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ORIGINAL RESEARCH



# Synthesis and biological evaluation of fluorescent GAT-ligands based on *meso*-substituted BODIPY dyes

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## Abstract

BODIPY dyes are well known for their outstanding spectroscopic properties and are therefore established in a range of fluorescence based analysis techniques for in vitro as well as for in vivo measurements. For the first time, we designed and synthesized a series of fluorescent ligands for the SLC6 family transporters mGAT1–mGAT4 based on BODIPY dyes as fluorogenic subunits. In the novel series of fluorescent compounds, BODIPY dye subunits are linked with an alkyl chain of three to five carbon atoms that originates from the *meso*-position of the BODIPY dye to the amino function of different cyclic amines. Screening of these fluorescent probes for their biological activity as GABA uptake inhibitors of mGAT1–mGAT4 revealed ligands with $pIC_{50}$ values up to 5.35.

**Keywords** BODIPY · Fluorescent ligand · GABA transporters · GAT · γ-aminobutyric acid · Biological activity

## Introduction

γ-Aminobutyric acid (GABA) is the major inhibitory neurotransmitter in the mammalian central nervous system. One mechanism to regulate GABA neurotransmission is the inhibition of GABA reuptake from the synaptic cleft into nerve axons and glial cells mediated by GABA transporters (GATs) (Kristensen et al. 2011). Hence, GATs form important drug targets for the treatment of diseases of the central nervous system associated with decreased levels of GABA like epilepsy (Treiman 2001), M. Parkinson (Ishiwari et al. 2004), M. Alzheimer (Rissman et al. 2007), Chorea Huntington (Frank 2014), depression (Kalueff and Nutt 2007), anxiety (Zwanzger and Rupprecht 2005), and insomnia (Plante et al. 2012).

The GATs are membrane bound transporter proteins of the SLC6 family, and four distinct subtypes are known to exist in humans and other species (Borden et al. 1992; Guastella et al. 1990). Since the biological test system operated in our group is based on GATs originating from mouse cells, the nomenclature established for the GABA transporters of this species, with the subtypes being denoted as mGAT1 (=SLC6A1), mGAT2 (=SLC6A12), mGAT3 (=SLC6A13), and mGAT4 (=SLC6A11) will be used in this manuscript (Liu et al. 1993). Of the four GABA transporter subtypes, which differ in their distribution in brain and body, mGAT1 and mGAT4 are clearly predominating in the brain where they mediate neuronal and glial reuptake of GABA (Borden 1996; Zhou and Danbolt 2013). In contrast, the expression levels of mGAT2 and mGAT3 are very low in brain and confined to specific brain regions, i.e. both transporter subtypes are restricted to the leptomeninges, additionally mGAT3 exists in a subset of blood vessels. Hence, these transporters that are present in high densities in liver and kidneys are not likely to significantly contribute to GABA inactivation in the brain (Kempson et al. 2014; Zhou and Danbolt 2013; Zhou et al. 2012).

Fluorescent labels and probes addressing a target of interest such as a GPCR, a ligand gated ion channel, or a transport protein are tool compounds of high value. With such compounds, a plethora of biological studies may be performed, which in particular is true when these compounds retain the pharmacological profile of the parent unlabeled ligands of the target of interest, they have been delineated from (Leopoldo et al. 2009).

**Supplementary information** The online version of this article (https://doi.org/10.1007/s00044-019-02483-6) contains supplementary material, which is available to authorized users.

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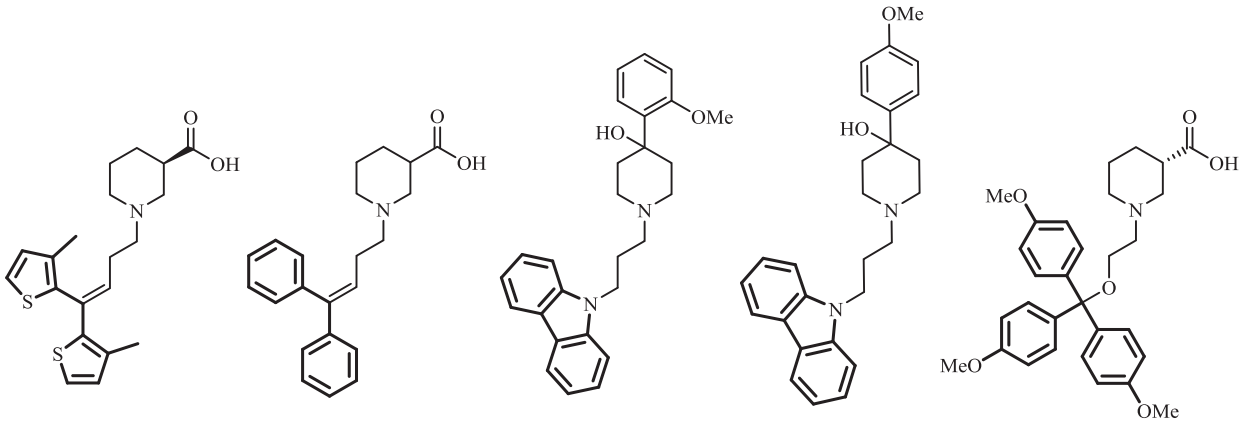
In confocal laser scanning microscopy experiments, fluorescent ligands are required in order to monitor processes triggered by ligand-receptor interactions in living cells such as internalization, trafficking, sequestration, and recycling. Fluorescent ligands are also indispensable in fluorescence correlation spectroscopy experiments providing subtle and specific differences in receptor binding characteristics between different areas of membranes of the same cell (Briddon and Hill 2007).

In fluorescence binding assays fluorescent probes may serve as reporter ligands similar to the function of radioligands in radioligand binding assays, whereby these assays have the clear advantage that they are devoid of any risks associated with the handling of radioactive compounds. Fluorescence polarization assays make use of fluorescent probes as well to monitor ligand-target binding. They are an attractive alternative to radioligand and fluorescence binding assays, as no separation of the ligand-target complex from the incubation system for the quantification of bound reporter-ligand is required (Leopoldo et al. 2009).

Furthermore, fluorescent ligands are also indispensable tool compounds in fluorescence resonance energy transfer (FRET) experiments, a method frequently used for in depth studies of protein dynamics and protein-protein interactions (Sohail et al. 2016; Stockmann et al. 2017).

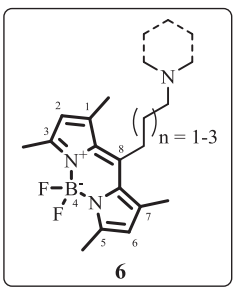
Hence, we envisaged it worthwhile to develop fluorescent ligands binding to GABA transporter proteins and to investigate their binding characteristics with our MS Binding and GABA uptake assays (Zepperitz et al. 2006; Kragler et al. 2008). The developed fluorescence ligands with known affinity to the GATs should be useful tool compounds for biological studies of GATs employing the different fluorescence-based techniques described above. For the design of these fluorescent compounds, we considered structural features of five representative GAT inhibitors **1**–**5** (Fig. 1a) which are Tiagabine (**1**), SKF 89976-A (**2**), NNC 05-2090 (**3**), NNC 05-2045 (**4**), and SNAP-5114

**A**



| | Tiagabine (**1**) | SKF 89976-A (**2**) | NNC 05-2090 (**3**) | NNC 05-2045 (**4**) | SNAP-5114 (**5**) |
|---|---|---|---|---|---|
| | $pIC_{50}$ [a)] | $pIC_{50}$ [a)] | $pIC_{50}$ [a)] | $pIC_{50}$ [a)] | $pIC_{50}$ [a)] |
| mGAT1 | 6.88±0.12 | 6.16±0.07 | 4.99±0.06 | 4.35±0.03 | 4.07±0.09 |
| mGAT2 | 50% | 3.43±0.07 | 5.09±0.06 | 4.97±0.11 | 63% |
| mGAT3 | 64% | 3.71±0.04 | 4.93±0.03 | 4.96±0.06 | 5.29±0.04 |
| mGAT4 | 73% | 3.56±0.06 | 4.78±0.10 | 5.35±0.03 | 5.65±0.02 |

**B**




**6**

**Fig. 1** **a** Structures of known GAT inhibitors Tiagabine (**1**), SKF 89976-a (**2**), NNC 05-2090 (**3**), NNC 05-2045 (**4**), as well as SNAP-5114 (**5**); [a)]$pIC_{50}$ values were determined using the same standard assay as for all tested compounds (Kragler et al. 2008). Percentages represent remaining [$^3$H]GABA uptake in the presence of 100 µM test compound. **b** General Structure of the target compounds with a BODIPY dye based fluorogenic subunit

(**5**). Tiagabine (**1**), which is marketed as a drug (Gabitril®), and SKF 89976-A (**2**) are selective inhibitors of mGAT1. NNC 05-2090 (**3**) as well as NNC 05-2045 (**4**) are described in literature as potent inhibitors of mGAT2 (Borden et al. 1994; Thomsen et al. 1997). NNC 05-2090 (**3**) is even described as subtype selective at mGAT2, yet a subtype selectivity of **3** could not be confirmed in our test system (see Table 2). SNAP-5114 (**5**) on the other hand is one of the most potent inhibitors known so far for mGAT4 (Dhar et al. 1994). Although the design of the fluorescent GABA inhibitors was based on compounds **1**–**5** as representative examples for the various classes of GAT inhibitors with certain subtype selectivities for the individual GAT subtypes, the development of subtype selective fluorescent ligands was not our primary focus. Rather by a first series of fluorescent GAT inhibitors, the suitability of the concept pursued for the design of fluorescent GAT inhibitors should be verified. In addition, also fluorescent GAT inhibitors lacking or having only low subtype selectivity may serve as valuable tool compounds providing data specific for a single GAT subtype as the specificity may also be warranted by employing target systems containing only the GAT subtype of interest as it is the case when the appropriate cell lines expressing the respective target are used.

In general, GAT inhibitors are composed of a cyclic amine or a cyclic amino acid like nipecotic acid (**7m**) and an "aryl moiety" connected by a linker of variable length originating from the amino nitrogen (Knutsen et al. 1999). Typical representatives for mGAT1 selective compounds like Tiagabine (**1**) and SKF 89976-A (**2**) (Fig. 1a) have two aromatic rings as "aryl moiety", whereas for mGAT2 the corresponding "aryl moiety" is in general more rigid, the two aromatic rings being bridged (see **3** and **4** Fig. 1a) to give a carbazole unit. For mGAT4, on the other hand, the "aryl moiety" is represented by a trityl unit in the most potent inhibitors like SNAP-5114 (**5**).

In the new fluorescent ligands for the GABA transporters envisaged by us, the before mentioned "aryl moieties" highlighted by bold lines in Fig. 1a should be replaced by a fluorescent dye of comparable size and shape (**6**, Fig. 1b). A group of fluorescent residues that we thought to fulfill these conditions are difluoroboraindacene (**bo**ron **dipy**rromethene, BODIPY) derived subunits (Fig. 1b, bold structure). BODIPYs comprising a tricyclic ring system with a central boradiazine ring flanked by two pyrrole units have been introduced as a class of compounds in 1968 by Treibs and Kreuzer (Treibs and Kreuzer 1968). BODIPY dyes are known for their excellent thermal and photochemical stability as well as their outstanding spectroscopic properties like high photostability, large extinction coefficients, and high quantum yields (Loudet and Burgess 2007; Ulrich et al. 2008). Moreover, with regard to their molecular size, BODIPY dyes seem to be able to partially mimic the "aryl moiety" of lead structures **1**–**5**. The pyrrole rings of the BODIPY dyes can be considered as a substitute for the aromatic rings present in **1** or **2** five- and six-membered aromatic ring systems, even though the core of the BODIPY dyes is more rigid, whereas their similarity to the tricyclic ring system in **3** and **4** is even higher. Like in the known GAT inhibitors, the used BODIPY dyes should finally be linked to the cyclic amine moiety by an alkyl spacer with varying length, from three to five carbons, that originate from the 8-position of the BODIPY, which is also called "*meso*-position".

In addition to the "aryl moiety" and linker, known GAT inhibitors vary also with respect to the cyclic amino or amino acid group representing the polar subunit of the overall compound. Therefore, we intended to also vary the structure of the cyclic amino and amino acid subunits. Hence, in addition to piperidine as the most basic six membered cyclic amine also substituted derivatives thereof should be employed in the synthesis.

As such more polar derivatives, compounds with an ether function (**7b**) or an additional OH group (**7c**, **7d**) or more lipophilic derivatives exhibiting an aryl substituent (**7e**, **7f**), should be employed. In addition, piperidine derivatives with both, i.e. possessing an OH function and an aryl residue (**7g**–**7k**), but also those exhibiting either a carboxylic acid ester moiety (**7l**) should be used as building blocks, whereas compounds with a carboxylic acid function (**7m**) should be accessed via the corresponding carboxylic acid esters. Overall, this should lead to BODIPY dye residues containing compounds displaying polar subunits well known from common GAT inhibitors (see e.g. **1**–**5**, Fig. 1).

In summary, this study envisaged fluorescent GAT ligands with the general structure **6** comprising a BODIPY dye unit linked with a cyclic amine moiety through an alkyl spacer originating from the *meso*-position of the BODIPY dye. The synthesis of these compounds should be accomplished by reaction of the respective BODIPY precursors exhibiting an alkyl chain with a terminal leaving group originating from the *meso*-position with amines **7a**–**m** to finally study the potencies of the final products at mGAT1–mGAT4 in [$^3$H]GABA uptake assays.

## Materials and methods

### Experimental

Unless noted otherwise, all reactions were performed in oven-dried glassware under moisture-free conditions and inert gas atmosphere. All commercial reagents were used without further purification. For the reactions, dried and freshly distilled solvents were used. $NEt_3$ was dried over sodium and distilled under nitrogen atmosphere when

needed. $CH_2Cl_2$ and MeCN were distilled from $CaH_2$ under nitrogen atmosphere. For chromatographic purposes, only distilled solvents were used. Flash-chromatography (FC) was performed according to Still et al. (1978) using silica gel. NMR spectra were measured with a Jeol Eclipse + 400 (400 MHz) and +500 (500 MHz) spectrometer. The coupling constants were stated with an accuracy of 0.5 Hz. MestreNova was used for further analysis of the spectra. IR spectra were recorded with a FT-IR spectrometer Paragon 1000 (Perkin-Elmer) and Spectrum v2.00 software (Perkin-Elmer) was used for analysis. Mass spectra were measured with a Mass Spectrometer 59827A with 59980 Particle Beam LC/MS interface (Hewlett Packard) or an Applied LC–MS/MS Mass spectrometer API 2000. High-resolution mass spectrometry (HRMS) was accomplished with an LTQ FT (ThermoFinnigan) or a JMS GCmate II (Jeol).

## Chemistry

### General procedures

**GP-1: Synthesis of BODIPYS** One equivalent of the appropriate acid chloride **12**, **13**, or **14** was added dropwise to a solution of two equivalents of 2,4-dimethylpyrrole (**11**) in $CH_2Cl_2$ under argon and stirred for 2 h at 50 °C. Afterwards, the solvent was removed and the remaining residue was resolved in a mixture of toluene and $CH_2Cl_2$ (95:5), 4.8 equivalents of $NEt_3$ were added and the mixture was stirred at room temperature for 30 min under argon. After adding of 6.9 equivalents of $BF_3$•$OEt_2$ and heating at 50 °C for 1.5 h, the solvent was removed and the remaining residue was purified by flash chromatography.

**GP-2: Ester hydrolysis** One equivalent of the ester was solved in a solution mixture of $CH_2Cl_2$:MeOH (1:2) and 2.5 equivalents of aqueous solution of LiOH was added dropwise. The reaction mixture was stirred at room temperature until no educt was detectable by thin layer chromatography. Afterwards the pH was adjusted to pH = 7 by adding phosphate buffer (pH = 7, 0.1 M) and extracted three times with $CH_2Cl_2$. The organic phase was dried over $MgSO_4$, and the solvent was removed. The remaining residue was resolved in bidest. $H_2O$, filtered, and freeze-tried.

**GP-3 (Method A): nucleophilic substitution of 15a** One equivalent of BODIPY **15a**, 1.4 equivalents of the corresponding amine as well as 2.8 equivalents of KI and three equivalents of $K_2CO_3$ were solved in acetone and stirred at 100 °C for 18 h in a microwave reactor. Afterwards, the solution was diluted with EtOAc and extracted with saturated citric acid. The pH of the aqueous phase was adjusted to 7 by adding of phosphate buffer (pH = 7, 0.1 M) at 0 °C and extracted with $CHCl_3$ afterwards. The organic phase was dried over $Na_2SO_4$, filtered, and the solvent was removed. The remaining residue was purified by flash chromatography.

**GP-3 (Method B): nucleophilic substitution of 15b** One equivalent of BODIPY **15b** and three equivalents of the corresponding amine were dissolved in MeCN and the reactor vessel was put in a preheated oil bath at 50 °C and stirred for 14 h. Afterwards water was added and the reaction mixture was diluted in EtOAc. The organic phase was washed with $H_2O$ and brine, dried over $Na_2SO_4$, filtered, and the solvent was removed. The remaining residue was purified by flash chromatography.

**GP-3 (Method C): nucleophilic substitution of 17** One equivalent of BODIPY **17**, 1.4 equivalents of the corresponding amine, as well as three equivalents $K_2CO_3$ were solved in MeCN and stirred at 80 °C for 14 h. After cooling to room temperature, the reaction mixture was filtered, and the solvent was removed. The remaining residue was purified by flash chromatography.

**GP-3 (Method D): nucleophilic substitution of 16** One equivalent of BODIPY **16**, 1.4 equivalents of the corresponding amine as well as 2.5 equivalents KI and three equivalents $K_2CO_3$ were solved in MeCN and stirred at 80 °C for 14 h. After cooling to room temperature, the reaction mixture was filtered, and the solvent was removed. The remaining residue was purified by flash chromatography.

### Synthesis of compounds

**4-(2-Methoxyphenyl)piperidin-4-ol (7h)** Compound **17** (900 mg, 2.64 mmol) solved in MeOH (18.0 mL) was hydrogenated with 10% Pd/C (168 mg) at room temperature for 30 min. After removal of the catalyst by filtration, the filtrate was concentrated under reduced pressure to give pure **7h**.

In total 578 mg (100%); white solid; mp 240 °C (dec.); IR (KBr) $\nu_{max}$ 3400, 3193, 2998, 2946, 2836, 2792, 2761, 2721, 2659, 2622, 2568, 2520, 2499, 2474, 2412, 2034, 1590, 1486, 1471, 1454, 1436, 1386, 1356, 1348, 1307, 1284, 1241, 1207, 1191, 1151, 1150, 1089, 1074, 1025 $cm^{-1}$; $^1H$ NMR (500 MHz, DMSO-D6, TMS): $\delta = 1.54$ (d, $J = 13.7$ Hz, 2H), 2.68 (td, $J = 5.0/13.6$ Hz, 2H), 3.08–3.20 (m, 4H), 3.81 (s, 3H, $H_3C$), 5.34 (s, 1H), 6.95 (td, $J = 1.1/7.6$ Hz, 1H), 6.99 (dd, $J = 0.9/8.2$ Hz, 1H), 7.25 (ddd, $J = 1.8/7.4/8.1$ Hz, 1H), 7.56 (dd, $J = 7.7/1.7$ Hz, 1H) ppm; $^{13}C$ NMR (125 MHz, DMSO-D6): $\delta = 31.4$ (2C, $NHCH_2\underline{C}H_2C$), 39.5 (2C, $NH\underline{C}H_2CH_2C$) 55.2 ($H_3\underline{C}$), 68.6 ($NHCH_2CH_2\underline{C}$), 115.8 ($CC_{ar}\underline{C}_{ar}H$), 120.2 ($CC_{ar}C_{ar}HC_{ar}H\underline{C}_{ar}H$), 126.3 ($CC_{ar}C_{ar}H\underline{C}_{ar}H$), 128.4 ($CC_{ar}C_{ar}\underline{C}_{ar}H$), 135.1 ($C\underline{C}_{ar}C_{ar}$), 156.1

($CC_{ar}\underline{C}_{ar}$) ppm; M ($C_{12}H_{17}NO_2$) = 207.13 MS (CI, $CH_5^+$) *m/z* (%): 208.05 (18, $[M+H]^+$), 190.05 (100); HRMS (EI+): $M^+$ calc. for $C_{12}H_{17}NO_2$, 207.1254; found: 207.1258.

**4-(2-Chlorphenyl)piperidin-4-ol (7j)** **23** (312 mg, 1.00 mmol) was solved in $Et_2O$ (10.0 ml) at 0 °C and HCl in $Et_2O$ (10.0 mmol, 5.0 mL, 2 M) was added dropwise. The resulting reaction mixture was stirred for 1 h at 0 °C and was then allowed to warm up to room temperature and stirred overnight. The solvent was removed, and the resulting residue was solved in $H_2O$ (2.0 ml) and cooled to 0 °C. $K_2CO_3$ (207 mg, 1.50 mmol) was added as well as DCM (10.0 ml) and the mixture was stirred vigorously at room temperature for 1 h. The aqueous phase was removed with $Na_2SO_4$, filtered, and the solvent was removed.

