bruker autoflex speed TOF mass spectrometer (Germany) equipped with a solid-state UV laser of 355 nm and operating in the positive reflection mode. The MALDI mass spectra were registered using steel targets (MTP 384 ground steel; Bruker Daltonics Inc., Germany) containing 384 cells for deposition of the analyte and matrix. Dithranol and DHB were tested as the matrices and used in THF solution. The course of the reactions and purity of the compounds were monitored by TLC using Kieselgel 60 F254 plates (Merck) (elution with CH_2Cl_2, CH_2Cl_2–acetone (4:1), or CH_2Cl_2–methanol (5:1)). Merck silica gel L 0.040–0.060 mesh was used for column chromatography (elution with CH_2Cl_2 for compounds **3**–**6**, CH_2Cl_2–acetone (4:1) for compounds **10**, **11**, **13**, **14**, **16**, and **17**, or CH_2Cl_2–methanol (5:1) for compounds **7** and **8**).

Syntheses

8-[4-(2-Chloro-N-acetylamido)phenyl]-4,4-difluoro-4-bora-3a,4a-diaza-s-indacene (3). Chloroacetyl chloride (300 mg (211 μL), 2.66 mmol) and Et_3N (287 mg (395 μL), 2.66 mmol) were sequentially added dropwise to a solution of BODIPY **1** (500 mg, 1.77 mmol) in dry CH_2Cl_2 (100 mL). The reaction mixture was stirred at room temperature under an argon atmosphere in the dark for 1 h. Then, water (400 mL) was added to the mixture. The organic phase was separated, washed with water (3×200 mL), dried over Na_2SO_4, and evaporated to dryness. The resulting residue was purified by column chromatography on silica gel (eluent: CH_2Cl_2). Yield: 574 mg (90%). UV–vis (CH_2Cl_2, λ_{max}/nm ($\varepsilon{\cdot}10^{-3}$)): 241 (14.4), 375 (11.5), 502 (43.2). IR (KBr, ν/cm^{-1}): 3272 (NH), 1683 (C=O), 1549, 1476 (C=C, C=N), 1257 (BF_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.49 (br. s, 1H, NH), 7.96 (br. s, 2H, pyrrole), 7.78 (d, J = 8.6 Hz, 2H, Ph), 7.61 (d, J = 8.3 Hz, 2H, Ph), 6.96 (d, J = 3.7 Hz, 2H, pyrrole), 6.58 (d, J = 2.4 Hz, 2H, pyrrole), 4.28 (s, 2H, CH_2) ppm. MS (MALDI): m/z $[M–F]^+$ calcd. for $C_{17}H_{13}BClFN_3O$ 340.082; found 340.106.

8-[4-(2-Chloro-N-acetylamido)-2,3,5,6-tetrafluorophenyl]-4,4-difluoro-4-bora-3a,4a-diaza-s-indacene (4). Chloroacetyl chloride (3.18 g (2.24 mL), 28.2 mmol) and Et_3N (2.85 g (3.92 mL), 28.2 mmol) were sequentially added dropwise to a solution of BODIPY **2** (1.0 g, 2.82 mmol) in dry CH_2Cl_2 (200 mL). The reaction mixture was stirred at room temperature under an argon atmosphere in the dark for 6 h. Then, water (500 mL) was added to the mixture. The organic phase was separated, washed with water (3×200 mL), dried over Na_2SO_4, and evaporated to dryness. The resulting residue was purified by column chromatography on silica gel (eluent: CH_2Cl_2). Yield: 512 mg (42%). UV–vis (CH_2Cl_2, λ_{max}/nm ($\varepsilon{\cdot}10^{-3}$)): 340 (7.6), 519 (50.0). IR (KBr, ν/cm^{-1}): 3441 (NH), 1710 (C=O), 1568, 1478 (C=C, C=N), 1258 (BF_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.15 (s, 1H, NH), 8.00 (s, 2H, pyrrole), 6.87 (d, J = 3.8 Hz, 2H, pyrrole), 6.60 (d, J = 4.1 Hz, 2H, pyrrole), 4.36 (s, 2H, CH_2) ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ –137.0 (d, J = 13.8 Hz, 2F, *ortho*-F), –142.5 (d, J = 13.8 Hz, 2F, *meta*-F), –144.8 (dd, J = 57.7, 27.5 Hz, 2F, BF_2) ppm. MS (MALDI): m/z $[M–F]^+$ calcd. for $C_{17}H_9BClF_5N_3O$ 412.045; found 412.074.