203 mg (96%); white solid; mp 164–167 °C; IR (KBr) $\nu_{max}$ 3419, 3289, 3266, 3055, 2995, 2944, 2933, 2858, 2804, 2629, 1469, 1463, 1443, 1426, 1369, 1355, 1321, 1321, 1278, 1232, 1200, 1161, 1134, 1142, 1157, 1091, 1064, 1041, 1025, 1000 $cm^{-1}$; $^1H$ NMR (500 MHz, $CD_2Cl_2$, TMS): $\delta$ = 1.85–1.90 (m, 2H), 2.23–2.31 (m, 2H), 2.89–2.95 (m, 2H), 3.10 (td, $J$ = 2.7/12.3 Hz, 2H), 7.19–7.24 (m, 1H), 7.29 (td, $J$ = 1.5/7.6 Hz, 1H), 7.37 (dd, $J$ = 1.4/7.9 Hz, 1H), 7.61 (dd, $J$ = 1.7/7.9 Hz, 1H) ppm; $^{13}C$ NMR (125 MHz, $CD_2Cl_2$): $\delta$ = 36.4 (2C, $NHCH_2\underline{C}H_2C$), 42.4 (2C, $NH\underline{C}H_2CH_2C$), 72.6 ($CH_2\underline{C}$), 127.6 ($CC_{ar}C_{ar}H$-$\underline{C}_{ar}H$), 127.7 ($CC_{ar}\underline{C}_{ar}H$), 128.8 ($CC_{ar}C_{ar}HC_{ar}H\underline{C}_{ar}H$), 132.1 ($CC_{ar}C_{ar}\underline{C}_{ar}H$), 132.3 ($CC_{ar}\underline{C}_{ar}$), 144.5 ($C\underline{C}_{ar}C_{ar}$) ppm; M ($C_{11}H_{14}ClNO$) = 211.08 MS (CI, $CH_5^+$) *m/z* (%): 212.15 (38, $[M+H]^+$), 196.15 (32), 194.15 (100); HRMS (EI+): $M^+$ calc. for $C_{11}H_{14}ClNO$, 211.0758; found: 211.0772.

**5,5-Difluoro-1,3,7,9-tetramethyl-10-[3-(piperidin-1-yl)propyl]-5*H*-4 λ⁴,5 λ⁴-dipyrrolo[1,2-*c*:2′,1′-*f*][1,3,2]diazaborinin-4-ium-5-uide (8a)** According to **Method B**: Compound **15b** (136 mg, 295 µmol) and piperidine (**7a**) (73.0 mg, 885 µmol, 84.0 µL) in MeCN (2.5 mL). Flash-SC (*n*-heptane/EtOAc = 8:1, 10% $NEt_3$).

87 mg (80%); orange solid; mp 168–169 °C; DC: $R_f$ = (0.3); IR (KBr) $\nu_{max}$ 3432, 2933, 2848, 2802, 2757, 2360, 1546, 1506, 1475, 1442, 1409, 1369, 1338, 1303, 1278, 1201, 1160, 1116, 1101, 1060 $cm^{-1}$; $^1H$ NMR (400 MHz, $CD_2Cl_2$, TMS): $\delta$ = 1.42 (m, 2H), 1.50–1.58 (m, 4H), 1.70–1.81 (m, 2H), 2.40 (m, 6H), 2.45 (s, 6H), 2.46 (s, 6H), 2.95–3.03 (m, 2H), 6.09 (s, 2H) ppm;. $^{13}C$ NMR (100 MHz, $CD_2Cl_2$, TMS): $\delta$ = 14.6 (2C, $H_3\underline{C}CN$), 16.6 (2C, $H_3\underline{C}CCN$), 24.9 ($NCH_2CH_2\underline{C}H_2$), 26.5 (2C, $NCH_2\underline{C}H_2CH_2$), 27.1 ($C\underline{C}H_2$), 29.8 ($CCH_2\underline{C}H_2$), 55.4 (2C, $CH_2N\underline{C}H_2CH_2CH_2$), 59.6 ($CCH_2CH_2\underline{C}H_2N$), 121.9 (2C, $C\underline{C}HC$), 131.8 (2C, $CHC\underline{C}C$), 141.3 (2C, $H_3C\underline{C}CN$), 147.5 ($C\underline{C}C$), 154.0 (2C, $H_3C\underline{C}N$) ppm; $^{19}F$ NMR (470 MHz, $CD_2Cl_2$): $\delta$ = −146.2 to −146.8 (m) ppm; $^{11}B$ NMR (160 MHz, $CD_2Cl_2$): $\delta$ = −2.24 (t, $J$ = 33.0 Hz) ppm; M ($C_{21}H_{30}BF_2N_3$) = 373.3 MS (EI 70 eV) m/z (%): 373.4 ($M^+$, 22), 262.25 (51), 98.25 (100), 55.10 (55); HRMS (FAB, NBA): $[M+H]^+$ calc. for $C_{21}H_{31}BF_2N_3$, 374.2574; found: 374.2570 $(M+H)^+$.

**5,5-Difluor-1,3,7,9-tetramethyl-10-(3-morpholinopropyl)-5*H*-4 λ⁴,5 λ⁴-dipyrrolo[1,2-*c*:2',1'-*f*][1,3,2]diazaborinin-4-ium-5-uide (8b)** According to **GP-3 (Method A)**: Compound **15a** (100 mg, 308 µmol) and morpoline (**7b**) (37.6 mg, 432 µmol, 38.0 µL) as well as KI (143.4 mg, 864 µmol) and $K_2CO_3$ (132 mg, 956 µmol) in acetone (5.0 mL). Flash-SC (EtOAc/*n*-heptane 6:3, 10% $NEt_3$).

63 mg (54%); red solid; mp 143–144 °C; DC: $R_f$ = 0.4 (EtOAc/*n*-heptane = 6:3, 10% $NEt_3$); IR (KBr) $\nu_{max}$ 3434, 2919, 2852, 2802, 2360, 2341, 1548, 1506, 1473, 1409, 1367, 1340, 1305, 1201, 1162, 1156, 1079, 1058 $cm^{-1}$; $^1H$ NMR (500 MHz, DMSO-D6, TMS): $\delta$ = 1.63–1.74 (m, 2H), 2.42 (m, 18H), 2.93–3.03 (m, 2H), 3.55 (t, $J$ = 4.4 Hz, 4H), 6.23 (s, 2H) ppm; $^{13}C$ NMR (125 MHz, DMSO-D6, TMS): $\delta$ = 14.0 (2C, $NC\underline{C}H_3$), 15.8 (2C, $CC\underline{C}H_3$), 26.0 ($C\underline{C}H_2$), 28.5 ($CCH_2\underline{C}H_2$), 53.5 (2C, $N\underline{C}H_2CH_2O$), 58.2 ($CCH_2CH_2\underline{C}H_2N$), 66.1 (2C, $NCH_2\underline{C}H_2O$), 121.6 (2C, $C\underline{C}HC$), 130.7 (2C, $CHC\underline{C}C$) 140.7 (2C $CCH\underline{C}CC$), 146.7 ($NC\underline{C}CH_2$), 152.9 (2C, $N\underline{C}CH$) ppm; $^{19}F$ NMR (470 MHz, $CDCl_3$): $\delta$ = −143.1 to −143.4 (m) ppm; $^{11}B$ NMR (160 MHz, $CDCl_3$): $\delta$ = −1.82 (t, $J$ = 33.2 Hz) ppm; M ($C_{20}H_{28}BF_2N_3O$) = 375.23 MS (EI, 70 eV) m/z (%): 375.25 (22, $M^+$), 262.25 (93), 247.25 (30), 242.25 (42), 229.25 (11). HRMS (EI+): $M^+$ calc. for $C_{20}H_{28}BF_2N_3O$, 375.2288; found: 375.2295.

**5,5-Difluoro-10-[3-(3-hydroxypiperidin-1-yl)propyl]-1,3,7,9-tetramethyl-5*H*-4 λ⁴,5 λ⁴-dipyrrolo[1,2-*c*:2′,1′-*f*][1,3,2]diazaborinin-4-ium-5-uide (8c)** According to **GP-3 (Method B)**: Compound **15b** (136 mg, 295 µmol) and 3-hydroxypiperidine (**7c**) (90.0 mg, 885 µmol) in MeCN (2.5 mL). Flash-SC (EtOAc, 1% MeOH, 5% $NEt_3$).

93 mg (81%); orange solid; mp 171 °C; DC: $R_f$ = 0.2 (EtOAc, 1% MeOH, 5% $NEt_3$); IR (KBr) $\nu_{max}$ 3565, 3547, 3473, 3119, 2935, 2857, 2803, 2760, 1548, 1507, 1474, 1409, 1368, 1337, 1305, 1277, 1224, 1202, 1161, 1096, 1080, 1061, 1028 $cm^{-1}$: $^1H$ NMR (500 MHz, DMSO-D6, TMS) $\delta$ = 0.99–1.09 (m, 1H), 1.38 (dd, $J$ = 24.6/12.3 Hz, 1H), 1.55–1.89 (m, 6H), 2.40 (s, 8H), 2.43 (s, 6H), 2.69 (d, $J$ = 11.0 Hz, 1H), 2.86 (d, $J$ = 7.8 Hz, 1H), 2.97 (dd, $J$ = 5.7/11.6 Hz, 2H), 3.39–3.48 (m, 1H), 4.60 (d, $J$ = 4.1 Hz, 1H), 6.23 (s, 2H) ppm; $^{13}C$ NMR (125 MHz, DMSO-D6, TMS) $\delta$ = 14.0 (2C, $NC\underline{C}H_3$), 15.8 (2C, $NCC\underline{C}H_3$), 23.2 ($NCH_2\underline{C}H_2CH_2CH$), 26.1 ($C\underline{C}H_2$), 28.9 ($CCH_2\underline{C}H_2$), 33.3 ($NCH_2CH_2\underline{C}H_2CH$), 53.2 ($N\underline{C}H_2CH_2CH_2CH$), 57.9 ($CCH_2CH_2\underline{C}H_2$), 61.7 ($N\underline{C}H_2CH$), 66.0 ($NCH_2\underline{C}H$), 121.5 (2C, $C\underline{C}HC$), 130.7 (2C, $NC\underline{C}CH_2$), 140.7 (2C, $NC\underline{C}CH$), 146.9 ($NC\underline{C}CH_2$), 152.9 (2C, $N\underline{C}CH_3$) ppm; $^{19}F$ NMR

(470 MHz, DMSO-D6) $\delta = -143.1$ to $-144.7$ (m) ppm; $^{11}$B NMR (160 MHz, DMSO-D6) $\delta = -2.42$ (t, $J =$ 33.1 Hz) ppm; M ($C_{21}H_{30}BF_2N_3O$) = 389.25. MS (CI, $CH_5^+$) m/z (%): 390.25 (19, $[M+H]^+$), 370.25 (100); HRMS (EI+): $M^+$ calc. for $C_{21}H_{30}BF_2N_3O$, 389.2445; found: 389.2449; $C_{21}H_{30}BF_2N_3O$ (389.25): calc. C 64.79, H 7.77 N 10.79; found. C 64.63, H 7.69, N 10.63.

**1-[3-(5,5-Difluoro-1,3,7,9-tetramethyl-5*H*-4λ$^4$,5λ$^4$-dipyrrolo[1,2-*c*:2′,1′-*f*][1,3,2]diazaborin-in-10-yl)propyl]piperidin-4-ol (8d)** According to **GP-3 (Method B)**: Compound **15b** (136 mg, 295 µmol) and 4-hydroxypiperidine (**7d**) (90.0 mg, 885 µmol) in MeCN (2.5 mL). Flash-SC (EtOAc, 1% MeOH, 5% $NEt_3$).

94.0 mg (82%); orange solid; mp 159–161 °C; DC: $R_f = 0.28$ (EtOAc, 1% MeOH, 5% $NEt_3$); IR (KBr) $\nu_{max}$ 3579, 3444, 2940, 2805, 2805, 2358, 1635, 1546, 1506, 1475, 1409, 1369, 1340, 1305, 1203, 1162, 1078 cm$^{-1}$; $^1$H NMR (500 MHz, DMSO-D6, TMS): $\delta = 1.36$ (td, $J =$ 3.4/12.6 Hz, 2H), 1.61–1.73 (m, 4H), 2.03 (t, $J = 10.9$ Hz, 2H), 2.40 (s, 8H), 2.42 (s, 6H), 2.72 (d, $J = 10.3$ Hz, 2H), 2.92–3.05 (m, 2H), 3.42 (s, 1H), 4.55 (d, $J = 3.8$ Hz, 1H), 6.23 (s, 2H) ppm; $^{13}$C NMR (125 MHz, DMSO-D6, TMS): $\delta = 14.0$ (2C, $H_3\underline{C}CCN$), 15.7 (2C, $H_3\underline{C}CN$), 26.1 ($C\underline{C}H_2CH_2CH_2N$), 29.2 ($CCH_2\underline{C}H_2CH_2N$), 34.4 (2C, $NCH_2\underline{C}H_2CH$), 51.3 (2C, $N\underline{C}H_2CH_2CH$), 57.7 ($CCH_2CH_2\underline{C}H_2N$), 66.2 ($NCH_2CH_2\underline{C}H$), 121.5 (2C, $C\underline{C}HC$), 130.7 (2C, $CHC\underline{C}$), 140.7 (2C, $H_3C\underline{C}CN$), 146.9 ($C\underline{C}C$), 152.9 ($H_3C\underline{C}N$) ppm; $^{19}$F NMR (470 MHz, DMSO-D6): $\delta = -143.6$ to $-143.9$ (m) ppm; $^{11}$B NMR (160 MHz, DMSO-D6): $\delta = -2.3$ (t, $J = 33.0$) ppm; M ($C_{21}H_{30}BF_2N_3O$) = 389.25. HRMS (ESI+): $[M+H]^+$ calc. for $C_{21}H_{31}BF_2N_3O$, 390.2523; found: 390.2523 (100, $[M+H]^+$).

**5,5-Difluoro-1,3,7,9-tetramethyl-10-[3-(4-phenylpiperidin-1-yl)propyl]-5*H*-4 λ$^4$,5 λ$^4$-di-pyrrolo[1,2-*c*:2',1'-*f*][1,3,2]diazaborinine (8e)** According to **GP-3 (Method B)**: Compound **15b** (136 mg, 295 µmol) and 4-Phenylpiperidine (**7e**) (143 mg, 885 µmol) in MeCN (2.5 mL). Flash-SC (1. *n*-heptane/EtOAc 7:2, 10% $NEt_3$. 2. Gradient: *n*-heptane/EtOAc 7:2 → *n*-heptane/EtOAc 7:2, 10% $NEt_3$).

116 mg (88%); orange solid; mp 167–168 °C; DC: $R_f =$ 0.27; IR (KBr) $\nu_{max}$ 3424, 2933, 2901, 2821, 2766, 1548, 1533, 1508, 1473, 1409, 1369, 1341, 1331, 1307, 1270, 1255, 1228, 1202, 1156, 1129, 1106, 1079, 1026, 1012 cm$^{-1}$; $^1$H NMR (500 MHz, $CD_2Cl_2$, TMS): $\delta = 1.67$–$1.76$ (m, 2H), 1.77–1.84 (m, 4H), 2.09 (td, $J = 2.4/11.7$ Hz, 2H), 2.43–2.54 (m, 15H), 2.99–3.05 (m, 4H), 6.09 (s, 2H), 7.14–7.20 (m, 1H), 7.20–7.25 (m, 2H), 7.25–7.32 (m, 2H) ppm; $^{13}$C NMR (125 MHz, $CD_2Cl_2$, TMS): $\delta = 14.6$ (2C, $NC\underline{C}H_3$), 16.6 (2C, $NCC\underline{C}H_3$), 27.1 ($C\underline{C}H_2$), 30.0 ($CCH_2\underline{C}H_2$), 34.0 (2C, $CH\underline{C}H_2$), 43.0 ($\underline{C}HC_{ar}$), 55.1 (2C, $N\underline{C}H_2CH_2CH$), 59.2 ($CCH_2CH_2\underline{C}H_2N$), 121.9 (2C, $C\underline{C}HC$), 126.4 ($C_{ar}C_{ar}HC_{ar}H\underline{C}_{ar}H$), 127.2 (2C, $C_{ar}C_{ar}H\underline{C}_{ar}HC_{ar}H$), 128.7 (2C, $C_{ar}\underline{C}_{ar}HC_{ar}HC_{ar}H$), 131.9 (2C, $N\underline{C}CCH_3$), 141.2 (2C, $NC\underline{C}CH_2$), 147.1 ($\underline{C}_{ar}C_{ar}HC_{ar}HC_{ar}H$), 147.4 ($NC\underline{C}CH_2$), 154.1 (2C, $N\underline{C}CH_3$) ppm; $^{19}$F NMR (470 MHz, $CD_2Cl_2$): $\delta = -146.0$ to $-146.9$ (m) ppm; $^{11}$B NMR (160 MHz, $CD_2Cl_2$): $\delta = -2.29$ (t, $J = 33.0$ Hz) ppm; M ($C_{27}H_{34}BF_2N_3$) = 449.28; MS (CI, $CH_5^+$) m/z (%): 450.20 (19, $[M+H]^+$), 430.25 (100); HRMS (EI+): $M^+$ calc. for $C_{27}H_{34}BF_2N_3$, 449.2808; found: 449.2815. $C_{27}H_{34}BF_2N_3$ (449.28) calc. C 72.16, H 7.63, N 9.35; found: C 71.88, H 7.63, N 9.33.

**5,5-Difluor-1,3,7,9-tetramethyl-10-{3-[4-phenyl-5,6-dihydropyridin-1(2*H*)-yl]propyl}-5*H*-4 λ$^4$,5 λ$^4$-dipyrrolo[1,2-*c*:2′,1′-*f*][1,3,2]diazaborinin-4-ium-5-uid (8f)** According to **GP-3 (Method B)**: Compound **15b** (136 mg, 295 µmol) and 4-Phenyl-1,2,3,6-tetrahydropyridine (**7f**) (141 mg, 885 µmol) in MeCN (2.5 mL). Flash-SC (1. *n*-Heptan/EtOAc 7:2, 10% $NEt_3$; 2. Gradient *n*-heptane/EtOAc 7:2 → *n*-heptane/EtOAc 7:2, 10% $NEt_3$).

99 mg (75%); orange solid; mp 157–160 °C; DC: $R_f =$ 0.3 (*n*-heptane/EtOAc 7:2, 10% $NEt_3$); IR (KBr) $\nu_{max}$ 3425, 3080, 3056, 2950, 2923, 2867, 2824, 2768, 2732, 1654, 1638, 1596, 1549, 1534, 1509, 1473, 1444, 1407, 1365, 1345, 1307, 1276, 1203, 1160, 1136, 1113, 1100, 1079, 1058, 1027 cm$^{-1}$; $^1$H NMR (500 MHz, $CD_2Cl_2$, TMS): $\delta = 1.82$–$1.90$ (m, 2H,), 2.47 (s, 12H), 2.51–2.56 (m, 2H), 2.61 (t, $J = 7.1$ Hz, 2H), 2.71 (t, $J = 5.7$ Hz, 2H), 3.01–3.07 (m, 2H), 3.16 (dd, $J = 2.8/6.1$ Hz, 2H), 6.07–6.11 (m, 3H), 7.21–7.25 (m, 1H), 7.29–7.34 (m, 2H), 7.40 (dt, $J = 1.8/3.0$ Hz, 2H) ppm; $^{13}$C NMR (125 MHz, $CD_2Cl_2$, TMS): $\delta = 14.6$ (2C, $NC\underline{C}H_3$), 16.6 (2C, $NCC\underline{C}H_3$), 27.0 ($NCC\underline{C}H_2$), 28.5 ($CHC\underline{C}H_2$) 30.0 ($CCCH_2\underline{C}H_2$), 50.9 ($N\underline{C}H_2CH_2CCH$), 58.55 ($N\underline{C}H_2CHC$), 121.95 ($NCH_2\underline{C}HC$), 122.26 (2C, $C\underline{C}HC$) 125.17 (2C, $CC_{ar}\underline{C}_{ar}H$), 127.4 ($C_{ar}C_{ar}HC_{ar}H\underline{C}_{ar}H$), 128.7 (2C, $C_{ar}C_{ar}H$-$\underline{C}_{ar}HC_{ar}H$), 131.8 (2C, $NCCCH_2$), 135.3 ($\underline{C}C_{ar}$), 141.2 (2C, $NC\underline{C}CH_3$), 147.2 ($NC\underline{C}CH_2$), 154.1 (2C, $N\underline{C}CH_3$) ppm; $^{19}$F NMR (470 MHz, $CD_2Cl_2$): $\delta = -146.4$ to $-146.6$ (m) ppm; $^{11}$B NMR (160 MHz, $CD_2Cl_2$): $\delta = -2.32$ (t, $J = 33.0$ Hz) ppm; M ($C_{27}H_{34}BF_2N_3$) = 448.27; MS (CI, $CH_5^+$) m/z (%): 448.20 (56, $M^+$), 428.25 (100); HRMS (EI+): $M^+$ calc. for $C_{27}H_{32}BF_2N_3$, 447.2652; found: 447.2656.

**5,5-Difluoro-10-[3-(4-hydroxy-4-phenylpiperidin-1-yl)propyl]-1,3,7,9-tetramethyl-5*H*-4 λ$^4$,5 λ$^4$-dipyrrolo[1,2-*c*:2′,1′-*f*][1,3,2]diazaborinin-4-ium-5-uide (8g)** According to **GP-3 (Method B)**: Compound **15b** (136 mg, 295 µmol) and 4-hydroxy-4-Phenylpiperidine (**7g**) (153 mg, 885 µmol) in MeCN (2.5 mL). Flash-SC (*n*-heptane/EtOAc 5:4, 10% $NEt_3$).

119 mg (87%); orange solid; mp 189–192 °C; DC: $R_f$ = 0.27 (*n*-heptane/EtOAc 5:4, 10% $NEt_3$); IR (KBr) $\nu_{max}$ 3533, 3423, 2943, 2818, 1546, 1530, 1506, 1474, 1448, 1406, 1370, 1304, 1275, 1229, 1203, 1156, 1138, 1108, 1080 1044 $cm^{-1}$; $^1H$ NMR (500 MHz, $CD_2Cl_2$, TMS): $\delta$ = 1.71 (dq, $J$ = 2.66/13.74 Hz, 2H), 1.82 (m, 2H), 2.09 (td, $J$ = 4.5/13.2 Hz, 2H), 2.44–2.50 (m, 14H), 2.55 (t, $J$ = 7.0 Hz, 2H), 2.78 (d, $J$ = 11.2 Hz, 2H), 3.00–3.07 (m, 2H), 6.09 (s, 2H), 7.23–7.27 (m, 1H), 7.32–7.37 (m, 2H), 7.50 (dt, $J$ = 1.8/3.1 Hz, 2H) ppm; $^{13}C$ NMR (125 MHz, $CD_2Cl_2$, TMS): $\delta$ = 14.6 (2C, NCC$\underline{C}H_3$), 16.7 (2C, NC$\underline{C}H_3$), 27.1 (C$\underline{C}H_2CH_2CH_2$), 30.0 ($CCH_2\underline{C}H_2CH_2$), 39.0 (2C, $NCH_2\underline{C}H_2C$), 50.3 (2C, N$\underline{C}H_2CH_2C$), 59.1 ($CCH_2CH_2\underline{C}H_2N$), 71.5 ($\underline{C}C_{ar}$), 121.9 (2C, C$\underline{C}$HC), 125.0 (2C, $C_{ar}\underline{C}_{ar}HC_{ar}HC_{ar}H$), 127.3 ($C_{ar}C_{ar}HC_{ar}H\underline{C}_{ar}H$), 128.6 (2C, $C_{ar}C_{ar}H\underline{C}_{ar}HC_{ar}H$), 131.9 (2C, N$\underline{C}$CCH), 141.2 (2C, NC$\underline{C}$CH), 147.4 (NC$\underline{C}CH_2$), 149.1 ($\underline{C}_{ar}$), 154.1 (2C, N$\underline{C}$CH) ppm; $^{19}F$ NMR (470 MHz, $CD_2Cl_2$): $\delta$ = −146.0 to −146.9) (m) ppm; $^{11}B$ NMR (160 MHz, $CD_2Cl_2$): $\delta$ = −2.28 (t, $J$ = 33.0 Hz) ppm; M ($C_{27}H_{34}BF_2N_3O$) = 465.28 MS (CI, $CH_5^+$) m/z (%): 466.20 (41, $[M+H]^+$), 448.20 (51), 446.30 (100) 428.25 (54); HRMS (EI+): $M^+$ calc. for $C_{27}H_{34}BF_2N_3O$, 465.2758; found: 465.2762; $C_{27}H_{34}BF_2N_3O$ (449.28) calc. C 69.68, H 7.36, N 9.03; found: C 69.55, H 7.45, N 8.97.

**1-[3-(5,5-Difluoro-1,3,7,9-tetramethyl-5*H*-4λ$^4$,5λ$^4$-dipyrrolo [1,2-*c*:2′,1′-*f*][1,3,2] diazaborinin-10-yl)propyl]-4-(2-methoxyphenyl)piperidin-4-ol (8h)** According to **GP-3 (Method A)**: Compound **15a** (100 mg, 308 µmol) and 4-(2-methoxyphenyl)piperidin-4-ol (**7h**) (89.0 mg, 432 µmol, 38.0 µL), as well as KI (143.4 mg, 864 µmol) and $K_2CO_3$ (132.1 mg, 956 µmol) in acetone (5.0 mL). Flash-SC (EtOAc/*n*-heptane 6:3, 10% $NEt_3$).

67 mg (44%); orange solid; mp 90 °C; DC: $R_f$ = 0.2 (EtOAc/*n*-heptane 6:3, 10% $NEt_3$); IR (KBr) $\nu_{max}$ 3441, 2924, 2816, 2768, 1549, 1510, 1472, 1409, 1372, 1307, 1230, 1202, 1160, 1107, 1080, 1041, 1026 $cm^{-1}$; $^1H$ NMR (500 MHz, DMSO-D6, TMS): $\delta$ = 1.38 (d, $J$ = 11.4 Hz, 2H), 1.65–1.75 (m, 2H), 2.41 (s, 8H), 2.44–2.49 (m, 10H), 2.66 (d, $J$ = 9.8 Hz, 2H,), 3.02–3.10 (m, 2H), 3.80 (s, 3H), 4.62 (s, 1H), 6.24 (s, 2H), 6.89–6.95 (m, 1H), 6.97 (d, $J$ = 8.2 Hz, 1H), 7.18–7.23 (m, 1H), 7.58 (dd, $J$ = 1.7/7.7 Hz, 1H) ppm; $^{13}C$ NMR (100 MHz, DMSO-D6, TMS): $\delta$ = 14.0 (2C, NC$\underline{C}H_3$), 15.8 (2C, NCC$\underline{C}H_3$), 26.3 (C$\underline{C}H_2CH_2CH_2N$), 29.2 ($CCH_2\underline{C}H_2CH_2N$), 34.6 (2C, $NCH_2\underline{C}H_2C$), 49.6 (2C, N$\underline{C}H_2CH_2C$), 55.1 ($H_3\underline{C}O$), 58.1 ($CCH_2CH_2\underline{C}H_2N$), 70.0 ($\underline{C}OH$), 115.6 ($CC_{ar}\underline{C}_{ar}H$), 120.0 ($CC_{ar}C_{ar}\underline{C}_{ar}H$), 121.5 (2C, C$\underline{C}$HC), 126.4 ($C_{ar}C_{ar}C_{ar}H\underline{C}_{ar}H$), 127.7 ($C_{ar}C_{ar}C_{ar}HC_{ar}H\underline{C}_{ar}H$), 130.7 (2C, N$\underline{C}$CCH), 136.7 ($C\underline{C}_{ar}C_{ar}$), 140.8 (2C, NC$\underline{C}$CH), 147.1 (NC$\underline{C}CH_2$), 152.8 (2C, N$\underline{C}$CH), 156.2 ($CC_{ar}\underline{C}_{ar}O$) ppm; $^{19}F$ NMR (470 MHz, DMSO-D6): $\delta$ = −144.0 to −143.6 (m) ppm; $^{11}B$ NMR (160 MHz, DMSO-D6): $\delta$ = −2.28 (t, $J$ = 32.6 Hz) ppm; M ($C_{28}H_{36}BF_2N_3O_2$) = MS (CI, $CH_5^+$) m/z (%): 496.40 (1, $[M+H]^+$), 83.00 (100), 85.00 (60); HRMS (EI+): $M^+$ calc. for $C_{28}H_{36}BF_2N_3O_2$, 495.2863; found: 495.2869.

**1-[3-(5,5-Difluoro-1,3,7,9-tetramethyl-5*H*-4λ$^4$,5λ$^4$-dipyrrolo [1,2-*c*:2′,1′-*f*][1,3,2]diaza-borinin-10-yl)propyl]-4-(4-methoxyphenyl)piperidin-4-ol (8i)** According to **GP-3 (Method A)**: Compound **15a** (100 mg, 308 µmol) and 4-(4-methoxyphenyl)piperidin-4-ol (**7i**) (89 mg, 432 µmol, 38.0 µL), as well as KI (143.4 mg, 864 µmol) and $K_2CO_3$ (132 mg, 956 µmol) in acetone (5.0 mL). Flash-SC (EtOAc/*n*-heptane 5:4, 10% $NEt_3$).

107 mg (70%); orange solid; mp 174–175; DC: $R_f$ = 0.36 (EtOAc/*n*-heptane 5:4, 10% $NEt_3$); IR (KBr) $\nu_{max}$ 3434, 2921, 2813, 1610, 1550, 1509, 1471, 1407, 1371, 1305, 1249, 1224, 1201, 1159, 1106, 1079, 1031 $cm^{-1}$; $^1H$ NMR (500 MHz, DMSO-D6, TMS): $\delta$ = 1.57 (d, $J$ = 12.2 Hz, 2H), 1.72 (s, 2H), 1.86 (td, $J$ = 4.1/12.8 Hz, 2H), 2.44 (m, 16H), 2.66 (d, $J$ = 10.5 Hz, 2H), 2.96–3.08 (m, 2H), 3.73 (s, 3H), 4.68 (s, 1H), 6.24 (s, 2H), 6.87 (d, $J$ = 8.8 Hz, 2H), 7.37 (d, $J$ = 8.8 Hz, 2H) ppm; $^{13}C$ NMR (125 MHz, DMSO-D6, TMS): $\delta$ = 14.0 (2C, NCC$\underline{C}H_3$), 15.8 (2C, NC$\underline{C}H_3$), 26.2 (C$\underline{C}H_2CH_2CH_2N$), 29.1 ($CCH_2\underline{C}H_2CH_2N$), 38.1 (2C, $NCH_2\underline{C}H_2C$), 49.6 (2C, N$\underline{C}H_2CH_2C$), 54.9 ($H_3\underline{C}O$), 58.0 ($CCH_2CH_2\underline{C}H_2N$), 69.1 ($\underline{C}OH$), 113.0 (2C, $C_{ar}C_{ar}HC_{ar}H\underline{C}_{ar}HC_{ar}O$), 121.5 (2C, C$\underline{C}$HC), 125.8 (2C, $C_{ar}\underline{C}_{ar}HC_{ar}HC_{ar}HC_{ar}O$), 130.7 (2C, N$\underline{C}$CCH), 140.7 ($CH_2C\underline{C}_{ar}$), 142.1 (2C, NC$\underline{C}$CH), 147.0 (NC$\underline{C}CH_2$), 152.9 (2C, N$\underline{C}$CH), 157.6 ($\underline{C}_{ar}O$) ppm; $^{19}F$ NMR (470 MHz, DMSO-D6): $\delta$ = −144.0 to −143.6 (m) ppm; $^{11}B$ NMR (160 MHz, DMSO-D6): $\delta$ = −2.33 (t, $J$ = 32.6 Hz) ppm; M ($C_{28}H_{36}BF_2N_3O_2$) = 495.28 MS (CI, $CH_5^+$) m/z (%): 496.15 (1, $[M+H]^+$), 140.20 (100); HRMS (EI+): $M^+$ calc. for $C_{28}H_{36}BF_2N_3O_2$, 495.2863; found: 495.2878; $C_{28}H_{36}BF_2N_3O_2$ (495.28) calc. C 67.88, H 7.32, N 8.48; found: C 67.65, H 7.44, N 8.41.

**4-(2-Chlorophenyl)-1-[3-(5,5-difluoro-1,3,7,9-tetramethyl-5*H*-4λ$^4$,5λ$^4$-dipyrrolo[1,2-*c*:2',1'-*f*][1,3,2]diazaborinin-10-yl) propyl]piperidin-4-ol (8j)** According to **GP-3 (Method B)**: Compound **15b** (136 mg, 295 µmol) and 4-(2-chlorophenyl)-4-hydroxypiperidine (**7j**) (187 mg, 885 µmol) in MeCN (2.5 mL). Flash-SC (*n*-heptane/EtOAc 4:5, 10% $NEt_3$).

110 mg (75%); orange solid; mp 212 °C; DC: $R_f$ = 0.2 (*n*-heptane/EtOAc 4:5, 10% $NEt_3$); IR (KBr) $\nu_{max}$ 3561, 3447, 2966, 2939, 2925, 2819, 2865, 2771, 1544, 1507, 1469, 1434, 1408, 1374, 1304, 1274, 128, 1200, 1158, 1105, 1080, 1058, 1038 $cm^{-1}$; $^1H$ NMR (500 MHz, $TCl_4$, TMS): $\delta$ = 1.82 (p, $J$ = 6.4/6.8 Hz, 2H), 2.02 (d, $J$ = 12.4 Hz, 2H), 2.31 (td, $J$ = 4.0/13.0 Hz, 2H), 2.49 (s, 6H), 2.54 (s, 6H), 2.52–2.57 (m, 4H), 2.74–2.83 (m, 3H), 2.95–3.04 (m, 2H),

6.08 (s, 2H), 7.23 (td, $J = 7.6/1.6$ Hz, 1H), 7.29 (td, $J = 1.4/7.6$ Hz, 1H), 7.38 (dd, $J = 1.4/7.9$ Hz, 1H), 7.54 (dd, $J = 1.5/7.9$ Hz, 1H) ppm; $^{13}$C NMR (100 MHz, $TCl_4$, TMS): $\delta = 14.5$ (2C, NC$\underline{C}H_3$), 16.4 (2C, NCC$\underline{C}H_3$), 26.0 (C$\underline{C}H_2CH_2CH_2N$), 28.3 (CCH$_2\underline{C}H_2CH_2N$), 34.5 (2C, NCH$_2\underline{C}H_2C$), 48.9 (2C, N$\underline{C}H_2CH_2C$), 57.6 (CCH$_2CH_2\underline{C}H_2N$), 71.1 (COH), 121.8 (2C, C$\underline{C}$HC), 127.0 (2C, CC$_{ar}\underline{C}_{ar}HC_{ar}H$), 127.3 (C$\underline{C}_{ar}C_{ar}$), 128.9 (CC$_{ar}C_{ar}HC_{ar}H\underline{C}_{ar}H$), 131.2 (2C, N$\underline{C}$CCH$_2$), 131.6 (CC$_{ar}C_{ar}\underline{C}_{ar}H$), 140.5 (2C, NC$\underline{C}$CH), 142.2 (C$\underline{C}_{ar}$), 145.5 (NC$\underline{C}$CH$_2$), 154.1 (2C, N$\underline{C}$CH) ppm; $^{19}$F NMR (470 MHz, $TCl_4$): $\delta = -144.7$ to $-146.3$ (m) ppm; $^{11}$B NMR (160 MHz): $\delta = -0.4$ (t, $J = 33.3$ Hz) ppm; M ($C_{27}H_{33}BClF_2N_3O$) = 499.23 MS (ESI+) m/z (%): 500.24 (100, $[M+H]^+$); HRMS (EI+): $[M+H]^+$ calc. for $C_{27}H_{34}BClF_2N_3O$, 500.2446; found: 500.2451 $[M+H]^+$.

**10-{3-[4-(4-Chlorophenyl)-4-hydroxypiperidin-1-yl]propyl}-5,5-difluoro-1,3,7,9-tetramethyl-5*H*-4 λ$^4$,5 λ$^4$-dipyrrolo[1,2-*c*:2',1'-*f*][1,3,2]diazaborinin-4-ium-5-uide (8k)** According to **GP-3 (Method B)**: Compound **15b** (136 mg, 295 µmol) and 4-(4-Chlorophenyl)-4-hydroxypiperidine (**7k**) (187 mg, 885 µmol) in MeCN (2.5 mL). Flash-SC (*n*-heptane/EtOAc 4:5, 10% $NEt_3$).

129 mg (88%); orange solid; mp 189–192 °C; DC: $R_f = 0.29$ (*n*-heptane/EtOAc 4:5, 10% $NEt_3$); IR (KBr) $\nu_{max}$ 3545, 3425, 2942, 2915, 2816, 1548, 1508, 1475, 1406, 1372, 1341, 1333, 1304, 1278, 1228, 1203, 1156, 1137, 1108, 1092, 1043, 1011 cm$^{-1}$; $^1$H NMR (500 MHz, $CD_2Cl_2$, TMS): $\delta = 1.69$ (d, $J = 12.0$ Hz, 2H), 1.77–1.85 (m, 2H), 2.05 (td, $J = 4.5/13.4$ Hz, 2H), 2.41–2.50 (m, 14H), 2.55 (t, $J = 7.0$ Hz, 2H), 2.78 (d, $J = 11.6$ Hz, 2H), 3.01–3.07 (m, 2H), 6.10 (s, 2H), 7.30–7.34 (m, 2H), 7.45 (d, $J = 8.8$ Hz, 2H) ppm; $^{13}$C NMR (125 MHz, $CD_2Cl_2$, TMS): $\delta = 14.6$ (2C, NCC$\underline{C}H_3$), 16.7 (2C, NC$\underline{C}H_3$), 27.1 (C$\underline{C}H_2CH_2CH_2N$), 29.9 (CCH$_2\underline{C}H_2CH_2N$), 39.0 (2C, NCH$_2\underline{C}H_2C$), 50.2 (2C, N$\underline{C}H_2CH_2C$), 59.0 (CCH$_2CH_2\underline{C}H_2N$), 71.3 (C$\underline{O}$H), 121.9 (2C, C$\underline{C}$HC), 126.7 (2C, C$_{ar}C_{ar}HC_{ar}H$-$\underline{C}_{ar}HC_{ar}$Cl), 128.6 (2C, C$_{ar}\underline{C}_{ar}HC_{ar}HC_{ar}HC_{ar}$Cl), 131.8 (2C, N$\underline{C}$CCH), 132.9 (CH$_2\underline{C}C_{ar}$), 141.2 (2C, NC$\underline{C}$CH), 147.3 (NC$\underline{C}$CH$_2$), 147.8 ($\underline{C}_{ar}$Cl), 154.1 (2C, N$\underline{C}$CH) ppm; $^{19}$F NMR (470 MHz, $CD_2Cl_2$): $\delta = -146.1$ to $-146.8$ (m) ppm; $^{11}$B NMR (160 MHz, $CD_2Cl_2$): $\delta = -2.30$ (t, $J = 33.0$ Hz) ppm; M ($C_{27}H_{33}BClF_2N_3O$) = 499.23 MS (CI, $CH_5^+$) m/z (%): 500.30 (26, $[M+H]^+$), 480.20 (100), 482.20 (70), 462.20 (42); HRMS (EI+): $M^+$ calc. for $C_{27}H_{33}BClF_2N_3O$, 499.2368; found: 499.2374; $C_{27}H_{33}BClF_2N_3O$ (499.23) calc. C 64.88, H 6.65, N 8.41; found: C 64.66, H 6.71, N 8.34.

**10-{3-[3-(Ethoxycarbonyl)piperidine-1-yl]butyl}-5,5-difluoro-1,3,7,9-tetramethyl-5*H*-4 λ$^4$,5 λ$^4$-dipyrrolo[1,2-*c*:2',1'-*f*][1,3,2]diazaborinin-4-ium-5-uide (8l)** According to **GP-3 (Method B)**: Compound **15b** (815 mg, 1.77 mmol) and ethyl piperidine-3-carboxylate (**7l**) (862 mg, 5.31 mmol, 850.0 µL) in MeCN (15.0 mL). Flash-SC (1. *n*-heptane/EtOAc 8:1, 10% $NEt_3$, 2. Gradient: *n*-heptane/EtOAc 8:1 → *n*-heptane/EtOAc 8:1, 10% $NEt_3$).

626 mg (79%); orange solid; mp 120 °C; DC: $R_f = 0.2$ (*n*-heptane/EtOAc 8:1, 10% $NEt_3$); IR (KBr) $\nu_{max}$ 3385, 2936, 2807, 1360, 2342, 1729, 1549, 1510, 1474, 1409, 1370, 1339, 1307, 1224, 1200, 1158, 1079, 1028, 985 cm$^{-1}$; $^1$H NMR (500 MHz, $CD_2Cl_2$, TMS): $\delta = 1.22$ (t, $J = 7.1$ Hz, 3H), 1.43 (dd, $J = 3.0/11.5$ Hz, 1H), 1.49–1.61 (m, 1H), 1.67–1.76 (m, 1H), 1.74–1.83 (m, 1H), 1.90 (d, $J = 12.5$, 1H), 2.05 (t, $J = 10.5$ Hz, 2H), 2.20 (t, $J = 10$, 1H), 2.44 (s, 6H), 2.46 (s, 6H), 2.48–2.56 (m, 3H), 2.72–2.80 (m, 1H), 2.97–3.03 (m, 3H), 4.09 (q, $J = 7.1$ Hz, 2H), 6.09 (s, 2H) ppm; $^{13}$C NMR (125 MHz, $CD_2Cl_2$, TMS): $\delta = 14.4$ (CH$_2\underline{C}H_3$), 14.6 (2C, NCC$\underline{C}H_3$), 16.7 (2C, NC$\underline{C}H_3$), 24.9 (NCH$_2\underline{C}H_2CH_2CHCH_2$), 27.0 (C$\underline{C}H_2CH_2CH_2N$), 27.3 (NCH$_2CH_2\underline{C}H_2CHCH_2$), 29.7 (CCH$_2CH_2\underline{C}H_2N$), 42.3 (NCH$_2CH_2CH_2\underline{C}HCH_2$), 54.4 (N$\underline{C}H_2CH_2CH_2CHCH_2$), 56.4 (NCHCH$_2CH_2CH\underline{C}H_2$), 59.0 (CCH$_2\underline{C}H_2CH_2N$), 60.6 (O$\underline{C}H_2CH_3$), 121.9, (2C, C$\underline{C}$HC), 131.8 (NC$\underline{C}$CH$_2$), 141.2 (2C, NC$\underline{C}$CH), 147.2 (2C, NC$\underline{C}$CH$_2$), 154.1 (2C, N$\underline{C}$CH), 174.2 ($\underline{C}$O) ppm; $^{19}$F NMR (500 MHz, $CD_2Cl_2$): $\delta = -146.3$ to $-146.7$ (m) ppm; $^{11}$B NMR (160 MHz, $CD_2Cl_2$): $\delta = -2.06$ (t, $J = 33.0$ Hz) ppm; M ($C_{24}H_{34}BF_2N_3O_2$) = 445.27; MS (CI, $CH_5^+$) m/z (%): 446 (18, $[M+H]^+$), 426 (100); HRMS (ESI+): [M+H]+calc. for $C_{24}H_{35}BF_2N_3O_2$, 446.2785; found: 446.2781.

**10-[3-(3-Carboxypiperidin-1-yl)propyl]-5,5-difluoro-1,3,7,9-tetramethyl-5*H*-4 λ$^4$,5 λ$^4$-dipyrrolo[1,2-*c*:2',1'-*f*][1,3,2]diazaborinin-4-ium-5-uide (8m)** According to **GP-2**: Compound **8l** (624 mg, 1.40 mmol) in 20.0 mL solvent mixture ($CH_2CL_2$/MeOH, 2:1) and LiOH (83.80 mg, 3.54 mmol) solved in $H_2O$ (3.5 mL). The reaction mixture was stirred for 6 d. The reaction mixture was diluted with $CH_2Cl_2$ and extracted three times with NaOH (0.1 M). Further work up according to general procedure.