8-[4-(2-Azido-N-acetylamido)phenyl]-4,4-difluoro-4-bora-3a,4a-diaza-s-indacene (5). Sodium azide (108 mg, 1.69 mmol) was added to a solution of BODIPY **3** (500 mg, 1.39 mmol) in dry DMF (20 mL). The reaction mixture was stirred at room temperature under an argon atmosphere in the dark for 1.5 h. After addition of water (500 mL), the target product was extracted with EtOAc (200 mL). The organic phase was separated, washed with water (2×200 mL), dried over Na_2SO_4, and evaporated to dryness. The resulting residue was purified by column chromatography on silica gel (eluent: CH_2Cl_2). Yield: 436 mg (86%). UV–vis (CH_2Cl_2, λ_{max}/nm ($\varepsilon{\cdot}10^{-3}$)): 244 (16.1), 379 (12.4), 502 (43.8). IR (KBr, ν/cm^{-1}): 3435 (NH), 2106 (N_3), 1683 (C=O), 1553, 1477 (C=C, C=N), 1258 (BF_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.26 (br. s, 1H, NH), 7.96 (br. s, 2H, pyrrole), 7.78 (d, J = 8.3 Hz, 2H, Ph), 7.61 (d, J = 8.6 Hz, 2H, Ph), 6.96 (d, J = 3.8 Hz, 2H, pyrrole), 6.58 (d, J = 2.7 Hz, 2H, pyrrole), 4.25 (s, 2H, CH_2) ppm. MS (MALDI): m/z $[M–F]^+$ calcd. for $C_{17}H_{13}BFN_6O$ 347.123; found 347.162.

8-[4-(2-Azido-N-acetylamido)-2,3,5,6-tetrafluorophenyl]-4,4-difluoro-4-bora-3a,4a-diaza-s-indacene (6). Sodium azide (181 mg, 2.79 mmol) was added to a solution of BODIPY **4** (400 mg, 0.93 mmol) in dry DMF (20 mL). The reaction mixture was stirred at room temperature under an argon atmosphere in the dark for 3 h. After addition of water (500 mL), the target product was extracted with EtOAc (200 mL). The organic phase was separated, washed with water (2×200 mL), dried over Na_2SO_4, and evaporated to dryness. The resulting residue was purified by column chromatography on silica gel (CH_2Cl_2). Yield: 350 mg (86%). UV–vis (CH_2Cl_2, λ_{max}/nm ($\varepsilon{\cdot}10^{-3}$)): 341 (4.4), 519 (29.8). IR (KBr, ν/cm^{-1}): 3441 (NH), 2114 (N_3), 1717 (C=O), 1568, 1479 (C=C, C=N), 1258 (BF_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.04 (s, 1H, NH), 8.00 (s, 2H, pyrrole), 6.87 (d, J = 3.5 Hz, 2H, pyrrole), 6.60 (d, J = 3.8 Hz, 2H, pyrrole), 4.35 (s, 2H, CH_2) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ –137.1 (d, J = 12.6 Hz, 2F, *ortho*-F), –142.5 (d, J = 12.6 Hz, 2F, *meta*-F), –144.8 (dd, J = 55.0, 27.5 Hz, 2F, BF_2) ppm. MS (MALDI): m/z $[M–F]^+$ calcd. for $C_{17}H_9BF_5N_6O$ 419.085; found 419.036.

8-[4-(2-Amino-N-acetylamido)phenyl]-4,4-difluoro-4-bora-3a,4a-diaza-s-indacene (7). Anhydrous $SnCl_2$ (313 mg, 1.65 mmol) was added to a solution of BODIPY **5** (200 mg, 0.55 mmol) in dry methanol (100 mL). The reaction mixture was stirred at room temperature under an argon atmosphere in the dark for 72 h. After the removal of the solvent *in vacuo*, the resulting residue was purified by column chromatography on