496 mg (85%); orange solid; mp 140 °C (dec); IR (KBr) $\nu_{max}$ 3431, 1934, 1718, 1629, 1550, 1511, 1474, 1409, 1372, 1308, 1224, 1200, 1159, 1080, 1026 cm$^{-1}$; $^1$H NMR (400 MHz, $C_2D_2Cl_4$, 80 °C, TMS): $\delta = 1.55$–1.98 (m, 6H), 2.27 (td, $J = 2.7/10.9$ Hz, 1H), 2.45 (m, 13H), 2.56–2.70 (m, 3H), 2.84–3.04 (m, 4H), 6.07 (s, 2H) ppm; $^{13}$C NMR (100 MHz, $C_2D_2Cl_4$, 80 °C): $\delta = 14.7$ (2C, NC$\underline{C}H_3$), 16.5 (2C, CC$\underline{C}H_3$), 22.4 (NCH$_2\underline{C}H_2CH_2CHCH_2$), 26.2 (CH$_2\underline{C}H_2CHCH_2$), 26.6 (CCH$_2\underline{C}H_2$), 28.4 (C$\underline{C}H_2$), 40.5 (C$\underline{C}$HCO), 53.3 (N$\underline{C}H_2CH_2CH_2CHCH_2$), 55.5 (N$\underline{C}H_2$CH), 57.9 ($\underline{C}H_2$NCH$_2$CH), 122.2 (2C, C$\underline{C}$HC), 131.6 (2C, C$\underline{C}$CH$_3$), 140.3 (2C, N$\underline{C}$CCH$_2$), 144.9 (NC$\underline{C}$CH$_2$), 154.7 (2C, N$\underline{C}$CH$_3$), 175.2 ($\underline{C}$O) ppm; $^{19}$F NMR (475 MHz, $CD_2Cl_2$): $\delta = -146.5$ to $-146.0$ (m) ppm; M ($C_{22}H_{30}BF_2N_3O_2$) = 417.24. MS (FAB$^+$, NBA) m/z (%):

418.6 ([M+H]$^+$); HRMS (FAB$^+$, NBA): [M+H]$^+$ calc. for $C_{22}H_{31}BF_2N_3O_2$, 418.2472; found: 418.2455.

**5,5-Difluoro-1,3,7,9-tetramethyl-10-[4-(piperidin-1-yl) butyl]-5*H*-4 λ$^4$,5 λ$^4$-dipyrrolo[1,2-*c*:2',1'-*f*][1,3,2]diazaborinin-4-ium-5-uide (9a)** According to **GP-3 (Method D)**: Compound **16** (200 mg, 590 µmol) and piperidine (**7a**) (70.3 mg, 826 µmol, 82.0 µL) as well as KI (246 mg, 1.48 mmol) and $K_2CO_3$ (245 mg, 1.77 mmol) in MeCN (5.0 mL). Flash-SC (Gradient $CH_2Cl_2$ → *n*-heptane/EtOAc 8:1, 10% $NEt_3$).

195 mg (86%); orange solid; mp 182–184 °C; DC: $R_f$ = 0.24 (*n*-heptane/EtOAc = 9:1, 10% NEt); IR (KBr) $\nu_{max}$ 3427, 2940, 2796, 2762, 1547, 1534, 1507, 1473, 1443, 1409, 1368, 1338, 1305, 1267, 1253, 1224, 1202, 1161, 1134, 1099, 1060, 1025, 983 cm$^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$, TMS): $\delta$ = 1.39–1.48 (m, 2H) 1.53–1.75 (m, 8H), 2.29–2.46 (m, 12H), 2.51 (s, 6H), 2.91–2.99 (m, 2H), 6.04 (s, 2H) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$, TMS): $\delta$ = 14.5 (2C, NCC$\underline{C}$H$_3$), 16.4 (2C, NC$\underline{C}$H$_3$), 24.5 (NCH$_2$CH$_2$$\underline{C}$H$_2$CH$_2$CH$_2$), 26.0 (2C, NCH$_2$ $\underline{C}$H$_2$CH$_2$*C*H$_2$CH$_2$), 27.6 (CCH$_2$CH$_2$$\underline{C}$H$_2$CH$_2$N), 28.2 (C$\underline{C}$H$_2$), 29.7 (CCH$_2$$\underline{C}$H$_2$), 54.6, (2C, N$\underline{C}$H$_2$CH$_2$CH$_2$CH$_2$ *C*H$_2$), 58.6 (CCH$_2$CH$_2$CH$_2$$\underline{C}$H$_2$N), 121.6 (2C, C$\underline{C}$HC), 131.4 (2C, N$\underline{C}$CCH$_2$), 140.4 (2C, NC$\underline{C}$CH), 146.4 (NC$\underline{C}$CH$_2$), 153.8 (2C, N$\underline{C}$CH$_3$) ppm; $^{19}$F NMR (500 MHz, $CDCl_3$,): $\delta$ = −146.21 to −146.90 (m) ppm;. $^{11}$B (160 MHz, $CDCl_3$): $\delta$ = −2.11 (t, $J$ = 33.1 Hz) ppm; M ($C_{22}H_{32}BF_2N_3$) = 387.27 MS (CI, $CH_5^+$) m/z (%): 388 (37, [M+H]$^+$), 368 (100); HRMS (EI+): M$^+$ calc. for $C_{22}H_{32}BF_2N_3$, 387.2652; found: 387.2660.

**5,5-Difluor-1,3,7,9-tetramethyl-10-(4-morpholinobutyl)-5*H*-4 λ$^4$,5 λ$^4$-dipyrrolo[1,2-*c*:2',1'-*f*][1,3,2]diazaborinin-4-ium-5-uide (9b)** According to **GP-3 (Method D)**: Compound **16** (200 mg, 590 µmol) and morpholine (**7b**) (72.0 mg, 826 µmol) as well as KI (246 mg, 1.48 mmol) and $K_2CO_3$ (245 mg, 1.77 mmol) in MeCN (5.0 mL). Flash-SC (*n*-heptan/EtOAc 6:3, 10% $NEt_3$).

179 mg (78%); orange solid; mp 172–173 °C; DC: $R_f$ = 0.26 (*n*-heptane/EtOAc 6:3, 10% $NEt_3$); IR (KBr) $\nu_{max}$ 3449, 2963, 2944, 2918, 1886, 1855, 1818, 1796, 1766, 2367, 2344, 1734, 1645, 1547, 1507, 1474, 1457, 1408, 1366, 1338, 1305, 1283, 1260, 1201, 1161, 1120, 1096, 1077, 1057, 1206 cm$^{-1}$; $^1$H NMR (400 MHz, $CD_2Cl_2$, TMS): $\delta$ = 1.58–1.78 (m, 4H), 2.33–2.41 (m, 6H), 2.44 (s, 6H), 2.46 (s, 6H), 2.92–3.02 (m, 2H), 3.64 (t, $J$ = 4.6 Hz, 4H), 6.09 (s, 2H) ppm; $^{13}$C NMR (125 MHz, $CD_2Cl_2$, TMS): $\delta$ = 14.6 (2C, H$_3$$\underline{C}$CC), 16.6 (2C, H$_3$$\underline{C}$CN), 27.2, (CCH$_2$CH$_2$$\underline{C}$H$_2$CH$_2$N), 28.5 (C$\underline{C}$H$_2$CH$_2$*C*H$_2$), 29.6 (CCH$_2$*C*H$_2$$\underline{C}$H$_2$CH$_2$N), 54.1 (2C, N$\underline{C}$H$_2$CH$_2$O) 58.2 (CCH$_2$CH$_2$CH$_2$$\underline{C}$H$_2$N), 67.3 (2C, NCH$_2$$\underline{C}$H$_2$O), 121.9 (2C, $\underline{C}$H), 131.8 (2C, C$\underline{C}$C), 141.2 (2C, H$_3$C$\underline{C}$CC), 147.2 (CH$_2$$\underline{C}$C), 154.1 (2C, H$_3$C$\underline{C}$N) ppm; $^{19}$F NMR (470 MHz, $CDCl_3$): $\delta$ = −146.3 to −146.7 (m) ppm; $^{11}$B NMR (160 MHz, $CDCl_3$): $\delta$ = −2.2 (t, $J$ = 33.0 Hz) ppm; M ($C_{21}H_{30}BF_2N_3O$) = 389.25 MS (EI, 70 eV) m/z (%): 389.40 (33, M$^+$), 369.40 (33), 326.25 (19), 229.25 (27), 140.25 (19), 126.25 (49) 100.25 (100); HRMS (EI+): M$^+$ calc. for $C_{21}H_{30}BF_2N_3O$, 389.2445; found: 389.2456; $C_{21}H_{30}BF_2N_3O$ (389.25): calc. C 64.79, H 7.77, N 10.79; gef. C 64.74, H 7.91, N 10.67.

**5,5-Difluoro-10-[4-(3-hydroxypiperidin-1-yl)butyl]-1,3,7,9-tetramethyl-5*H*-4 λ$^4$,5 λ$^4$-dipyrrolo[1,2-*c*:2',1'-*f*][1,3,2]diazaborinin-4-ium-5-uide (9c)** According to **GP-3 (Method D)**: Compound **16** (200 mg, 590 µmol) and 3-hydroxypiperidine (**7c**) (84.0 mg, 826 µmol) as well as KI (246 mg, 1.48 mmol) and $K_2CO_3$ (245 mg, 1.77 mmol) in MeCN (5.0 mL). Flash-SC (n-heptane/EtOAc 8:1, 10% $NEt_3$). The product was dissolved in EtOAc and extracted three times with buffer (pH = 2). The combined aqueous phases were mixed with $CHCl_3$ cooled to 0 °C and the pH was adjusted to pH = 9 by adding buffer (pH = 10). The aqueous layer was extracted with $CHCl_3$, dried over $MgSO_4$, filtered, and the solvent was removed.

96 mg (81%); orange solid; mp 169 °C; DC: $R_f$ = 0.37 (*n*-heptane/EtOAc (8:1, 10% $NEt_3$); IR (KBr) $\nu_{max}$ 3444, 2937, 2865, 2803, 2362, 2343, 1718, 1636, 1549, 1506, 1474, 1409, 1368, 1305, 1263, 1224, 1162, 10993 1079, 1059, 1027 cm$^{-1}$; $^1$H NMR (500 MHz, DMSO-D6, TMS): $\delta$ = 0.98–1.08 (m, 1H), 1.30–1.41 (m, 1H), 1.54–1.66 (m, 6H), 1.70–1.82 (m, 2H), 2.26–2.37 (m, 2H), 2.40 (s, 6H), 2.43 (s, 6H), 2.64 (d, $J$ = 10.1 Hz, 1H), 2.82 (d, $J$ = 10.4 Hz, 1H), 2.90–2.98 (m, 2H), 3.37–3.45 (m, 1H), 4.58 (d, $J$ = 5.0 Hz, 1H), 6.23 (s, 2H) ppm; $^{13}$C NMR (125 MHz, DMSO-D6, TMS): $\delta$ = 14.0 (2C, H$_3$$\underline{C}$CN), 15.7 (2C, H$_3$$\underline{C}$CC), 23.1 (N$\underline{C}$H$_2$CH), 26.5 (CCH$_2$$\underline{C}$H$_2$CH$_2$CH$_2$N), 27.3 (C$\underline{C}$H$_2$CH$_2$ CH$_2$CH$_2$N), 28.7 (CCH$_2$CH$_2$$\underline{C}$H$_2$CH$_2$N), 33.3 (NCH$_2$$\underline{C}$H$_2$ CH$_2$CH), 52.9 (N$\underline{C}$H$_2$CH$_2$CH$_2$CH), 56.5 (CCH$_2$CH$_2$CH$_2$ $\underline{C}$H$_2$N), 61.2 (NCH$_2$CH$_2$$\underline{C}$H$_2$CH), 66.0 (NCH$_2$$\underline{C}$H), 121.5 (2C, C$\underline{C}$HC), 130.6 (2C, C$\underline{C}$C), 140.8 (2C, H$_3$C$\underline{C}$C), 146.8 (NC$\underline{C}$CH$_2$), 152.9 (2C, H$_3$C$\underline{C}$N) ppm; $^{19}$F NMR: (470 MHz, DMSO-D6): $\delta$ = −143.4 to −144.2 ppm; $^{11}$B NMR: (160 MHz, DMSO-D6): $\delta$ = −2.2 (t, $J$ = 32.9 Hz) ppm; M ($C_{22}H_{32}BF_2N_3O$) = 403.26 MS (EI, 70 eV) m/z (%): 403.25 (31, M$^+$), 383.25 (21), 114.25 (100); HRMS (EI+): M$^+$ calc. for $C_{22}H_{32}BF_2N_3O$, 403.2601; found: 403.2597.

**5,5-Difluoro-10-[4-(4-hydroxypiperidin-1-yl)butyl]-1,3,7,9-tetramethyl-5*H*-4 λ$^4$,5 λ$^4$-dipyrrolo[1,2-*c*:2′,1′-*f*][1,3,2]diazaborinin-4-ium-5-uide (9d)** According to **GP-3 (Method D)**: Compound **16** (200 mg, 590 µmol) and 4-hydroxypiperidine (**7d**) (84.0 mg, 826 µmol), as well as KI (246 mg, 1.48 mmol) and $K_2CO_3$ (245 mg, 1.77 mmol) in MeCN (5.0 mL). Flash-SC (EtOAc, 10% $NEt_3$).

176 mg (74%); orange solid; mp 140 °C (dec); DC: $R_f$ = 0.24 (EtOAc, 10% $NEt_3$); IR (KBr) $\nu_{max}$ 3429, 2931, 2805, 2363, 2344, 1636, 1550, 1510, 1473, 1410, 1367, 1308, 1224, 1201, 1160, 1108, 1078, 1026 $cm^{-1}$; $^1H$ NMR (500 MHz, DMSO-D6, TMS): $\delta$ = 1.29–1.39 (m, 2H), 1.52–1.65 (m, 4H), 1.69 (d, $J$ = 9.8 Hz, 2H), 1.95 (s, 2H), 2.26–2.38 (m, 2H), 2.40 (s, 6H), 2.43 (s, 6H), 2.67 (s, 2H), 2.88–2.97 (m, 2H), 3.41 (s, 1H), 4.55 (s, 1H), 6.23 (s, 2H) ppm; $^{13}C$ NMR (100 MHz, DMSO-D6, TMS): $\delta$ = 14.0 (2C, $H_3\underline{C}CN$), 15.7 (2C, $H_3\underline{C}CC$) 26.6 ($CCH_2\underline{C}H_2$), 27.3 ($C\underline{C}H_2$), 28.7 ($CCH_2CH_2\underline{C}H_2$), 34.3 (2C, $N\underline{C}H_2CH_2CH$), 50.9 (2C, $NCH_2\underline{C}H_2CH$), 56.3 ($\underline{C}H_2NCH_2CH_2CH$) 66.3 ($NCH_2CH_2\underline{C}H$), 121.5 (2C, $C\underline{C}HC$), 130.6 (2C, $N\underline{C}CCH_2$), 140.8 (2C, $H_3C\underline{C}C$), 146.9 ($NC\underline{C}CH_2$), 152.9 (2C $H_3C\underline{C}N$) ppm;$^{19}F$ NMR (470 MHz, $CDCl_3$): $\delta$ = −143.7 to −144.0 ppm; $^{11}B$ NMR (160 MHz, $CDCl_3$): $\delta$ = −2.2 (t, $J$ = 32.9 Hz) ppm; M ($C_{22}H_{32}BF_2N_3O$) = 403.26 MS (EI, 70 eV) m/z (%): 403.40 (49, $M^+$), 383.40 (16), 269.25 (12), 154.25 (13), 140.25 (45), 114.25 (100); HRMS (EI+): $M^+$ calc. for $C_{22}H_{32}BF_2N_3O$, 403.2601; found: 403.2627.

**5,5-Difluoro-1,3,7,9-tetramethyl-10-[4-(4-phenylpiperidin-1-yl)butyl]-5*H*-4 λ⁴,5 λ⁴-dipyrrolo[1,2-*c*:2',1'-*f*][1,3,2]diazaborinin-4-ium-5-uide (9e):** According to **GP-3 (Method D)**: Compound **16** (200 mg, 590 µmol) and 4-phenylpiperidine (**7e**) (137 mg, 826 µmol) as well as KI (246 mg, 1.48 mmol) and $K_2CO_3$ (245 mg, 1.77 mmol) in MeCN (5.0 mL). Flash-SC (1.*n*-heptan/EtOAc 7:2, 10% $NEt_3$ 2. Gradient: *n*-heptane/EtOAc 7:2→ n-heptane/EtOAc 7:2, 10% $NEt_3$).

235 mg (86%); orange solid; mp 167 °C; DC: $R_f$ = 0.3 (*n*-heptane/Ethylacetat (7:2, 10% $NEt_3$); IR (KBr) $\nu_{max}$ 3425, 3020, 2965, 2927, 2862, 2907, 2770, 2742, 1550, 1507, 1475, 1446, 1410, 1376, 1367, 1310, 1256, 1225, 1202, 1159, 1101, 1074, 1066, 1028 $cm^{-1}$; $^1H$ NMR (400 MHz, $CD_2Cl_2$, TMS): $\delta$ = 1.55–1.76 (m, 6H), 1.76–1.86 (m, 2H), 2.00 (td, $J$ = 2.5/11.7 Hz, 2H), 2.36–2.43 (m, 2H), 2.43–2.55 (m 13H), 2.91–3.05 (m, 4H), 6.09 (s, 2H CCHC), 7.15–7.20 (m, 1H), 7.20–7.25 (m, 2H), 7.26–7.32 (m, 2H) ppm; $^{13}C$ NMR (125 MHz, $CD_2Cl_2$, TMS): $\delta$ = 14.6 (2C, $NC\underline{C}H_3$), 16.6 (2C, $NCC\underline{C}H_3$), 27.9 ($CCH_2\underline{C}H_2CH_2CH_2N$), 28.6 ($C\underline{C}H_2CH_2CH_2CH_2N$), 29.8 ($CCH_2CH_2\underline{C}H_2CH_2N$), 34.0 (2C, $NCH_2\underline{C}H_2CH$), 43.2 ($NCH_2CH_2\underline{C}H$), 54.8 (2C, $N\underline{C}H_2CH_2CH$), 58.2 ($\underline{C}H_2NCH_2CH_2CH$), 121.9 (2C, $C\underline{C}HC$), 126.4 ($CC_{ar}\underline{C}_{ar}HC_{ar}H\text{-}\underline{C}_{ar}H$), 127.2 (2C, $CC_{ar}\underline{C}_{ar}HC_{ar}HC_{ar}H$), 128.7 (2C, $CC_{ar}\text{-}C_{ar}H\underline{C}_{ar}HC_{ar}H$), 131.8 (2C, $NC\underline{C}CH_2$), 141.3 (2C, $NC\underline{C}CH_3$), 147.2 ($NC\underline{C}CH_2$), 147.4 ($C\underline{C}_{ar}$), 154.0 (2C, $N\underline{C}CH_3$) ppm; $^{19}F$ NMR (470 MHz, $CD_2Cl_2$): $\delta$ = −145.0 to −148.5 (m) ppm; $^{11}B$ NMR (160 MHz, $CD_2Cl_2$): $\delta$ = −0.45 (t, $J$ = 32.9 Hz) ppm; M ($C_{28}H_{36}BF_2N_3$) = 463.29 MS (ESI+) m/z (%): 464.30 (100, $[M+H]^+$); HRMS (ESI+): $[M+H]^+$ calc. for $C_{28}H_{37}BF_2N_3$, 464.3043; found: 464.3042 $[M+H]^+$; $C_{28}H_{36}BF_2N_3$ (389.25): calc. C 72.57, H 7.83 N 9.07; found: C 72.43, H 7.74, N 9.10.

**5,5-Difluor-1,3,7,9-tetramethyl-10-{4-[4-phenyl-5,6-dihydropyridin-1(2*H*)-yl]butyl}-5*H*-4 λ⁴,5 λ⁴-dipyrrolo[1,2-*c*:2′,1′-*f*][1,3,2]diazaborinin-4-ium-5-uid (9f)** According to **GP-3 (Method D)**: Compound **16** (488 mg, 1.44 mmol) and 4-phenyl-1,2,3,6-tetrahydropyridine (**7f**) (321 mg, 2.02 mmol), as well as KI (598 mg, 3.60 mmol) and $K_2CO_3$ (597 mg, 4.32 mmol) in MeCN (5.0 mL). Flash-SC (1. *t*BuOMe/pentane 7:3, 2% $NEtMe_2$ 2. *t*BuOMe/pentane 7:3 → *t*BuOMe/pentane 7:3, 3% $NEtMe_2$).

268 mg (40%); orange solid; mp 185–187 °C; DC: $R_f$ = 0.25 (*t*BuOMe/pentane 7:3, 3% $NEtMe_2$); IR (KBr) $\nu_{max}$ 3433, 2919, 2867, 1551, 1509, 1467, 1306, 1203, 1077, 1060, 984, 813, 749, 714, 694 $cm^{-1}$; $^1H$ NMR (400 MHz, $CD_2Cl_2$): $\delta$ = 1.57–1.68 (m, 4H), 2.36 (s, 6H), 2.37 (s, 6H), 2.38–2.48 (m, 4H), 2.58 (t, $J$ = 5.6 Hz, 2H), 2.88–2.95 (m, 2H), 3.02 (q, $J$ = 3.0 Hz, 2H), 5.97–6.01 (m, 3H), 7.10–7.17 (m, 1H), 7.19–7.26 (m, 2H), 7.27–7.34 (m, 2H) ppm; $^{13}C$ NMR (101 MHz, $CD_2Cl_2$): $\delta$ = 14.2 (t, $J$ = 2.6 Hz, $H_3\underline{C}CN$), 16.1 ($H_3\underline{C}CCN$), 27.6 ($CCH_2\underline{C}H_2\underline{C}H_2CH_2N$), 28.1 ($NCH_2\underline{C}H_2C$), 28.2 ($C\underline{C}H_2CH_2CH_2CH_2N$), 29.4 ($CCH_2\underline{C}H_2\underline{C}H_2CH_2N$), 50.3 ($N\underline{C}H_2CH_2C$), 53.3 ($N\underline{C}H_2CH$), 57.2 ($CCH_2CH_2CH_2\underline{C}H_2N$), 121.5 (2C, $C\underline{C}HC$), 122.0 ($NCH_2\underline{C}H$), 124.7 (2C, $CC_{ar}\underline{C}_{ar}H$), 126.9 ($C_{ar}C_{ar}HC_{ar}H\underline{C}_{ar}H$), 128.2 (2C, $CC_{ar}H\underline{C}_{ar}HC_{ar}H$), 131.4 (2C, $N\underline{C}CCH_2$), 134.8 ($NCH_2CH_2\underline{C}$), 140.9 (2C, $H_3C\underline{C}CN$), 146.9 (2C, $\underline{C}C_{ar}$, $NC\underline{C}CH_2$), 153.6 (2C, $H_3C\underline{C}N$). ppm; $^{19}F$ NMR (470 MHz, $CD_2Cl_2$): $\delta$ = −146.7 to −146.4 (m) ppm; $^{11}B$ NMR (160 MHz, $CD_2Cl_2$): $\delta$ = 0.52 (t, $J$ = 33.1 Hz) ppm; HRMS (ESI): $[M+H]^+$ calc. for $C_{28}H_{35}BF_2N_3$, 462. 2887; found: 462.2890.

**5,5-Difluoro-10-[4-(4-hydroxy-4-phenylpiperidin-1-yl)butyl]-1,3,7,9-tetramethyl-5*H*-4 λ⁴,5 λ⁴-dipyrrolo[1,2-*c*:2',1'-*f*][1,3,2]diazaborinin-4-ium-5-uide (9g)** According to **GP-3 (Method D)**: Compound **16** (200 mg, 590 µmol) and 4-hydroxy-4-phenylpiperidine (**7g**) (146 mg, 826 µmol) as well as KI (246 mg, 1.48 mmol) and $K_2CO_3$ (245 mg, 1.77 mmol) in MeCN (5.0 mL). Flash-SC (n-heptane/EtOAc 6:3, 10% $NEt_3$).

222 mg (78%); orange solid; mp 184–186 °C; DC: $R_f$ = 0.27 (*n*-heptane/EtOAc = 6:3, 10% $NEt_3$); IR (KBr) $\nu_{max}$ 3556, 2478, 2953, 2925, 2794, 2769, 1551, 1511, 1473, 1467, 1445, 1410, 1368, 1307, 1269, 1255, 1202, 1158, 1129, 1108, 1079, 1046, 1025 $cm^{-1}$; $^1H$ NMR (500 MHz, DMSO-D6; TMS): $\delta$ = 1.55–1.71 (m, 6H), 1.88 (td, $J$ = 4.3/13.0 Hz, 2H), 2.31–2.43 (m, 10H), 2.46 (s, 6H), 2.65 (d, $J$ = 10.2 Hz, 2H), 2.99 (m, 2H), 4.77 (s, 1H), 6.25 (s, 2H), 7.20 (t, $J$ = 7.3 Hz, 1H), 7.31 (t, $J$ = 7.7 Hz, 2H), 7.45–7.49 (m, 2H) ppm; $^{13}C$ NMR (125 MHz, DMSO-D6): $\delta$ = 14.1 (2C, $H_3\underline{C}CN$), 15.8 (2C, $H_3\underline{C}CCN$), 26.7

($CCH_2\underline{C}H_2CH_2CH_2N$), 27.5 ($NCC\underline{C}H_2$), 29.0 ($CCH_2CH_2\underline{C}H_2CH_2N$), 38.1 (2C, $NCH_2\underline{C}H_2C$), 49.1 (2C, $N\underline{C}H_2CH_2C$), 56.8 ($CCH_2CH_2CH_2\underline{C}H_2N$), 69.7 ($NCH_2CH_2\underline{C}$), 121.7 (2C, $C\underline{C}HC$), 124.8 (2C, $CC_{ar}\underline{C}_{ar}H$), 126.2 ($C_{ar}$-$C_{ar}HC_{ar}H\underline{C}_{ar}H$), 127.9 (2C, $CC_{ar}H\underline{C}_{ar}HC_{ar}H$), 130.8 (2C, $NCCCH_2$), 140.9 (2C, $H_3C\underline{C}CN$), 147.1 ($NC\underline{C}CH_2$), 150.3 ($\underline{C}C_{ar}$), 153.0 (2C, $H_3C\underline{C}N$) ppm; $^{19}$F NMR (470 MHz, DMSO): $\delta = -143.7$ to $-143.9$ (m) ppm; $^{11}$B NMR (160 MHz, DMSO): $\delta = -2.3$ (t, $J = 32.6$ Hz) ppm; M ($C_{28}H_{36}BF_2N_3O$) = 479.29 MS (EI, 70 eV) m/z (%): 479.50 (30, $M^+$), 269.25 (10), 229.15 (15), 216.25 (21), 190.25 (42), 172.25 (17), 83.00 (100); HRMS (EI+): M calc. for $C_{28}H_{36}BF_2N_3O$, 479.2914; found: 479.2916.

**5,5-Difluoro-10-{4-[4-hydroxy-4-(2-methoxyphenyl)piperidin-1-yl]butyl}-1,3,7,9-tetramethyl-5*H*-4 λ$^4$,5 λ$^4$-dipyrrolo[1,2-*c*:2',1'-*f*][1,3,2]diazaborinin-4-ium-5-uide (9h)** According to **GP-3 (Method D)**: Compound **16** (100 mg, 295 µmol) and 4-(2-methoxyphenyl)piperidin-4-ol (**7h**) (86.0 mg, 413 µmol) as well as KI (122 mg, 737 µmol) and $K_2CO_3$ (122 mg, 885 µmol) in MeCN (2.5 mL). Flash-SC (1. *n*-heptane/EtOAc 5:4, 10% $NEt_3$, 2. Gradient: *n*-heptane/EtOAc 5:4 → *n*-heptane/EtOAc 5:4, 10% $NEt_3$).

121 mg (81%); orange solid; mp 174–175 °C; DC: $R_f$ = 0.27 (*n*-heptane/EtOAc 5:4, 10% $NEt_3$); IR (KBr) $\nu_{max}$ 3548, 3425, 2934, 2807, 2360, 2343, 16545, 1637, 1629, 1551, 1533, 1509, 1488, 1466, 1466, 1407, 1370, 1307, 1260, 1232, 1208, 1159, 1137, 1097, 1080, 1042, 1023 cm$^{-1}$; $^1$H NMR (500 MHz, DMSO-D6, TMS): $\delta = 1.37$ (d, $J$ = 13.2 Hz, 2H), 1.59–1.74 (m, 4H), 2.25–2.49 (m, 16H), 2.62 (d, $J = 9.6$ Hz, 2H), 2.96–3.04 (m, 2H), 3.76 (s, 3H), 4.62 (s, 1H), 6.26 (s, 2H), 6.92 (t, $J = 7.5$ Hz, 1H), 6.96 (d, $J$ = 8.2 Hz, 1H), 7.20 (td, $J = 8.1/1.7$ Hz, 1H), 7.57 (dd, $J = 7.7/1.7$ Hz, 1H) ppm; $^{13}$C NMR (125 MHz, DMSO-D6, TMS): $\delta = 14.0$ (2C, $H_3\underline{C}CN$), 15.7 (2C, $H_3\underline{C}CC$), 26.5 ($CCH_2\underline{C}H_2CH_2CH_2N$), 27.3 ($C\underline{C}H_2CH_2CH_2CH_2N$), 28.8 ($CCH_2CH_2\underline{C}H_2CH_2N$), 34.6, (2C, $NCH_2\underline{C}H_2C$) 49.0 (2C, $N\underline{C}H_2CH_2C$), 55.1 ($H_3\underline{C}O$), 56.5 ($CCH_2CH_2CH_2\underline{C}H_2N$), 70.1 ($CH_2\underline{C}C_{ar}$), 115.5 ($C_{ar}C_{ar}HC_{ar}HC_{ar}H\underline{C}_{ar}HC_{ar}$), 120.0 ($C_{ar}C_{ar}H\underline{C}_{ar}HC_{ar}HC_{ar}HC_{ar}$), 121.5 (2C, $C\underline{C}HC$), 126.4 ($C_{ar}\underline{C}_{ar}HC_{ar}HC_{ar}HC_{ar}HC_{ar}$), 127.6 ($C_{ar}C_{ar}HC_{ar}H\underline{C}_{ar}HC_{ar}H$-$C_{ar}$), 130.6 ($NC\underline{C}CH_2$), 136.7 ($C\underline{C}_{ar}C_{ar}H$), 140.9 (2C, $NC\underline{C}CH_3$), 147.0 (2C, $NCCCH_3$), 152.9 (2C, $H_3C\underline{C}N$), 156.2 ($\underline{C}_{ar}OCH_3$) ppm; $^{19}$F NMR: (470 MHz, DMSO-D6): $\delta = -143.6$ to $-144.0$ ppm; $^{11}$B NMR: (160 MHz, DMSO-D6): $\delta = -2.1$ (t, $J = 32.9$ Hz) ppm; M ($C_{29}H_{38}BF_2N_3O_2$) = 509.30 MS (FAB, NBA) m/z: 510.5 ($[M+H]^+$); HRMS (FAB, NBA): $[M+H]^+$ calc. for $C_{29}H_{39}BF_2N_3O_2$, 510.3098; found: 510.3108.

**5,5-Difluoro-10-{4-[4-hydroxy-4-(4-methoxyphenyl)piperidin-1-yl]butyl}-1,3,7,9-tetramethyl-5*H*-4 λ$^4$,5 λ$^4$-dipyrrolo[1,2-*c*:2',1'-*f*][1,3,2]diazaborinin-4-ium-5-uide (9i)** According to **GP-3 (Method D)**: Compound **16** (100 mg, 295 µmol) and 4-(4-methoxyphenyl)piperidin-4-ol (**7i**) (86.0 mg, 413 µmol) as well as KI (122 mg, 737 µmol) and $K_2CO_3$ (122 mg, 885 µmol) in MeCN (2.5 mL). Flash-SC (n-heptane/EtOAc 5:4, 10% $NEt_3$).

115 mg (74%); orange solid; mp 190 °C; DC: $R_f = 0.27$ (EtOAc/*n*-heptane 5:4, 10% $NEt_3$); IR (KBr) $\nu_{max}$ 3440, 3411, 2988, 2945, 2924, 2865, 2804, 2769, 2366, 2345, 1609, 1546, 1508, 1471, 1458, 1443, 1411, 1375, 1366, 1341, 1304, 1266, 1255, 1201, 1162, 1134, 1103, 1059, 1028 cm$^{-1}$; $^1$H NMR (500 MHz, $CD_2Cl_2$, TMS): $\delta$ = 1.68–1.75 (m, 6H,), 2.04 (td, $J = 4.4/13.2$ Hz, 2H), 2.38 (t, $J = 10.9$ Hz, 2H), 2.42–2.50 (m, 14H), 2.74 (d, $J$ = 11.2 Hz, 2H), 2.96–3.06 (m, 2H), 3.78 (s, 3H), 6.09 (s, 2H), 6.85–6.89 (m, 2H), 7.39–7.43 (m, 2H) ppm; $^{13}$C NMR (125 MHz, $CD_2Cl_2$, TMS): $\delta = 14.6$ (2C, $NCC\underline{C}H_3$), 16.6 (2C, $NC\underline{C}H_3$), 27.9 ($CCH_2\underline{C}H_2CH_2CH_2N$), 28.6 ($C\underline{C}H_2CH_2CH_2CH_2N$), 29.8 ($CCH_2CH_2\underline{C}H_2CH_2N$), 39.0 (2C, $NCH_2\underline{C}H_2C$), 50.0 (2C, $N\underline{C}H_2CH_2C$), 55.6 ($H_3\underline{C}O$), 58.0 ($CCH_2CH_2CH_2\underline{C}H_2N$), 71.2 ($NCH_2CH_2\underline{C}$), 113.8 ($C_{ar}C_{ar}H\underline{C}_{ar}HC_{ar}O$), 121.9 ($C\underline{C}HC$), 126.2 ($C_{ar}\underline{C}_{ar}HC_{ar}H$-$C_{ar}O$), 131.8 ($N\underline{C}C$), 141.3 (3C, $H_3C\underline{C}C$ und $CH_2C\underline{C}_{ar}$-$C_{ar}H$), 147.4 ($CC\underline{C}CH_2$), 154.0 (2C, $NC\underline{C}CH_3$), 159.0 ($H_3\underline{C}O$) ppm; $^{19}$F NMR (470 MHz, $CD_2Cl_2$): $\delta = -143.4$ to $-146.7$ (m) ppm; $^{11}$B NMR (160 MHz, $CD_2Cl_2$): $\delta$ = $-2.14$ (t, $J = 33.0$ Hz) ppm; M ($C_{29}H_{38}BF_2N_3O_2$) = 509.30 MS (FAB, NBA) m/z: 510.5 ($[M+H]^+$); HRMS (FAB, NBA): $[M+H]^+$. calc. for $C_{29}H_{39}BF_2N_3O_2$, 510.3098; found: 510.3124.

**10-{4-[4-(2-Chlorophenyl)-4-hydroxypiperidin-1-yl]butyl}-5,5-difluoro-1,3,7,9-tetramethyl-5*H*-4 λ$^4$,5 λ$^4$-dipyrrolo[1,2-*c*:2',1'-*f*][1,3,2]diazaborinin-4-ium-5-uide (9j)** According to **GP-3 (Method D)**: Compound **16** (200 mg, 590 µmol) and 4-(2-chlorophenyl)piperidin-4-ol (**7j**) (175 mg, 826 µmol) as well as KI (245 mg, 1.48 mmol) and $K_2CO_3$ (245 mg, 1.77 mmol) in MeCN (5.0 mL). Flash-SC (1. *n*-heptane/EtOAc 4:5, 10% $NEt_3$, 2. Gradient: *n*-heptane/EtOAc 4:5 → *n*-heptane/EtOAc 4:5, 10% $NEt_3$).

276 mg (91%); orange solid; mp 218–219 °C; DC: $R_f$ = 0.37 (EtOAc/*n*-heptane 5:4, 10% $NEt_3$); IR (KBr) $\nu_{max}$ 3553, 3537, 3442, 2926, 2861, 2820, 1550, 1508, 1469, 1433, 1407, 1372, 1307, 1262, 1225, 1204, 1158, 1107, 1079, 1063, 1039 cm$^{-1}$; $^1$H NMR (500 MHz, DMSO-D6, TMS): $\delta = 1.49$ (d, $J = 12.3$ Hz, 2H), 1.66 (s, 4H), 2.32–2.42 (m, 10H) 2.47 (s, 6H), 2.57 (td, $J = 4.0/12.8$ Hz, 2H), 2.67 (d, $J = 9.9$ Hz, 2H), 2.95–3.04 (m, 2H), 4.99 (s, 1H), 6.24 (s, 2H), 7.25 (td, $J = 7.6/1.7$ Hz, 1H), 7.32 (dd, $J = 1.3/7.8$ Hz, 1H), 7.34–7.38 (m, 1H), 7.82 (dd, $J = 1.6/8.0$ Hz, 1H) ppm; $^{13}$C NMR (125 MHz, DMSO-D6): $\delta = 14.1$ (2C, $NC\underline{C}H_3$), 15.8 (2C, $NCC\underline{C}H_3$), 26.7 ($NCCCH_2\underline{C}H_2$), 27.5 ($NCC\underline{C}H_2$), 28.9 ($CCH_2CH_2\underline{C}H_2CH_2N$), 34.1 (2C, $NCH_2\underline{C}H_2C$), 49.0 (2C, $N\underline{C}H_2$

$CH_2C$), 56.6 ($CCH_2CH_2CH_2\underline{C}H_2N$), 70.8 ($NCH_2CH_2\underline{C}$), 121.6 (2C, $C\underline{C}HC$), 127.0 ($CC_{ar}C_{ar}\underline{C}_{ar}H$), 128.3 (2C, $CC_{ar}C_{ar}HC_{ar}H\underline{C}_{ar}HC_{ar}H$), 128.3 ($CC_{ar}\underline{C}_{ar}HC_{ar}HC_{ar}HC_{ar}H$), 130.5 ($CC_{ar}\underline{C}_{ar}$), 130.7 (2C, $N\underline{C}CCH2$), 131.3 ($CC_{ar}HC_{ar}H\text{-}\underline{C}_{ar}H$), 140.9 (2C, $NC\underline{C}CH_3$), 145.6 ($C\underline{C}_{ar}$), 147.1 ($NC\underline{C}CH_2$), 153.0 (2C, $N\underline{C}CH_3$) ppm; $^{19}$F NMR (470 MHz, DMSO-D6): $\delta = -144.2$ to $-143.3$ (m) ppm; $^{11}$B NMR (160 MHz, DMSO-D6): $\delta = -0.55$ (t, $J = 32.8$ Hz) ppm; M ($C_{28}H_{35}BClF_2N_3O$) = 513.25 MS (EI, 70 eV) m/z (%): 513.4 (12, $M^+$), 189.01 (100); HRMS (EI+): $M^+$ calc. for $C_{28}H_{35}BClF_2N_3O$, 513.2524; found: 513.2524.

**10-{4-[4-(4-Chlorophenyl)-4-hydroxypiperidin-1-yl]butyl}-5,5-difluoro-1,3,7,9-tetramethyl-5*H*-4 λ$^4$,5 λ$^4$-dipyrrolo[1,2-*c*:2',1'-*f*][1,3,2]diazaborinin-4-ium-5-uide (9k)** According to **GP-3 (Method D)**: Compound **16** (100 mg, 295 µmol) and 4-(4-chlorophenyl)piperidin-4-ol (**7k**) (87.0 mg, 413 µmol) as well as KI (122 mg, 737 µmol) and $K_2CO_3$ (122 mg, 885 µmol) in MeCN (2.5 mL). Flash-SC (*n*-heptane/EtOAc 5:4, 10% $NEt_3$).

124 mg (82%); orange solid; mp 218–219 °C; DC: $R_f$ = 0.37 (EtOAc/*n*-heptane 5:4, 10% $NEt_3$); IR (KBr) $\nu_{max}$ = 3573, 3425, 2947, 2923, 2820 2362, 2345 1637, 1549, 1507, 1481, 1405, 1370, 1348, 1307, 1244, 1203, 1160, 1130 1083 cm$^{-1}$; $^1$H NMR (500 MHz, DMSO-D6, TMS): $\delta = 1.57$ (d, $J = 12.0$ Hz, 2H), 1.60–1.69 (m, 4H), 1.86 (td, $J = 4.1/12.9$ Hz, 2H), 2.34 (t, $J = 10.7$ Hz, 2H), 2.38–2.41 (m, 8 H), 2.46 (s, 6H), 2.64 (d, $J = 10.8$ Hz, 2H), 2.94–3.02 (m, 2H), 4.89 (s, 1H), 6.25 (s, 2H), 7.34–7.38 (m, 2H), 7.48 (d, $J = 8.6$ Hz, 2H) ppm; $^{13}$C NMR (100 MHz, DMSO-D6, TMS): $\delta = 14.0$ (2C, $H_3\underline{C}CCN$), 15.7 (2C, $H_3\underline{C}CN$), 26.6 ($CCH_2CH_2\underline{C}H_2CH_2N$), 27.4 ($C\underline{C}H_2CH_2CH_2CH_2N$), 28.8 ($CCH_2\underline{C}H_2CH_2CH_2N$), 37.8 (2C, $NCH_2\underline{C}H_2C$), 48.9 (2C, $N\underline{C}H_2CH_2C$), 56.7 ($CCH_2CH_2CH_2\underline{C}H_2N$), 69.4 ($NCH_2CH_2\underline{C}$), 121.6 (2C, $C\underline{C}HC$), 126.7 (2C, $C_{ar}\underline{C}_{ar}HC_{ar}HC_{ar}Cl$), 127.6 (2C, $C_{ar}C_{ar}H\underline{C}_{ar}HC_{ar}Cl$), 130.6 ($\underline{C}_{ar}C_{ar}HC_{ar}HC_{ar}Cl$ und $NC\underline{C}CH_2$), 140.8 (2C, $H_3C\underline{C}CN$), 146.9 (2C, $CHCC\underline{C}$), 149.1 ($\underline{C}_{ar}Cl$), 152.9 (2C, $H_3C\underline{C}N$) ppm; $^{19}$F NMR (470 MHz, DMSO): $\delta = -143.7$ to $-143.9$ (m) ppm; $^{11}$B NMR (160 MHz, DMSO): $\delta = -2.3$ (t, $J = 32.2$ Hz) ppm; M ($C_{28}H_{35}BF_2ClN_3O$) = 513.25 MS (EI, 70 eV) m/z (%): 513.4 (2, $M^+$), 296.4 (11), 295.40 (51), 157.25 (12), 170.25 (54), 156.25 (100); HRMS (EI+): $M^+$ calc. for $C_{28}H_{35}BF_2ClN_3O$, 513.2524; found: 513.2513.

**10-{4-[3-(Ethoxycarbonyl)piperidine-1-yl]butyl}-5,5-difluoro-1,3,7,9-tetramethyl-5*H*-4 λ$^4$,5 λ$^4$-dipyrrolo[1,2-*c*:2',1'-*f*][1,3,2]diazaborinin-4-ium-5-uide (9l)** According to **GP-3 (Method D)**: Compound **16** (300 mg, 885 µmol) and ethyl piperidine-3-carboxylate (**7l**) (201 mg, 1.24 mmol, 0.2 mL) as well as KI (367 mg, 2.21 mmol) and $K_2CO_3$ (367 mg, 2.65 mmol) in MeCN (7.5 mL). Flash-SC (1. *n*-heptane/EtOAc 8:1, 10% $NEt_3$, 2. Gradient: *n*-heptane/EtOAc 8:1 → *n*-heptane/EtOAc 8:1, 10% $NEt_3$).