silica gel (eluent: CH_2Cl_2–methanol (5:1)). Yield: 176 mg (94%). UV–vis (acetone, λ_{max}/nm ($\varepsilon \cdot 10^{-3}$)): 372 (4.0), 497 (8.1). IR (KBr, ν/cm^{-1}): 3396 (NH), 1687 (C=O), 1554, 1474 (C=C, C=N), 1259 (BF_2). ^{1}H NMR (400 MHz, $(CD_3)_2CO$): δ 8.21 (br. s, 1H, NH), 8.01 (s, 2H, pyrrole), 7.94 (d, J = 8.6 Hz, 2H, Ph), 7.71 (d, J = 8.6 Hz, 2H, Ph), 7.10 (d, J = 3.8 Hz, 2H, pyrrole), 6.68 (d, J = 3.8 Hz, 2H, pyrrole), 4.38 (s, 2H, CH_2), 2.25 (s, 2H, NH_2) ppm. MS (MALDI): m/z $[M–F]^+$ calcd. for $C_{17}H_{15}BFN_4O$ 321.132; found 321.156.

8-[4-(2-Amino-N-acetylamido)-2,3,5,6-tetrafluorophenyl]-4,4-difluoro-4-bora-3a,4a-diaza-s-indacene (8). Anhydrous $SnCl_2$ (97 mg, 0.51 mmol) was added to a solution of BODIPY **6** (150 mg, 0.34 mmol) in dry methanol (100 mL). The reaction mixture was stirred at room temperature under an argon atmosphere in the dark for 12 h. After the removal of the solvent *in vacuo*, the resulting residue was purified by column chromatography on silica gel (eluent: CH_2Cl_2–methanol (5:1)). Yield: 135 mg (96%). UV–vis (acetone, λ_{max}/nm ($\varepsilon \cdot 10^{-3}$)): 513 (33.4). IR (KBr, ν/cm^{-1}): 3444 (NH), 1713 (C=O), 1569, 1478 (C=C, C=N), 1258 (BF_2). ^{1}H NMR (400 MHz, $(CD_3)_2CO$): δ 8.36 (s, 1H, NH), 8.14 (s, 2H, pyrrole), 7.27 (d, J = 3.8 Hz, 2H, pyrrole), 6.72 (d, J = 4.1 Hz, 2H, pyrrole), 4.57 (s, 2H, CH_2), 2.10 (s, 2H, NH_2) ppm. ^{19}F NMR (282 MHz, $(CD_3)_2CO$): δ –137.2 (br. s, 2F, *ortho*-F), –140.2 (m, 4F, *meta*-F, BF_2) ppm. MS (MALDI): m/z $[M–F]^+$ calcd. for $C_{17}H_{11}BF_5N_4O$ 393.095; found 393.102.

8-{4-[2-(1-Maleimido-1,2,3-triazol-4-yl)-N-acetylamido]-phenyl}-4,4-difluoro-4-bora-3a,4a-diaza-s-indacene (10). $Cu(OAc)_2$ (5 mg, 0.028 mmol) and sodium ascorbate (15 mg, 0.076 mmol) were added to a solution of BODIPY **5** (150 mg, 0.55 mmol) and propargyl maleimide **9** (371 mg, 2.75 mmol) in dry DMSO (6 mL). The reaction mixture was stirred at room temperature under an argon atmosphere in the dark for 1 h. After addition of water (200 mL), the target product was extracted with EtOAc (100 mL). The organic phase was separated, washed with water (2×100 mL), dried over Na_2SO_4, and evaporated to dryness. The resulting residue was purified by column chromatography on silica gel (eluent: CH_2Cl_2–acetone (4:1)). Yield: 162 mg (59%). UV–vis (CH_2Cl_2, λ_{max}/nm ($\varepsilon \cdot 10^{-3}$)): 376 (13.0), 502 (46.0). IR (KBr, ν/cm^{-1}): 3465 (NH), 1709 (C=O), 1555, 1476 (C=C, C=N), 1260 (BF_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.38 (s, 1H, triazole CH), 7.94 (br. s, 1H, NH), 7.92 (br. s, 2H, pyrrole), 7.72 (d, J = 8.3 Hz, 2H, Ph), 7.51 (d, J = 8.3 Hz, 2H, Ph), 6.90 (d, J = 3.5 Hz, 2H, pyrrole), 6.72 (s, 2H, maleimide CH=CH), 6.53 (d, J = 2.2 Hz, 2H, pyrrole), 5.32 (s, 2H, CH_2), 4.87 (s, 2H, CH_2) ppm. MS (MALDI): m/z $[M–F]^+$ calcd. for $C_{24}H_{18}BFN_7O_3$ 482.155; found 482.104.