327 mg (80%); orange solid; mp 109 °C; DC: $R_f = 0.2$ (*n*-heptane/EtOAc 8:1, 10% $NEt_3$); IR (KBr) $\nu_{max}$ 3383, 2934, 2865, 2806, 1730, 1550, 1511, 1470, 1410, 1371, 1309, 1263, 1224, 1202, 1158, 1078, 1029, 986 cm$^{-1}$; $^1$H NMR: (500 MHz, $CD_2Cl_2$, TMS): $\delta = 1.21$ (t, $J = 7.1$, 3H), 1.36–1.57 (m, 2H), 1.57–1.75 (m, 5H), 1.84–1.92 (m, 1H), 1.97 (t, $J = 10.7$, 1H), 2.12 (t, $J = 10.8$, 1H), 2.35–2.40 (m, 2H), 2.40–2.48 (m, 13H), 2.70 (d, $J$ = 11.1 Hz, 1H), 2.91 (d, $J = 11.2$, 1H), 2.93–2.99 (m, 2H), 4.07 (qd, $J = 2.8/7.1$ Hz, 2H), 6.08 (s, 2H) ppm; $^{13}$C NMR (125 MHz, $CD_2Cl_2$, TMS): $\delta = 14.4$ ($OCH_2\underline{C}H_3$), 14.6 (2C, $NC\underline{C}H_3$), 16.6 (2C, $NCC\underline{C}H_3$), 25.1 ($\underline{C}H_2CH_2CH$), 27.4 ($NCH_2CH_2\underline{C}H_2CH$), 27.7 ($NCH_2\underline{C}H_2CH_2CH_2C$), 28.6 ($NCH_2CH_2CH_2\underline{C}H_2C$), 29.8 ($NCH_2CH_2\underline{C}H_2CH_2C$), 42.4 ($NCH_2CH_2CH_2\underline{C}H$), 53.4 ($N\underline{C}H_2CH_2CH_2CH$), 55.9 ($NCH\underline{C}H_2$), 58.1 ($N\underline{C}H_2CH_2CH_2CH_2C$), 60.6 ($O\underline{C}H_2CH_3$), 121.9 (2C, $C\underline{C}HC$), 131.8 (2C, $N\underline{C}CCH_3$), 141.3 (2C, $NC\underline{C}CH_3$), 147.4 ($NC\underline{C}CH_2$), 154.0 (2C, $N\underline{C}CH_3$), 174.4 (CO) ppm; $^{19}$F NMR (470 MHz, $CD_2Cl_2$): $\delta = -146.3$ to $-146.7$ (m) ppm; $^{11}$B NMR (160 MHz, $CD_2Cl_2$): $\delta = -0.5$ (t, $J = 32.9$ Hz) ppm; M ($C_{25}H_{36}BF_2N_3O_2$) = 459.29 MS (CI, $CH_5^+$) m/z (%): 460 (44, $[M+H]^+$), 440 (100); HRMS (EI+): $M^+$ calc. for $C_{25}H_{36}BF_2N_3O_2$, 459.2869; found: 459.2872.

**10-[4-(3-Carboxypiperidine-1-yl)butyl]-5,5-difluoro-1,3,7,9-tetramethyl-5*H*-4 λ$^4$,5 λ$^4$-dipyrrolo[1,2-*c*:2',1'-*f*][1,3,2]diazaborinin-4-ium-5-uide (9m)** According to **GP-2**: Compound **9l** (322 mg, 0.70 mmol) in 10.0 mL solvent mixture ($CH_2CL_2$/MeOH, 2:1) and LiOH (42.0 mg, 1.75 mmol) solved in $H_2O$ (1.8 mL). The reaction mixture was stirred for 4 d.

214 mg (71%); orange solid; mp 119 °C; IR (KBr): $\tilde{\nu}$ = 3432, 2932, 2868, 1708, 1550, 1511, 1474, 1408, 1371, 1308, 1265, 1224, 1200, 1159, 1080, 1026 cm$^{-1}$; $^1$H NMR (400 MHz, $C_2D_2Cl_4$, 40 °C, TMS): $\delta = 1.50$–1.92 (m, 8H), 1.97 (d, $J = 12.4$ Hz, 1H), 2.27–2.36 (m, 1H), 2.41 (s, 6H), 2.49 (s, 6H), 2.56 (t, $J = 7.5$ Hz, 2H), 2.67 (s, 1H), 2.90–3.04 (m, 3H), 3.11 (d, $J = 12.7$ Hz, 1H), 6.08 (s, 2H) ppm; $^{13}$C NMR (100 MHz, $C_2D_2Cl_4$, 40 °C): $\delta = 14.8$ (2C, $CC\underline{C}H_3$), 16.6 (2C, $NC\underline{C}H_3$), 22.0 ($NCH_2\underline{C}H_2CH_2CH$), 26.4 ($NCH_2CH_2\underline{C}H_2CH$), 26.5 ($CCH_2\underline{C}H_2$), 28.1 ($C\underline{C}H_2$), 29.6 ($CCH_2CH_2\underline{C}H_2$), 40.2 ($\underline{C}HCO$), 53.5 ($N\underline{C}H_2CH_2CH_2CH$), 55.2 ($N\underline{C}H_2CH$), 57.3 ($\underline{C}H_2NCH_2CH$), 122.1 (2C, $C\underline{C}HC$), 131.5 (2C, $NC\underline{C}CH_3$), 140.6 (2C, $NC\underline{C}CH_2$), 145.5 ($NC\underline{C}CH_2$), 154.5 (2C, $N\underline{C}CH_3$), 176.4 ($\underline{C}O$) ppm; $^{19}$F NMR (375 MHz, $C_2D_2Cl_4$): $\delta = -145.1$ to $-145.9$ (m) ppm; $^{11}$B NMR (128 MHz, $C_2D_2Cl_4$): $\delta = 0.5$ (t, $J = 33$. Hz) ppm; M ($C_{23}H_{32}BF_2N_3O_2$) = 431.25 MS ($FAB^+$, NBA) m/z (%): 432.3 ($[M+H]^+$); HRMS ($FAB^+$,

NBA): $[M+H]^+$ calc. for $C_{23}H_{33}BF_2N_3O_2$, 432.2628; found: 432.2623.

**5,5-Difluoro-1,3,7,9-tetramethyl-10-[5-(piperidin-1-yl)pentyl]-5*H*-4 λ⁴,5 λ⁴-dipyrrolo[1,2-*c*:2',1'-*f*][1,3,2]diazaborinin-4-ium-5-uide (10a)** According to **GP-3 (Method C)**: Compound **17** (117 mg, 295 µmol) and piperidine (**7a**) (35.0 mg, 413 µmol, 42.0 µL) and $K_2CO_3$ (122 mg, 855 µmol) in MeCN (2.5 mL). Flash-SC (*n*-heptane/EtOAc 8:1, 10% $NEt_3$).

93.2 mg (78%); orange solid; Mp 103–104 °C; DC: $R_f =$ 0.2 (*n*-heptane/EtOAc 8:1, 10% $NEt_3$); IR (KBr) $\nu_{max}$ 3119, 2932, 2861, 2851, 1797, 1759, 1734, 1689, 1667, 1550, 1507, 1473, 1443, 1410, 1370, 1350, 1305, 1278, 1260, 1248, 1224, 1202, 1164, 1106, 1069, 1011 $cm^{-1}$; $^1H$ NMR (500 MHz, $CD_2Cl_2$, TMS): $\delta = 1.41$ (s, 2H), 1.47–1.57 (m, 8H), 1.64 (s, 2H), 2.26 (t, $J = 6.9$ Hz, 2H), 2.32 (s, 4H), 2.43 (s, 6H), 2.46 (s, 6H), 2.93–2.97 (m, 2H), 6.09 (s, 2H) ppm; $^{13}C$ NMR (125 MHz, $CD_2Cl_2$, TMS): $\delta = 14.6$ (2C, NCCH$_3$), 16.6 (2C, NCCCH$_3$), 25.0 ($CH_2NCH_2CH_2CH_2$), 26.5 (2C, $CH_2NCH_2CH_2CH_2$), 27.0 ($CCH_2CH_2CH_2$), 28.6 ($CCH_2CH_2$), 29.0 ($CCH_2$), 32.1 ($CH_2CH_2NCH_2CH_2CH_2$), 55.0 (2C, $CH_2NCH_2CH_2CH_2$), 59.3 ($CH_2NCH_2CH_2CH_2$), 121.9 (2C, CCHC), 131.8 (2C, NCCCH$_2$), 141.2 (2C, NCCCH), 147.4 (NCCCH$_2$), 154.0 (2C, NCCH) ppm; $^{19}F$ NMR (4710 MHz, $CD_2Cl_2$): $\delta = -146.2$ to $-146.7$ (m) ppm; $^{11}B$ NMR (160 MHz, $CD_2Cl_2$): $\delta = -2.23$ (t, $J =$ 33.0 Hz) ppm; M ($C_{23}H_{34}BF_2N_3$) = 401.28. MS (CI, $CH_5^+$) m/z (%): 402.25 (44, $[M+H]^+$), 382.25 (100); HRMS (EI+): $M^+$ calc. for $C_{23}H_{34}BF_2N_3$, 401.2808; found: 401.2815.

**5,5-Difluor-1,3,7,9-tetramethyl-10-(5-morpholinpentyl)-5*H*-4 λ⁴,5 λ⁴-dipyrrolo[1,2-*c*:2',1'-*f*][1,3,2]diazaborinin-4-ium-5-uide (10b)** According to **GP-3 (Method C)**: Compound **17** (117 mg, 295 µmol) and morpholine (**7b**) (36.0 mg, 413 µmol) and $K_2CO_3$ (122 mg, 855 µmol) in MeCN (2.5 mL). Flash-SC (1. *n*-heptan/EtOAc 5:4, 10% $NEt_3$, 2. Gradient: *n*-heptane/EtOAc 5:4 → *n*-heptane/EtOAc 5:4, 10% $NEt_3$).

97.5 mg (82%); orange solid; mp 95–101 °C; DC: $R_f =$ 0.25 (*n*-heptane/EtOAc 5:4, 10% $NEt_3$); IR (KBr) $\nu_{max}$ 3431, 2938, 2853, 2807, 1637, 1549, 1508, 1474, 1410, 1370, 1307, 1279, 1202, 1163, 1159, 1070, 1033 $cm^{-1}$; $^1H$ NMR (500 MHz, $CD_2Cl_2$, TMS): $\delta = 1.49$–1.58 (m, 4H), 1.60–1.69 (m, 2H), 2.31 (t, $J = 6.8$ Hz, 2H), 2.37 (s, 4H), 2.43 (s, 6H), 2.46 (s, 6H), 2.92–3.00 (m, 2H), 3.64 (t, $J = 4.7$ Hz, 4H), 6.09 (s, 2H) ppm; $^{13}C$ NMR (125 MHz, $CD_2Cl_2$): $\delta = 14.2$ (2C, NCCH$_3$), 16.2 (2C, NCCCH$_3$), 26.2 ($CCH_2CH_2CH_2CH_2CH_2N$), 28.0 ($CCH_2CH_2CH_2CH_2N$), 28.6 ($CCH_2$), 31.7 ($CCH_2CH_2$), 53.8 (2C, NCH$_2$CH$_2$O), 58.5 (CH$_2$NCH$_2$CH$_2$O), 67.0 (2C, NCH$_2$CH$_2$O), 121.6 (2C, CCHC), 131.4 (2C, NCCCH$_2$), 140.8 (2C, NCCCH$_3$), 146.9 (NCCCH$_2$), 153.7 (2C, NCCH$_3$) ppm; $^{19}F$ NMR (470 MHz, $CD_2Cl_2$): $\delta = -146.2$ to $-147.0$ (m) ppm; $^{11}B$ NMR (160 MHz, $CD_2Cl_2$): $\delta =$ $-0.5$ (t, $J = 33.0$ Hz) ppm; M ($C_{22}H_{32}BF_2N_3O$) = 403.26. MS (DIE+) m/z (%): 403.49 (36.06, $M^+$), 670.50 (100); HRMS (DEI+): $M^+$ calc. for $C_{22}H_{32}BF_2N_3O$, 403.2601; found: 403.2600.

**5,5-Difluoro-10-[5-(3-hydroxypiperidin-1-yl)pentyl]-1,3,7,9-tetramethyl-5*H*-4 λ⁴,5 λ⁴-dipyrrolo[1,2-*c*:2',1'-*f*][1,3,2]diazaborinin-4-ium-5-uide (10c)** According to **GP-3 (Method C)**: Compound **17** (117 mg, 295 µmol) and 3-hydroxypiperidine (**7c**) (42.0 mg, 413 µmol) and $K_2CO_3$ (122 mg, 855 µmol) in MeCN (2.5 mL). Flash-SC (EtOAc/*n*-heptane 7:2, 10% $NEt_3$). The product was solved in EtOAc and extracted three time with buffer (pH = 2). The combined aqueous phases were cooled to 0 °C, and the pH was adjusted to pH = 9 by adding buffer (pH = 10). The aqueous phase was extracted three times with $CHCl_3$. The solvent was removed, and the remaining residue was solved with MeCN, and the product was precipitated by adding $H_2O$. The MeCN was removed, and the remaining rest was freeze-dried.

72 mg (58%); orange solid; mp 73 °C; DC: $R_f = 0.22$ (EtOAc/*n*-heptane 7:2, 10% $NEt_3$); IR (KBr) $\nu_{max}$ 3407, 2933, 2862, 2802, 2770, 1550, 1510, 1474, 1409, 1371, 1309, 1225, 1201, 1159, 1079, 1027 $cm^{-1}$; $^1H$ NMR (400 MHz, DMSO-D6, 100 °C, TMS): $\delta = 1.13$ (q, $J =$ 10.4 Hz, 1H), 1.42 (dd, $J = 24.3/11.0$ Hz, 1H), 1.52 (s, 4H), 1.58–1.70 (m, 3H), 1.74–1.81 (m, 1H), 1.85 (t, $J = 9.3$ Hz, 1H), 1.96 (t, $J = 10.7$ Hz, 1H), 2.35 (s, 2H), 2.43 (s, 6H), 2.45 (s, 6H), 2.56–2.71 (m, 1H), 2.81 (dd, $J = 10.5/3.3$ Hz, 1H), 2.89–3.19 (m, 2H), 3.51 (s, 1H), 4.19 (2, 1H), 6.21 (s, 2H) ppm; $^{13}C$ NMR (100 MHz, DMSO-D6, 100 °C, TMS): $\delta = 13.9$ (2C, NCCH$_3$), 15.7 (2C, NCCCH$_3$), 22.8 ($NCH_2CH_2CH_2CH$), 25.9 ($CCH_2CH_2CH_2$), 27.4 ($CCH_2$ $CH_2CH_2$), 27.94($CCH_2$), 31.3 ($CH_2CH_2NCH_2CH$), 33.1 ($NCH_2CHCH_2$), 53.0 ($NCH_2CH_2CH_2CH$), 57.5 ($CH_2NCH_2$ CH), 61.0 ($NCH_2CH$), 65.9 (CHOH), 121.6 (2C, CCHC), 131.0 (2C, NCCCH$_2$), 140.7 (2C, NCCCH$_3$), 147.0 (NCCCH$_2$), 153.1 (2C, NCCH$_3$) ppm; $^{19}F$ NMR (470 MHz, DMSO-D6): $\delta = -144.3$ to $-143.2$ (m) ppm; $^{11}B$ NMR (160 MHz, DMSO-D6): $\delta = -2.39$ (t, $J =$ 33.1 Hz) ppm; M ($C_{23}H_{34}BF_2N_3O$) = 417.28. MS (CI, $CH_5^+$) m/z (%): 418.25 (34, $[M+H]^+$), 1398.40 (100); HRMS (EI+): $M^+$ calc. for $C_{23}H_{34}BF_2N_3O$, 417.2758; found: 417.2769.

**5,5-Difluoro-10-[5-(4-hydroxypiperidin-1-yl)pentyl]-1,3,7,9-tetramethyl-5*H*-4 λ⁴,5 λ⁴-dipyrrolo[1,2-*c*:2',1'-*f*][1,3,2]diazaborinin-4-ium-5-uide (10d)** According to **GP-3 (Method C)**: Compound **17** (117 mg, 295 µmol) and 4-hydroxypiperidine (**7d**) (42.0 mg, 413 µmol) and $K_2CO_3$ (122 mg, 855 µmol) in MeCN (2.5 mL). Flash-SC (1.

EtOAc/Isopropanol 8:1, 10% $NEt_3$, 2. Gradient: EtOAc/Isopropanol 8:1 → EtOAc/Isopropanol 8:1, 10% $NEt_3$).

98 mg (80%); orange solid; mp 83 °C; DC: $R_f = 0.33$ (EtOAc/Isopropanol 8:1, 10% $NEt_3$); IR (KBr) $\nu_{max}$ 3627, 3391, 2861, 2810, 1550, 1508, 1474, 1410, 1367, 1307, 1225, 1202, 1162, 1079, 987 $cm^{-1}$; $^1H$ NMR (400 MHz, DMSO-D6, TMS): $\delta = 1.27–1.40$ (m, 2H), 1.47 (s, 4H), 1.56 (s, 2H), 1.64–1.72 (m, 2H), 1.91 (t, $J = 10.6$ Hz, 2H), 2.19–2.26 (m, 2H), 2.40 (s, 6H), 2.42 (s, 6H), 2.60–2.70 (m, 2H), 2.87–2.98 (m, 2H), 3.36 (s, 1H), 4.55 (d, $J = 4.2$ Hz, 1H), 6.24 (s, 2H) ppm; $^{13}C$ NMR (125 MHz, DMSO-D6, TMS): $\delta = 14.0$ (2C, $NC\underline{C}H_3$), 15.7 (2C, $NCC\underline{C}H_3$), 26.0 ($CCH_2CH_2\underline{C}H_2$), 27.4 ($CCH_2CH_2CH_2\underline{C}H_2CH_2N$), 27.8 ($C\underline{C}H_2$), 31.0 ($CCH_2\underline{C}H_2$), 34.4 (2C, $NCH_2\underline{C}H_2CH$), 51.0 (2C, $N\underline{C}H_2CH_2CH$), 57.2 ($\underline{C}H_2NCH_2CH_2CH$), 66.4 ($\underline{C}HOH$), 121.5 (2C, $C\underline{C}HC$), 130.6 (2C, $NC\underline{C}CH_2$), 140.7 (2C, $NC\underline{C}CH_3$), 146.8 ($NC\underline{C}CH_2$), 152.9 (2C, $N\underline{C}CH_3$) ppm; $^{19}F$ NMR (470 MHz, DMSO-D6): $\delta = -144.3$ to $-143.4$ (m) ppm; $^{11}B$ NMR (160 MHz, DMSO-D6): $\delta = -2.41$ (t, $J = 32.9$ Hz) ppm; M ($C_{23}H_{34}BF_2N_3O$) = 417.28. MS (EI, 70 eV) m/z (%): 417.25 (14, $M^+$), 114.15 (100); HRMS (EI+): $M^+$ calc. for $C_{23}H_{34}BF_2N_3O$, 417.2758; found: 417.2762.

**5,5-Difluoro-1,3,7,9-tetramethyl-10-[5-(4-phenylpiperidin-1-yl)pentyl]-5*H*-4 λ⁴,5 λ⁴-dipyrrolo[1,2-*c*:2',1'-*f*][1,3,2]diazaborinin-4-ium-5-uide (10e)** According to **GP-3 (Method C)**: Compound **17** (117 mg, 295 µmol) and 4-phenylpiperidine (**7e**) (67.0 mg, 413 µmol) and $K_2CO_3$ (122 mg, 855 µmol) in MeCN (2.5 mL). Flash-SC (1. *n*-heptane/EtOAc 7:2, 10% $NEt_3$, 2. Gradient: *n*-heptane/EtOAc 7:2 → *n*-heptane/EtOAc 7:2, 10% $NEt_3$).

122 mg (87%); orange solid; mp 109–111 °C; DC: $R_f = 0.33$ (EtOAc/*n*-heptane 7:2, 10% $NEt_3$); IR (KBr) $\nu_{max}$ 3424, 3028, 2925, 2861, 2801, 1768, 1550, 1510, 1470, 1409, 1364, 1307, 1261, 1225, 1200, 1156, 1109, 1074, 1025 $cm^{-1}$; $^1H$ NMR (500 MHz, DMSO-D6): $\delta = 1.46–1.55$ (m, 4H), 1.55–1.65 (m, 4H), 1.71 (d, $J = 10.9$ Hz, 2H), 1.93 (t, $J = 10.8$ Hz, 2H), 2.30 (t, $J = 6.5$ Hz, 2H), 2.40 (s, 6H), 2.43 (s, 7H), 2.90–2.98 (m, 4H), 6.24 (s, 2H), 7.15–7.20 (m, 1H), 7.22 (dd, $J = 3.3/5.0$ Hz, 2H), 7.25–7.31 (m, 2H) ppm; $^{13}C$ NMR (125 MHz, DMSO-D6, TMS): $\delta = 14.0$ (2C, $NC\underline{C}H_3$), 15.8 (2C, $NCC\underline{C}H_3$), 25.8 ($CCH_2CH_2\underline{C}H_2$), 27.5 ($CCH_2\underline{C}H_2$), 27.8 ($C\underline{C}H_2$), 31.1 ($\underline{C}H_2CH_2NCH_2CH_2C$), 33.1 (2C, $N\underline{C}H_2CH_2C$), 41.9 ($\underline{C}C_{ar}$), 53.7 (2C, $NCH_2\underline{C}H_2C$), 57.7 ($\underline{C}H_2NCH_2CH_2C$), 121.6 (2C, $C\underline{C}HC$), 125.9 ($CC_{ar}C_{ar}HC_{ar}H\underline{C}_{ar}H$), 126.6 (2C, $CC_{ar}C_{ar}H\underline{C}_{ar}HC_{ar}H$), 128.2 (2C, $CC_{ar}\underline{C}_{ar}HC_{ar}HC_{ar}H$), 130.6 (2C, $NC\underline{C}CH_2$), 140.7 (2C, $NC\underline{C}CH_3$), 146.2 ($C\underline{C}_{ar}$), 146.8 ($NC\underline{C}CH_2$), 152.9 (2C, $N\underline{C}CH_3$) ppm; $^{19}F$ NMR (470 MHz, DMSO-D6): $\delta = -143.8$ to $-144.3$ (m) ppm; $^{11}B$ NMR (160 MHz, DMSO-D6): $\delta = -2.39$ (t, $J = 32.9$ Hz) ppm; M ($C_{29}H_{38}BF_2N_3$) = 477.31 MS (CI, $CH_5^+$) m/z (%): 478.30 (58, $[M+H]^+$), 458.30 (100), 174.15 (44); HRMS (EI+): $M^+$ calc. for $C_{29}H_{38}BF_2N_3$, 477.3121; found: 477.3129.

**5,5-Difluor-1,3,7,9-tetramethyl-10-{5-[4-phenyl-5,6-dihydropyridin-1(2*H*)-yl]pentyl}-5*H*-4 λ⁴,5 λ⁴-dipyrrolo[1,2-*c*:2',1'-*f*][1,3,2]diazaborinin-4-ium-5-uid (10f)** According to **GP-3 (Method C)**: Compound **17** (560 mg, 1.41 mmol) and 4-Phenyl-1,2,3,6-tetrahydropyridine (**7f**) (314 mg, 1.97 mmol) and $K_2CO_3$ (585 mg, 4.23 mmol) in MeCN (12.0 mL). Flash-SC (1. *n*-heptane/EtOAc 8:2, 1% $NEtMe_2$, 2. Gradient: *n*-heptane/EtOAc 8:2 → *n*-heptane/EtOAc 8:2, 2% $NEtMe_2$).

483 mg (72%); orange solid; mp 46–48 °C; DC: $R_f = 0.25$ (EtOAc/*n*-heptane 8:2, 2% $NEtMe_2$); IR (KBr) $\nu_{max} = 2926$, 28,63, 1549, 1510, 1473, 1309, 1200, 985, 747, 714, 693 $cm^{-1}$; $^1H$ NMR (400 MHz, $CD_2Cl_2$): $\delta = 1.42–1.67$ (m, 6H), 2.36 (s, 6H), 2.38 (s, 6H), 2.34–2.40 (m, 2H), 2.41–2.48 (m, 2H), 2.57 (t, $J = 5.6$ Hz, 2H), 2.85–2.94 (m, 2H), 3.02 (q, $J = 3.0$ Hz, 2H), 5.96–6.04 (m, 3H), 7.09–7.19 (m, 1H), 7.18–7.27 (m, 2H), 7.27–7.35 (m, 2H) ppm; $^{13}C$ NMR (101 MHz, $CD_2Cl_2$): $\delta = 14.2$ (t, $J = 2.5$ Hz, 2C, $H_3\underline{C}CN$), 16.2 (2C, $H_3\underline{C}CCN$), 26.9 ($CCH_2\underline{C}H_2CH_2CH_2CH_2N$), 28.1 (2C, $CCH_2CH_2CH_2\underline{C}H_2CH_2N$, $NCH_2\underline{C}H_2C$), 28.5 ($C\underline{C}H_2CH_2CH_2CH_2CH_2N$), 31.8 ($C\underline{C}H_2CH_2CH_2CH_2CH_2N$), 50.4 ($N\underline{C}H_2CH_2C$), 53.3 ($N\underline{C}H_2CH$), 57.9 ($CCH_2CH_2CH_2CH_2\underline{C}H_2N$), 121.5 (2C, $C\underline{C}HC$), 122.1 ($NCH_2\underline{C}H$), 124.7 (2C, $CC_{ar}\underline{C}_{ar}H$), 126.8 ($C_{ar}C_{ar}HC_{ar}H\underline{C}_{ar}H$), 128.2 (2C, $CC_{ar}H\underline{C}_{ar}HC_{ar}H$), 131.3 (2C, $NC\underline{C}CH_2$), 134.8 ($\underline{C}C_{ar}$), 140.8 (2C, $H_3C\underline{C}CN$), 140.9 ($\underline{C}C_{ar}$), 146.9 ($NC\underline{C}CH_2$), 153.6 (2C, $H_3C\underline{C}N$) ppm; $^{19}F$ NMR (470 MHz, $CD_2Cl_2$): $\delta = -146.7$ to $-146.5$ (m) ppm; $^{11}B$ NMR (160 MHz, $CD_2Cl_2$): $\delta = 0.52$ (t, $J = 33.1$ Hz) ppm; HRMS (ESI): $[M+H]^+$ calc. for $C_{29}H_{37}BF_2N_3$,476.3043; found: 476.3047.

**1-[5-(5,5-Difluoro-1,3,7,9-tetramethyl-5*H*-4λ⁴,5λ⁴-dipyrrolo[1,2-*c*:2',1'-*f*][1,3,2]diaza-borinin-10-yl)pentyl]-4-phenylpiperidin-4-ol (10g)** According to **GP-3 (Method C)**: Compound **17** (117 mg, 295 µmol) and 4-hydroxy-4-phenylpiperidin (**7g**) (73.0 mg, 413 µmol) and $K_2CO_3$ (122 mg, 855 µmol) in MeCN (2.5 mL). Flash-SC (1. *n*-heptane/EtOAc 5:4, 10% $NEt_3$, 2. Gradient: *n*-heptane/EtOAc 5:4 → *n*-heptane/EtOAc 5:4, 10% $NEt_3$).

126 mg (87%); orange solid; mp 162–164 °C; DC: $R_f = 0.15$ (EtOAc/*n*-heptane 5:4, 10% $NEt_3$); IR (KBr) $\nu_{max}$ 3425, 2924, 2828, 2780, 1554, 1535, 1513, 1471, 1447, 1411, 1311, 1257, 1207, 1158, 1139, 1117, 1103, 1080, 1061, 1022 $cm^{-1}$; $^1H$ NMR (500 MHz, $CD_2Cl_2$, TMS): $\delta = 1.57$ (s, 4H), 1.63–1.73 (m, 4H), 2.09 (td, $J = 4.4/13.2$ Hz, 2H), 2.32–2.42 (m, 4H), 2.44 (s, 6H), 2.47 (s, 6H) 2.76 (d, $J = 11.4$ Hz, 2H), 2.95–3.00 (m, 2H), 6.09 (s, 2H), 7.25 (t, $J = 7.3$ Hz, 1H), 7.35 (t, $J = 7.7$ Hz, 2H), 7.50 (dd, $J = 1.0/8.2$ Hz, 2H) ppm; $^{13}C$ NMR (100 MHz, $CD_2Cl_2$, TMS): $\delta = 14.6$ (2C, $NC\underline{C}H_3$), 16.6 (2C, $NCC\underline{C}H_3$), 27.2 ($CCH_2\underline{C}H_2$),

28.6 ($CCH_2CH_2\underline{C}H_2$), 29.0 ($C\underline{C}H_2$), 32.2 ($\underline{C}H_2CH_2NCH_2CH_2C$), 39.1 (2C, $N\underline{C}H_2CH_2C$), 50.0 (2C, $NCH_2\underline{C}H_2C$), 58.7 ($\underline{C}H_2NCH_2CH_2C$), 71.6 ($\underline{C}OH$), 121.9 (2C, $C\underline{C}HC$), 125.0 (2C, $C_{ar}\underline{C}_{ar}HC_{ar}HC_{ar}H$), 127.2 ($C_{ar}\underline{C}_{ar}HC_{ar}H\underline{C}_{ar}H$), 128.6 (2C, $C_{ar}C_{ar}H\underline{C}_{ar}HC_{ar}H$), 131.8 (2C, $NCCCH_2$), 141.2 (2C, $NC\underline{C}CH_3$), 147.4 ($NC\underline{C}CH_2$), 149.26 ($C\underline{C}_{ar}$), 154.0 (2C, $N\underline{C}CH_3$) ppm; $^{19}$F NMR (470 MHz, $CD_2Cl_2$): $\delta = -146.1$ to $-146.9$ (m) ppm; $^{11}$B NMR (160 MHz, $CD_2Cl_2$): $\delta = -2.31$ (t, $J = 33.0$ Hz) ppm; M ($C_{29}H_{38}BF_2N_3O$) = 493.31 MS (CI, $CH_5^+$) m/z (%): 494.30 (39, $[M+H]^+$), 476.30 (47), 259.15 (100); HRMS (EI+): $M^+$ calc. for $C_{29}H_{38}BF_2N_3O$, 493.3071; found: 493.3070.

**5,5-Difluoro-10-{5-[4-hydroxy-4-(2-methoxyphenyl)piperidin-1-yl]pentyl}-1,3,7,9-tetramethyl-5*H*-4 λ$^4$,5 λ$^4$-dipyrrolo[1,2-*c*:2',1'-*f*][1,3,2]diazaborinin-4-ium-5-uide (10h)** According to **GP-3 (Method C)**: Compound **17** (117 mg, 295 µmol) and 4-(2-methoxyphenyl)piperidin-4-ol (**7h**) (86.0 mg, 413 µmol) and $K_2CO_3$ (122 mg, 855 µmol) in MeCN (2.5 mL). Flash-SC (*n*-heptane/EtOAc 5:4, 10% $NEt_3$).

112 mg (73%); orange solid; mp 78 °C; DC: $R_f = 0.42$ (EtOAc/*n*-heptane 5:4, 10% $NEt_3$); IR (KBr) $\nu_{max}$ 3433, 2928, 2864, 2812, 2771, 1550, 1511, 1490, 1471, 1437, 1409, 1372, 1309, 1229, 1201, 1159, 1109, 1080, 1041, 1025 cm$^{-1}$; $^1$H NMR (500 MHz, MeOD-D3, TMS): $\delta =$ 1.55 (q, $J = 8.14$ Hz, 2H) 1.62–1.74 (m, 6H), 2.39–2.46 (m, 12H), 2.46–2.57 (m, 4H), 2.61 (t, $J = 11.8$ Hz, 2H), 2.83 (d, $J = 11.2$ Hz, 2H), 2.94–3.03 (m, 2H), 3.85 (s, 3H), 6.12 (s, 2H), 6.93 (t, $J = 7.6$ Hz, 1H), 6.98 (d, $J =$ 8.2 Hz, 1H), 7.21–7.25 (m, 1H), 7.48 (dd, $J = 1.7/7.8$ Hz, 1H) ppm; $^{13}$C NMR (125 MHz, MeOD-D3): $\delta = 14.4$ (2C, $NC\underline{C}H_3$), 16.6 (2C, $NCC\underline{C}H_3$), 27.2 ($\underline{C}H_2CH_2NCH_2CH_2C$), 29.2 ($CC\underline{C}H_2CH_2$), 29.3 ($CCCH_2\underline{C}H_2$), 32.9 ($\underline{C}H_2CH_2CH_2NCH_2CH_2C$), 35.5 (2C, $N\underline{C}H_2CH_2C$), 50.4 (2C, $NCH_2\underline{C}H_2C$), 55.6 ($O\underline{C}H_3$), 59.7 ($\underline{C}H_2NCH_2CH_2C$), 71.9 ($\underline{C}OH$), 112.7 ($CC_{ar}C_{ar}\underline{C}_{ar}H$), 121.7 ($CC_{ar}C_{ar}H\underline{C}_{ar}H$), 122.6 (2C, $C\underline{C}HC$), 127.0 ($CC_{ar}\underline{C}_{ar}H$), 129.5 ($C_{ar}C_{ar}C_{ar}H\underline{C}_{ar}H$), 132.6 (2C, $NCCCH_2$), 136.5 ($C\underline{C}_{ar}$), 142.2 (2C, $NC\underline{C}CH_3$), 148.1 ($NC\underline{C}CH_2$), 154.9 (2C, $N\underline{C}CH_3$), 158.3 ($\underline{C}_{ar}O$) ppm; $^{19}$F NMR (470 MHz, MeOD-D3): $\delta = -147.5$ to $-146.9$ (m) ppm; $^{11}$B NMR (160 MHz, MeOD-D3): $\delta = -2.25$ (t, $J = 32.5$ Hz) ppm; M ($C_{30}H_{40}BF_2N_3O_2$) = 523.32 MS (FAB$^+$, NBA) m/z (%): 524.3 ($[M+H]^+$); HRMS (FAB$^+$, NBA): $[M+H]^+$ calc. for $C_{30}H_{41}BF_2N_3O_2$, 524.3254; found: 524.3264.

**5,5-Difluoro-10-{5-[4-hydroxy-4-(4-methoxyphenyl)piperidin-1-yl]pentyl}-1,3,7,9-tetramethyl-5*H*-4 λ$^4$,5 λ$^4$-dipyrrolo[1,2-*c*:2',1'-*f*][1,3,2]diazaborinin-4-ium-5-uide (10i)** According to **GP-3 (Method C)**: Compound **17** (117 mg, 295 µmol) and 4-(4-methoxyphenyl)piperidin-4-ol (**7i**) (86.0 mg, 413 µmol) and $K_2CO_3$ (122 mg, 855 µmol) in MeCN (2.5 mL). Flash-SC (*n*-heptane/EtOAc 5:4, 10% $NEt_3$).

86 mg (56%); orange solid; mp 99–108 °C; DC: $R_f = 0.28$ (EtOAc/*n*-heptane 5:4, 10% $NEt_3$); IR (KBr) $\nu_{max}$ 3375, 2926, 2852, 1609, 1549, 1510, 1471, 1410, 1373, 1308, 1249, 1224, 1200, 1159, 1109, 1079, 1030 cm$^{-1}$; $^1$H NMR (500 MHz, MeOD-D3, TMS): $\delta = 1.50$–$1.59$ (m, 2H), 1.60–1.70 (m, 4H), 1.74 (d, $J = 12.4$ Hz, 2H), 2.07 (td, J = 4.3/13.4 Hz, 2H) 2.42 (s, 6H), 2.42–2.44 (m, 8H), 2.53 (t, $J = 11.1$ Hz, 2H), 2.80 (d, $J = 11.3$ Hz, 2H), 2.94–3.01 (m, 2H), 3.76 (s, 3H), 6.12 (s, 2H), 6.85–6.90 (m, 2H), 7.36–7.42 (m, 2H) ppm; $^{13}$C NMR (125 MHz, MeOD-D3): $\delta = 14.4$ (2C, $NC\underline{C}H_3$), 16.6 (2C, $NCC\underline{C}H_3$), 27.4 ($CCH_2CH_2CH_2\underline{C}H_2$), 29.3 ($CCCH_2\underline{C}H_2$), 29.3 ($CC\underline{C}H_2$), 32.9 ($CCH_2CH_2\underline{C}H_2$), 38.8 (2C, $N\underline{C}H_2CH_2C$), 50.7 (2C, $NCH_2\underline{C}H_2C$), 55.6 ($O\underline{C}H_3$), 59.8 ($\underline{C}H_2NCH_2CH_2C$), 71.2 ($\underline{C}OH$), 114.4 (2C, $C_{ar}C_{ar}H\underline{C}_{ar}HC_{ar}O$), 122.6 (2C, $C\underline{C}HC$), 126.9 (2C, $C_{ar}\underline{C}_{ar}HC_{ar}HC_{ar}O$), 132.6 (2C, $NCCCH_2$), 142.0 ($C\underline{C}_{ar}$), 142.2 (2C, $NC\underline{C}CH_3$), 148.1 ($NC\underline{C}CH_2$), 154.9 (2C, $N\underline{C}CH_3$), 160.0 ($\underline{C}_{ar}O$) ppm; $^{19}$F NMR (470 MHz, MeOD-D3): $\delta = -147.6$ to $-146.6$ (m) ppm; $^{11}$B NMR (160 MHz, MeOD-D3): $\delta = -2.27$ (t, $J = 32.6$ Hz, H) ppm; M ($C_{30}H_{40}BF_2N_3O_2$) = 523.32 MS (CI, $CH_5^+$) m/z (%): 524.20 (63, $[M+H]^+$), 606.30 (63), 486.20 (100); HRMS (EI+): $M^+$ calc. for $C_{30}H_{40}BF_2N_3O_2$, 523.3176; found: 523.3183.

**4-(2-Chlorophenyl)-1-[5-(5,5-difluoro-1,3,7,9-tetramethyl-5*H*-4λ$^4$,5λ$^4$-dipyrrolo[1,2-*c*:2′,1′-*f*][1,3,2]diazaborinin-10-yl) pentyl]piperidin-4-ol (10j)** According to **GP-3 (Method C)**: Compound **17** (117 mg, 295 µmol) and 4-(2-chlorophenyl) piperidin-4-ol (**7j**) (87.0 mg, 413 µmol) and $K_2CO_3$ (122 mg, 855 µmol) in MeCN (2.5 mL). Flash-SC (1. *n*-heptane/EtOAc 1:1, 10% $NEt_3$, 2. Gradient: *n*-heptane/EtOAc 1:1 → *n*-Heptane/EtOAc 1:1, 10% $NEt_3$).

130 mg (83%); orange solid; mp 160 °C dec. DC: $R_f =$ 0.2 (*n*-heptane/EtOAc 1:1, 10% $NEt_3$); IR (KBr) $\nu_{max}$ 3427, 2925, 2864, 2811, 1625, 1550, 1510, 1471, 1432, 1409, 1371, 1309, 1263, 1225, 1201, 1158, 1107, 1079, 1063, 1037 cm$^{-1}$; $^1$H NMR (500 MHz, $CD_2Cl_2$, TMS): $\delta =$ 1.51–1.62 (m, 4H), 1.64–172 (m, 2H), 1.95 (dd, $J = 2.4/$ 13.4 Hz, 2H), 2.27–2.43 (m, 6H), 2.44 (s, 6H), 2.46 (s, 6H), 2.76 (d, $J = 10.9$ Hz, 2H), 2.93–3.01 (m, 2H), 6.09 (s, 2H), 7.22 (td, $J = 1.7/7.6$ Hz, 1H), 7.28 (td, $J = 1.5/7.6$ Hz, 1H), 7.37 (dd, $J = 1.4/7.8$ Hz, 1H), 7.60 (dd, $J = 1.7/7.9$ Hz, 1H) ppm; $^{13}$C NMR (125 MHz, $CD_2Cl_2$, TMS): $\delta = 14.6$ (2C, $NCC\underline{C}H_3$), 16.6 (2C, $NCC\underline{C}H_3$), 27.2 ($CCH_2CH_2\underline{C}H_2$), 28.6 ($CCH_2\underline{C}H_2CH_2$), 29.0 ($NCC\underline{C}H_2$), 32.2 ($CCH_2CH_2CH_2\underline{C}H_2$), 36.1 (2C, $N\underline{C}H_2CH_2C$), 49.7 (2C, $NCH_2\underline{C}H_2C$), 58.6 ($\underline{C}H_2NCH_2CH_2C$), 72.4 ($\underline{C}OH$), 121.9 (2C, $C\underline{C}HC$), 127.5 ($CC_{ar}\underline{C}_{ar}H$), 127.7 ($CC_{ar}C_{ar}H\underline{C}_{ar}H$), 128.8 ($C_{ar}C_{ar}C_{ar}H\underline{C}_{ar}H$), 131.8 (2C, $N\underline{C}CCH_2$), 132.0 ($C_{ar}C_{ar}\underline{C}_{ar}H$), 132.3 ($\underline{C}_{ar}Cl$), 141.2 (2C, $NC\underline{C}CH_3$), 144.4

($C\underline{C}_{ar}$), 147.4 ($NC\underline{C}CH_2$), 154.0 (2C, $NC\underline{C}H_3$) ppm; $^{19}F$ NMR (470 MHz, $CD_2Cl_2$): $\delta = -146.1$ to $-146.9$ (m) ppm; $^{11}B$ NMR (160 MHz, $CD_2Cl_2$): $\delta = -0.47$ (t, $J = 33.0$ Hz) ppm; M ($C_{29}H_{37}BClF_2N_3O$) = 527.27 MS (EI, 70 eV) m/z (%): 527.36 (20, $M^+$), 224.05 (69), 199 (90), 94.05 (100); HRMS (EI+): $M^+$ calc. for $C_{29}H_{37}BClF_2N_3O$, 527.2681; found: 527.2681.

**10-{5-[4-(4-Chlorophenyl)-4-hydroxypiperidin-1-yl]pentyl}-5,5-difluoro-1,3,7,9-tetramethyl-5*H*-4 λ⁴,5 λ⁴-dipyrrolo[1,2-*c*:2′,1′-*f*][1,3,2]diazaborinin-4-ium-5-uide (10k)** According to **GP-3 (Method C)**: Compound **17** (117 mg, 295 µmol) and 4-(4-chlorophenyl)piperidin-4-ol (**7k**) (87.0 mg, 413 µmol) and $K_2CO_3$ (122 mg, 855 µmol) in MeCN (2.5 mL). Flash-SC (1. *n*-heptane/EtOAc 5:4, 10% $NEt_3$, 2. Gradient: *n*-heptane/EtOAc 5:4 → *n*-heptane/EtOAc 5:4, 10% $NEt_3$).