8-{4-[2-(1-Maleimido-1,2,3-triazol-4-yl)-N-acetylamido]-2,3,5,6-tetrafluorophenyl}-4,4-difluoro-4-bora-3a,4a-diaza-s-indacene (11). $Cu(OAc)_2$ (5 mg, 0.028 mmol) and sodium ascorbate (15 mg, 0.076 mmol) were added to a solution of BODIPY **6** (150 mg, 0.34 mmol) and propargyl maleimide **3** (137 mg, 1.02 mmol) in dry DMSO (6 mL). The reaction mixture was stirred at room temperature under an argon atmosphere in the dark for 15 min. After addition of water (200 mL), the target product was extracted with EtOAc (100 mL). The organic phase was separated, washed with water (2×100 mL), dried over Na_2SO_4, and evaporated to dryness. The resulting residue was purified by column chromatography on silica gel (eluent: CH_2Cl_2–acetone (4:1)). Yield: 167 mg (86%). UV–vis (CH_2Cl_2, λ_{max}/nm ($\varepsilon \cdot 10^{-3}$)): 342 (6.3), 519 (47.6). IR (KBr, ν/cm^{-1}): 3439 (NH), 1711 (C=O), 1569, 1479 (C=C, C=N), 1260 (BF_2). ^{1}H NMR (400 MHz, $(CD_3)_2CO$): δ 10.25 (br. s, 1H, triazole CH), 8.14 (br. s, 2H, pyrrole), 8.03 (s, 1H, NH), 7.26 (d, J = 3.5 Hz, 2H, pyrrole), 6.94 (s, 2H, maleimide CH=CH), 6.71 (d, J = 3.8 Hz, 2H, pyrrole), 5.60 (s, 2H, CH_2), 4.80 (s, 2H, CH_2) ppm. ^{19}F NMR (282 MHz, $(CD_3)_2CO$): δ –141.7 (m, 2F, *ortho*-F), –144.6 (m, 4F, *meta*-F, BF_2) ppm. MS (MALDI): m/z $[M–F]^+$ calcd. for $C_{24}H_{14}BF_5N_7O_3$ 554.117; found 554.175.

8-{4-[2-(3-((m-Carboran-9-yl)thio)pyrrolidine]-2,5-dione-1-yl)-N-acetylamido]phenyl}-4,4-difluoro-4-bora-3a,4a-diaza-s-indacene (13). Carborane **12** (176 mg, 1.0 mmol) and NaOAc (17 mg, 0.2 mmol) were added to a solution of BODIPY **10** (100 mg, 0.2 mmol) in dry THF (10 mL). The reaction mixture was stirred at room temperature under an argon atmosphere in the dark for 1 h. After addition of water (100 mL), the target product was extracted with EtOAc (50 mL). The organic phase was separated, washed with water (2×100 mL), dried over Na_2SO_4, and evaporated to dryness. The resulting residue was purified by column chromatography on silica gel (eluent: CH_2Cl_2–acetone (4:1)). Yield: 95 mg (70%). UV–vis (CH_2Cl_2, λ_{max}/nm ($\varepsilon \cdot 10^{-3}$)): 241 (18.2), 374 (11.5), 502 (38.5). IR (KBr, ν/cm^{-1}): 3441 (NH), 3070 (carborane CH), 2605 (carborane BH), 1709 (C=O), 1555, 1476 (C=C, C=N), 1260 (BF_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.52 (br. s, 1H, triazole CH), 7.95 (br. s, 1H, NH), 7.91 (br. s, 2H, pyrrole), 7.78 (d, J = 7.6 Hz, 2H, Ph), 7.53 (d, J = 7.3 Hz, 2H, Ph), 6.92 (br. s, 2H, pyrrole), 6.53 (br. s, 2H, pyrrole), 5.31 (br. s, 2H, CH_2), 4.86 (br. s, 2H, CH_2), 3.90 (br. s, 1H, succinimide CH), 3.28 (dd, J = 18.3, 8.7 Hz, 1H, succinimide CH_2), 3.02 (br. s, 2H, carborane CH), 2.77 (dd, J = 18.3, 1.6 Hz, 1H, succinimide CH_2) ppm. ^{11}B NMR (128 MHz, $CDCl_3$): δ 0.2 (t, J = 31 Hz, 1B, BF_2), –1.1 (br. s, 1B), –6.4 (m, 2B), –9.8 (d, J = 147 Hz, 1B), –13.6 (d, J = 139 Hz, 5B), –17.3 (d, J = 184 Hz, 1B) ppm. MS (MALDI): m/z $[M–F]^+$ calcd. for $C_{26}H_{30}B_{11}FN_7O_3S$ 658.321; found 658.365.

8-{4-[2-(3-((m-Carboran-9-yl)thio)pyrrolidine-2,5-dione-1-yl)-N-acetylamido]-2,3,5,6-tetrafluorophenyl}-4,4-difluoro-4-bora-3a,4a-diaza-s-indacene (14). Carborane **12** (150 mg, 0.85 mmol) and NaOAc (14 mg, 0.17 mmol) were added to a solution of BODIPY **11** (100 mg, 0.17 mmol) in dry THF (10 mL). The reaction mixture was stirred at room temperature under an argon atmosphere in the dark for 3 h. After addition of water (100 mL), the target product was extracted with EtOAc (50 mL). The organic phase was separated, washed with water (2×100 mL), dried over Na_2SO_4, and evaporated to dryness. The resulting residue was purified by column chromatography on silica gel (eluent: CH_2Cl_2–acetone (4:1)). Yield: 108 mg (85%). UV–vis (CH_2Cl_2, λ_{max}/nm ($\varepsilon \cdot 10^{-3}$)): 340 (4.5), 519 (42.7). IR (KBr, ν/cm^{-1}): 3441 (NH), 3078 (carborane CH), 2600 (carborane BH), 1709 (C=O), 1570, 1477 (C=C, C=N), 1260 (BF_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.09 (br. s, 1H, triazole CH), 8.03 (br. s, 1H, NH), 7.95 (br. s, 2H, pyrrole), 6.91 (br. s, 2H, pyrrole), 6.54 (br. s, 2H, pyrrole), 5.57 (br. s, 2H, CH_2), 4.82 (br. s, 2H, CH_2), 3.86 (br. s, 1H, succinimide CH), 3.25 (dd, J = 18.3, 8.7 Hz, 1H, succinimide CH_2), 3.02 (br. s, 2H, carborane CH), 2.75 (dd, J = 18.3, 2.4 Hz, 1H, succinimide CH_2) ppm. ^{11}B NMR (128 MHz, $CDCl_3$): δ 0.2 (t, J = 28 Hz, 1B, BF_2), –1.1 (br.

s, 1B), –6.4 (m, 2B), –9.8 (d, J = 149 Hz, 1B), –13.6 (m, 5B), –17.2 (d, J = 168 Hz, 1B) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ –138.0 (d, J = 13.8 Hz, 2F, *ortho*-F), –142.5 (d, J = 13.8 Hz, 2F, *meta*-F), –144.7 (dd, J = 59.7, 27.5 Hz, 2F, BF_2) ppm. MS (MALDI): m/z $[M–F]^+$ calcd. for $C_{26}H_{26}B_{11}F_5N_7O_3S$ 730.283; found 730.233.

8-{4-[2-(3-Amino-1-(N-(o-carborane-3-yl))maleimido)-N-acetylamido]phenyl}-4,4-difluoro-4-bora-3a,4a-diaza-s-indacene (16). Carborane **15** (184 mg, 0.58 mmol) and NaOAc (48 mg, 0.58 mmol) were added to a solution of BODIPY **7** (100 mg, 0.29 mmol) in dry THF (10 mL). The reaction mixture was stirred at room temperature under an argon atmosphere in the dark for 1 h. After addition of water (100 mL), the target product was extracted with EtOAc (50 mL). The organic phase was separated, washed with water (2×100 mL), dried over Na_2SO_4, and evaporated to dryness. The resulting residue was purified by column chromatography on silica gel (eluent: CH_2Cl_2–acetone (4:1)). Yield: 79 mg (47%). UV–vis (CH_2Cl_2, λ_{max}/nm ($\varepsilon \cdot 10^{-3}$): 241 (15.0), 367 (8.6), 503 (25.4). IR (KBr, ν/cm^{-1}): 3429 (NH), 3076 (carborane CH), 2597 (carborane BH), 1707 (C=O), 1555, 1478 (C=C, C=N), 1260 (BF_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.22 (br. s, 1H, NH), 7.93 (s, 2H, pyrrole), 7.69 (d, J = 8.6 Hz, 2H, Ph), 7.54 (d, J = 8.6 Hz, 2H, Ph), 6.91 (d, J = 4.0 Hz, 2H, pyrrole), 6.55 (dd, J = 4.1, 1.9 Hz, 2H, pyrrole), 6.38 (br. s, 1H, NH), 5.07 (s, 1H, maleimide CH), 4.41 (br. s, 2H, carborane CH), 4.09 (d, J = 5.3 Hz, CH_2) ppm. ^{11}B NMR (128 MHz, $CDCl_3$): δ 0.3 (t, J = 28 Hz, 1B, BF_2), –3.5 (m, 1B), –13.1 (m, 9B) ppm. MS (MALDI): m/z $[M–F]^+$ calcd. for $C_{23}H_{26}B_{11}FN_5O_3$ 558.312; found 558.346.

8-{4-[2-(3-Amino-1-(N-(o-carborane-3-yl))maleimido)-N-acetylamido]-2,3,5,6-tetrafluorophenyl}-4,4-difluoro-4-bora-3a,4a-diaza-s-indacene (17). Carborane **15** (153 mg, 0.48 mmol) and NaOAc (39 mg, 0.48 mmol) were added to a solution of BODIPY **8** (100 mg, 0.24 mmol) in dry THF (10 mL). The reaction mixture was stirred at 45–50 °C under an argon atmosphere in the dark for 6 h. After addition of water (100 mL), the target product was extracted with EtOAc (50 mL). The organic phase was separated, washed with water (2×100 mL), dried over Na_2SO_4, and evaporated to dryness. The resulting residue was purified by column chromatography on silica gel (eluent: CH_2Cl_2–acetone (4:1)). Yield: 44 mg (28%). UV–vis (CH_2Cl_2, λ_{max}/nm ($\varepsilon \cdot 10^{-3}$)): 519 (29.2). IR (KBr, ν/cm^{-1}): 3439 (NH), 3063 (carborane CH), 2606 (carborane BH), 1710 (C=O), 1569, 1479 (C=C, C=N), 1260 (BF_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.99 (br. s, 2H, pyrrole), 7.95 (br. s, 1H, NH), 6.84 (br. s, 2H, pyrrole), 6.58 (br. s, 2H, pyrrole), 6.30 (br. s, 1H, NH), 5.14 (s, 1H, maleimide CH), 4.41 (br. s, 2H, carborane CH), 4.23 (d, J = 5.1 Hz, CH_2) ppm. ^{11}B NMR (128 MHz, $CDCl_3$): δ 0.2 (t, J = 28 Hz, 1B, BF_2), –3.4 (m, 1B), –12.1 (m, 9B) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ –136.8 (d, J = 17.2 Hz, 2F, *ortho*-F), –142.5 (d, J = 12.6 Hz, 2F, *meta*-F), –144.6 (dd, J = 57.4, 28.7 Hz, 2F, BF_2) ppm. MS (MALDI): m/z $[M–F]^+$ calcd. for $C_{23}H_{22}B_{11}F_5N_5O_3$ 630.274; found 630.248.

Conclusions

The practical synthesis of the carborane BODIPY dyes bearing succinimide and maleimide groups was developed based on the transformations of the chloroacetylamido-substituted BODIPY derivatives through the formation of the corresponding azido and amino functionalized compounds. The succinimide-substituted BODIPYs were obtained *via* the synthesis of the corresponding maleimides using the click reaction conjugations of the BODIPY azide groups to *N*-propargyl maleimide followed by the Michael addition reaction with 9-mercapto-*m*-carborane. The carborane maleimide-substituted BODIPYs were prepared by the reactions of the corresponding amino-substituted BODIPYs with 3-bromo-1-(*N*-(*o*-carborane-3'-yl)maleimide. All the reactions proceeded smoothly at room temperature, affording the desired compounds in good yields. These compounds are promising candidates for further biomedical investigations.

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Electronic supplementary information

Electronic supplementary information (ESI) available online: ^{1}H, ^{11}B, and ^{19}F NMR spectra as well as mass spectra of the newly synthesized compounds. For ESI, see DOI: 10.32931/io2201a.

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