121 mg (77%); orange solid; mp 119 °C; DC: $R_f = 0.24$ (*n*-heptane/EtOAc 5:4, 10% $NEt_3$); IR (KBr): $\tilde{\nu} = 3426$, 2929, 2863, 2813, 2361, 2342, 1550, 1510, 1474, 1409, 1373, 1309, 1225, 12101, 1159, 1080 $cm^{-1}$. $^1H$ NMR (500 MHz, $CD_2Cl_2$, TMS): $\delta = 1.50$–$1.62$ (m, 4H), 1.63–1.71 (m, 4H), 2.01–2.10 (m, 2H), 2.30–2.43 (m, 4H), 2.44 (s, 6H), 2.47 (s, 6H), 2.76 (d, $J = 10.6$ Hz, 2H), 2.94–2.99 (m, 2H), 6.09 (s, 2H), 7.30–7.34 (m, 2H), 7.43–7.47 (m, 2H) ppm; $^{13}C$ NMR (100 MHz, $CD_2Cl_2$, TMS): $\delta = 14.6$ (2C, $NC\underline{C}H_3$), 16.6 (2C, $NCC\underline{C}H_3$), 27.1 ($CCCH_2\underline{C}H_2$), 28.6 ($CCCH_2CH_2\underline{C}H_2$), 28.9 ($CC\underline{C}H_2$), 32.1 ($CH_2\underline{C}H_2CH_2N$), 38.9 (2C, $NCH_2\underline{C}H_2C$), 49.8 (2C, $N\underline{C}H_2CH_2C$), 58.6 ($\underline{C}H_2NCH_2CH_2C$), 71.4 ($\underline{C}OH$), 121.9 (2C, $C\underline{C}HC$), 126.7 (2C, $C_{ar}\underline{C}_{ar}H\underline{C}_{ar}HC_{ar}Cl$), 128.6 (2C, $C_{ar}\underline{C}_{ar}HC_{ar}HC_{ar}Cl$), 131.8 (2C, $N\underline{C}CCH_2$), 132.8 ($\underline{C}_{ar}Cl$) 141.2 (2C, $NC\underline{C}CH_3$), 147.3 ($NC\underline{C}CH_2$), 147.9 ($C\underline{C}_{ar}$), 154.0 (2C, $NC\underline{C}CH_3$) ppm; $^{19}F$ NMR (470 MHz, $CD_2Cl_2$): $\delta = -146.2$ to $-146.9$ (m) ppm; $^{11}B$ NMR (160 MHz, $CD_2Cl_2$): $\delta = -2.30$ (t, $J = 33.0$ Hz) ppm; M ($C_{29}H_{37}BClF_2N_3O$) = 527.27 MS (FAB, NBA) = 528.30 ($[M+H]^+$). HRMS (FAB, NBA): $[M+H]^+$ calc. for $C_{29}H_{38}BClF_2N_3O$, 528.2759; found: 528.2766.

**10-{5-[3-(Ethoxycarbonyl)piperidin-1-yl]pentyl}-5,5-difluoro-1,3,7,9-tetramethyl-5*H*-4 λ⁴,5 λ⁴-dipyrrolo[1,2-*c*:2',1'-*f*][1,3,2]diazaborinin-4-ium-5-uide (10l)** According to **GP-3 (Method C)**: Compound **17** (351 mg, 885 µmol) and ethyl piperidine-3-carboxylate (**7l**) (201 mg, 1.24 mmol, 0.2 mL) and $K_2CO_3$ (367 mg, 2.65 mmol) in MeCN (7.5 mL). Flash-SC (1. *n*-heptane/EtOAc 8:1, 10% $NEt_3$, 2. Gradient: *n*-heptane/EtOAc 8:1 → *n*-heptane/EtOAc 1:1, 10% $NEt_3$).

398 mg (95%); red oil. DC: $R_f = 0.16$ (*n*-heptane/EtOAc 8:1, 10% $NEt_3$); IR (film) $\nu_{max}$ 2939, 2864, 2805, 2770, 1730, 1550, 1511, 1474, 1410, 1371, 1309, 1224, 1201, 1159, 1079, 1029 $cm^{-1}$; $^1H$ NMR (500 MHz, $CD_2Cl_2$, TMS): $\delta = 1.23$ (t, $J = 7.14$ Hz, 3H), 1.37–1.60 (m, 6H), 1.60–1.73 (m, 3H), 1.84–1.92 (m, 1H), 1.95 (t, $J = 10.1$ Hz, 1H), 2.11 (t, $J = 10.7$ Hz, 1H), 2.32 (t, $J = 6.9$ Hz, 2H), 2.43 (s, 6H), 2.46 (s, 7H), 2.68 (d, $J = 10.7$ Hz, 1H), 2.89 (d, $J = 9.9$ Hz, 1H), 2.92–2.99 (m, 2H), 4.08 (q, $J = 7.1$ Hz, 2H), 6.09 (s, 2H) ppm; $^{13}C$ NMR (125 MHz, $CD_2Cl_2$, TMS): $\delta = 14.4$ (2C, $NCC\underline{C}H_3$), 14.6 ($OCH_2\underline{C}H_3$), 16.6 (2C, $NCC\underline{C}H_3$), 25.1 ($NCH_2\underline{C}H_2CH_2CH$), 27.0 ($\underline{C}H_2CH_2NCH_2CH$), 27.5 ($NCH_2CH_2CH_2\underline{C}H$), 28.4 ($CCH_2CH_2\underline{C}H_2$), 29.0 ($C\underline{C}H_2$), 32.1 ($CCH_2\underline{C}H_2$), 42.4 ($NCH_2\underline{C}H$), 53.8 ($N\underline{C}H_2CH_2CH_2CH$), 56.0 ($N\underline{C}H_2CH$), 58.7 ($\underline{C}H_2NCH_2CH$), 60.5 ($O\underline{C}H_2$), 121.9 (2C, $C\underline{C}HC$), 131.8 (2C, $N\underline{C}CCH_2$), 141.2 (2C, $NC\underline{C}CH_3$), 147.4 ($NC\underline{C}CH_2$), 154.0 (2C, $N\underline{C}CH_3$), 174.5 ($\underline{C}O$) ppm; $^{19}F$ NMR (375 MHz, $CD_2Cl_2$): $\delta = -146.3$ to $-146.8$ (m) ppm; $^{11}B$ NMR (160 MHz, $CD_2Cl_2$): $\delta = -0.47$ (t, $J = 32.9$ Hz) ppm; M ($C_{26}H_{38}BF_2N_3O_2$) = 473.30 MS ($FAB^+$, NBA) m/z (%): 473.5 ($M^+$); HRMS ($FAB^+$, NBA): $M^+$ calc. for $C_{26}H_{38}BF_2N_3O_2$, 473.3020; found: 473.3028.

**10-[5-(3-Carboxypiperidin-1-yl)pentyl]-5,5-difluoro-1,3,7,9-tetramethyl-5*H*-4 λ⁴,5 λ⁴-dipyrrolo[1,2-*c*:2',1'-*f*][1,3,2]diazaborinin-4-ium-5-uide (10m)** According to **GP-2**: Compound **10l** (389 mg, 0.82 mmol) in 11.0 mL solvent mixture ($CH_2Cl_2$/MeOH, 2:1) and LiOH (49.0 mg, 2.10 mmol) solved in $H_2O$ (2.1 mL). The reaction mixture was stirred for 7 d. The pH was adjusted to pH = 7 by adding HCl (0.1 M).

281 mg (77%); orange solid; Mp 105–107 °C dec; IR (KBr) $\nu_{max}$ 3433, 2933, 2866, 1702, 1629, 1549, 1511, 1474, 1408, 1371, 1308, 1224, 1200, 1159, 1080, 1028 $cm^{-1}$. $^1H$ NMR (400 MHz, $C_2D_2Cl_4$, 40 °C, TMS): $\delta = 1.45$–$1.76$ (m, 8H), 1.79–1.95 (m, 1H), 2.01 (d, $J = 13.8$ Hz, 1H), 2.28 (t, $J = 11.9$ Hz, 1H), 2.41 (s, 7H), 2.49 (s, 6H), 2.56 (dt, $J = 3.9/7.5$ Hz, 2H), 2.68 (s, 1H), 2.95 (dd, $J = 7.0/9.8$ Hz, 2H), 3.03 (d, $J = 11.7$ Hz, 1H), 3.13 (d, $J = 11.2$ Hz, 1H), 6.08 (s, 2H) ppm; $^{13}C$ NMR (100 MHz, $C_2D_2Cl_4$, 40 °C, TMS): $\delta = 14.5$ (2C, $NC\underline{C}H_3$), 16.3 (2C, $CC\underline{C}H_3$), 21.7 ($NCH_2\underline{C}H_2CH_2CH$), 25.5 ($CCH_2\underline{C}H_2$), 26.2 ($CH_2\underline{C}H_2CHC$), 27.6 ($CCH_2CH_2\underline{C}H_2$), 28.1 ($C\underline{C}H_2$), 31.4 ($CCH_2CH_2CH_2\underline{C}H_2$), 39.8 ($\underline{C}HCO$), 53.0 ($N\underline{C}H_2CH_2CH_2CH$), 55.0 ($N\underline{C}H_2CH$), 57.0 ($CCH_2CH_2CH_2CH_2\underline{C}H_2N$), 121.8 (2C, $C\underline{C}HC$), 131.3 (2C, $C\underline{C}CH_3$), 140.4 (2C, $N\underline{C}CCH_2$), 145.8 ($\underline{C}CH_2$), 154.0 (2C, $N\underline{C}CH_3$), 176.2 ($\underline{C}O$) ppm; $^{19}F$ NMR (470 MHz, $C_2D_2Cl_4$): $\delta = -144.3$ to $-147.0$ (m) ppm; $^{11}B$ NMR (160 MHz, $C_2D_2Cl_4$): $\delta = -0.45$ (t, $J = 32.9$ Hz) ppm; M ($C_{24}H_{34}BF_2N_3O_2$) = 445.27; MS ($FAB^+$, NBA) m/z (%): 446.3 ($[M+H]^+$); HRMS ($FAB^+$, NBA): $[M+H]^+$ calc. for $C_{24}H_{35}BF_2N_3O_2$, 446.2785; found: 446.2787.

**10-(3-Chloropropyl)-5,5-difluoro-1,3,7,9-tetramethyl-5*H*-4 λ⁴,5 λ⁴-dipyrrolo[1,2-*c*:2',1'-*f*][1,3,2]diazaborinin-4-ium-5-uide (15a)** According to **GP-1**: 4-Chlorobutyrylchloride (**12**) (1.15 g, 8.15 mmol, 915.0 µL) and 2,4-Dimethylpyrrole (**11**) (1.57 g, 16.5 mmol, 1.7 mL) in $CH_2Cl_2$ (90.0 mL), as well as $NEt_3$ (3.89 g, 38.0 mmol, 5.4 mL) and $BF_3$•$OEt_2$ (7.83 g, 55.2 mmol, 7.0 mL) in toluene (190.0 mL) and $CH_2Cl_2$ (10.0 mL). Flash-SC (*n*-Pentane/EtOAc = 9:1) (Kamkaew and Burgess 2013).

930 mg (35%); orange solid; mp 169 °C; DC: $R_f = 0.55$ (*n*-pentane/EtOAc = 9:1); IR (KBr) $\nu_{max}$3416, 2962, 2923, 2362, 1702, 1551, 1531, 1508, 1478, 1444, 1430, 1405, 1365, 1349, 1306, 1270, 1210, 1194, 1155, 1099, 1075, 1048, 1022, 990 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$, TMS): $\delta = 2.05–2.12$ (m, 2H), 2.44 (s, 6H), 2.52 (s, 6H), 3.11–3.17 (m, 2H), 3.71 (t, $J = 6.0$, 2H), 6.06 (s, 2H) ppm $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta = 14.7$ (2C, CHC($\underline{C}H_3$)CC), 16.7 (2C, NC$\underline{C}H_3$), 26.1 ($\underline{C}H_2$C), 34.2 (ClCH$_2\underline{C}H_2$), 44.9 (Cl$\underline{C}H_2$), 122.0 (2C, C$\underline{C}$HC), 131.6 (2C, NCCCH), 140.5 (2C, NC$\underline{C}$CH), 144.6 (NC$\underline{C}$CH$_2$), 154.5 (2C, N$\underline{C}$CH) ppm; $^{19}F$ NMR (470 MHz, $CDCl_3$): $\delta =$ −146.7 to −146.1 (m) ppm; $^{11}B$ NMR (160 MHz, $CDCl_3$): $\delta = -1.99$ (t, $J = 32.9$) ppm; M ($C_{16}H_{20}BClF_2N_2$) = 324.14 MS (CI) m/z (%): 325 (35, $[M+H]^+$), 305 (100); HRMS (EI): M calc. for $C_{16}H_{20}BClF_2N_2$, 324.1371; found: 324.1369.

**5,5-Difluoro-1,3,7,9-tetramethyl-10-[3-(tosyloxy)propyl]-5*H*-4 λ⁴,5 λ⁴-dipyrrolo[1,2-*c*:2',1'-*f*][1,3,2]diazaborinin-4-ium-5-uide (15b)** **19** (1.38 g, 4.51 mmol) was solved in $CH_2Cl_2$ (45.0 mL) and cooled to 0 °C. After adding of $NEt_3$ (1.46 g, 14.4 mmol, 1.9 mL) and DMAP (55.0 mg, 0.450 mmol), *p*-toluolsulfonylchloride (1.72 g, 9.02 mmol) was added and the reaction mixture was allowed to warm up to room temperature and was stirred overnight afterwards. After washing with $H_2O$ and brine, the organic phase was dried over $Na_2SO_4$, filtered, and the solvent was removed. The remaining residue was purified by flash-SC ($CH_2Cl_2$/*iso*-hexane 3:1).

1.94 g (94%); orange solid; mp 171–173 °C; $R_f = 0.3$ ($CH_2Cl_2$/*iso*-Hexan 3:1); IR (KBr) $\nu_{max}$ 2960, 2924, 1598, 1552, 1512, 1473, 1408, 1361, 1307, 1277, 1224, 1203, 1176, 1159, 1096, 1077, 1026 $cm^{-1}$; $^1H$ NMR (400 MHz, $CD_2Cl_2$, TMS): $\delta = 1.94$ (dt, $J = 5.8/17.2$ Hz, 2H), 2.36 (s, 6H), 2.45 (s, 9 H), 2.96–3.02 (m, 2H), 4.16 (t, $J = 5.9$ Hz, 2H), 6.08 (s, 2H), 7.39 (d, $J = 7.9$ Hz, 2H), 7.78 (d, $J =$ 8.3 Hz, 2H) ppm; $^{13}C$ NMR (100 MHz, $CD_2Cl_2$, TMS): $\delta =$ 14.6 (2C, NC$\underline{C}H_3$), 16.6 (2C, NCC$\underline{C}H_3$), 21.8 ($H_3\underline{C}C_{ar}$), 25.0 ($\underline{C}H_2$), 31.2 ($\underline{C}H_2CH_2O$), 70.1 ($\underline{C}H_2O$), 122.2 (2C, C$\underline{C}$HC), 128.2 (2C, $SC_{ar}C_{ar}H\underline{C}_{ar}HC_{ar}$), 130.4 (2C, $SC_{ar}$-$\underline{C}_{ar}HC_{ar}HC_{ar}$), 131.6 (2C, NCCCH), 133.1 (S$\underline{C}_{ar}$), 141.1 (2C, NC$\underline{C}$CH), 144.8 (NC$\underline{C}$CH$_2$), 145.76 ($H_3C\underline{C}_{ar}$), 154.7 (2C, N$\underline{C}$CH) ppm; $^{19}F$ NMR (470 MHz, $CD_2Cl_2$): $\delta =$ −146.1 to −146.7 (m) ppm; $^{11}B$ NMR (160 MHz, $CD_2Cl_2$): $\delta = -2.34$ (t, $J = 32.8$ Hz) ppm; M ($C_{23}H_{27}BF_2N_2O_3S$) = 460.18. MS (CI, $CH_5^+$) m/z (%): 461.12 (12, $[M+H]^+$), 442.20 (31), 441.20 (100); HRMS (EI+): $M^+$ calc. for $C_{23}H_{27}BF_2N_2O_3S$, 460.1798; found: 460.1821.

**10-(4-Chlorobutyl)-5,5-difluoro-1,3,7,9-tetramethyl-5*H*-4 λ⁴,5 λ⁴-dipyrrolo[1,2-*c*:2',1'-*f*][1,3,2]diazaborinin-4-ium-5-uide (16)** According to **GP-1**: 5-Chloropentanoylchloride (**13**) (1.86 g, 12.0 mmol, 1.6 mL) and 2,4-Dimethylpyrrole (**11**) (2.35 g, 24.0 mmol, 2.6 mL) in $CH_2Cl_2$ (135.0 mL), as well as $NEt_3$ (5.83, 57.0 mmol 8.0 mL) and $BF_3$•$OEt_2$ (11.8 g, 83.0 mmol, 10.5 mL) in toluene (285.0 mL) and $CH_2Cl_2$ (15.0 mL). Flash-SC (*i*-Hexane/$CH_2CL_2$ = 1:1) (Esfandiari et al. 2010).

1.86 g (46%); orange solid; mp 168 °C; DC: $R_f = 0.27$ (*i*-hexane/$CH_2Cl_2$ = 1:1); IR (KBr) $\nu_{max}$ 3127, 2995, 2963 2927, 2874, 1549, 1534, 1508, 1476, 1446, 1409, 1366, 1308, 1254, 1204, 1161, 1111, 1079, 1071, 1023, 988 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$, TMS): $\delta = 1.76–1.84$ (m, 2H), 1.93–2,00 (m, 2H), 2.41 (s, 6H), 2.52 (s, 6H), 2.94–2.99 (m, 2H), 3.58 (t, $J = 6.4$, 2H), 6.06 (s, 2H) ppm; $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta = 14.7$ (2C, NC$\underline{C}H_3$), 16.6 (2C, NCC$\underline{C}H_3$), 27.8 (C$\underline{C}H_2$), 29.1 (CCH$_2\underline{C}H_2$), 33.1 ($\underline{C}H_2CH_2Cl$), 44.5 ($\underline{C}H_2Cl$) 121.9 (2C, C$\underline{C}$HC), 131.6 (2C, NCCCH), 140.5 (2C, NC$\underline{C}$CH), 145.6 (NC$\underline{C}$CH$_2$), 154.3 (2C, N$\underline{C}$CH$_3$) ppm; $^{19}F$ NMR (500 MHz, $CDCl_3$): $\delta =$ −146.4 to −146.7 ppm; $^{11}B$ NMR (160 MHz, $CDCl_3$): $\delta = -1.91$ (t $J = 32.9$ Hz) ppm; M ($C_{17}H_{22}BClF_2N_2$) = 338.15. MS (CI, $CH_5^+$) m/z (%): 339 (33, $[M+H]^+$), 319 (100); HRMS (EI+): M calc. for $C_{17}H_{22}BClF_2N_2$, 338.1533; found: 338.1537.

**10-(5-Bromopentyl)-5,5-difluoro-1,3,7,9-tetramethyl-5*H*-4 λ⁴,5 λ⁴-dipyrrolo[1,2-*c*:2',1'-*f*][1,3,2]diazaborinin-4-ium-5-uide (17)** According to **GP-1**: 5-Bromovalerylchloride (**14**) (1.71 g, 8.00 mmol, 1.2 mL) and 2,4-Dimethylpyrrol (**11**) (1.57 g, 16.0 mmol, 1.7 mL) in $CH_2CL_2$ (90.0 mL), as well as $NEt_3$ (3.89 g, 38.0 mmol, 5.4 mL) and $BF_3$•$OEt_2$ (7.83 g, 55.0 mmol, 7.0 mL) in toluene (190.0 mL) and $CH_2CL_2$ (10.0 mL). Flash-SC (*n*-heptane/EtOAc = 9:1).

1.43 g (45%); orange solid; mp 134 °C; DC: $R_f = (0.27)$; IR (KBr) $\nu_{max}$ 3442, 2956, 2929, 2867, 1552, 1532, 1509, 1475, 1439, 1408, 1371, 1340, 1307, 1270, 1251, 1224, 1200, 1157, 1106, 1079, 1070, 1062, 1026 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$, TMS): $\delta = 1.62–1.68$ (m, 4H), 1.85–1.99 (m, 2H), 2.42 (s, 6H), 2.51 (s, 6H), 2.93–2.98 (m, 2H), 3.43 (t, $J = 6.6$ Hz, 2H), 6.06 (s, 2H) ppm; $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta = 14.6$ (2C, NC$\underline{C}H_3$), 16.6 (2C, NCC$\underline{C}H_3$), 28.4 (C$\underline{C}H_2$), 28.7 (CCH$_2\underline{C}H_2$), 31.0 ($\underline{C}H_2CH_2CH_2Br$), 32.3 ($\underline{C}H_2CH_2Br$), 33.5 ($\underline{C}H_2Br$), 121.8 (2C, C$\underline{C}$HC), 131.5 (2C, NC$\underline{C}$CH$_2$), 140.4 (2C, NC$\underline{C}$CH), 146.0 (NC$\underline{C}$CH$_2$), 154.1 (2C, N$\underline{C}$CH) ppm; $^{19}F$ NMR

(470 MHz, $CDCl_3$): $\delta = -147.1$ to $-146.1$ (m) ppm; $^{11}B$ NMR (160 MHz, $CDCl_3$): $\delta = -2.16$ (t, $J = 33.0$ Hz) ppm; M ($C_{18}H_{24}BBrF_2N_2$) = 396.11. MS (CI, $CH_5^+$) m/z (%): 397.15 (33, $[M+H]^+$), 379.15 (100); HRMS (EI+): $M^+$ calc. for $C_{18}H_{24}BBrF_2N_2$, 396.1179; found: 396.1174.

**5,5-Difluoro-10-(3-hydroxypropyl)-1,3,7,9-tetramethyl-5*H*-4 λ⁴,5 λ⁴-dipyrrolo[1,2-*c*:2',1'-*f*][1,3,2]diazaborinin-4-ium-5-uide (19)** BODIPY **18** (1.88 g, 4.13 mmol) was dissolved in $CH_2Cl_2$ (40.0 mL) and MeOH (20.0 mL) and LiOH (237 mg, 9.91 mmol) dissolved in $H_2O$ (10.0 mL) was added dropwise. The reaction mixture was stirred at room temperature for 4 h, and the solvent was removed. The remaining residue was dissolved in EtOAc and washed with $H_2O$ and brine. The organic phase was dried with $Na_2SO_4$, filtered, and the solvent was removed to gain pure **19**.

1.21 g (96%); orange solid; mp 188–190 °C; IR (KBr) $\nu_{max}$ 3560, 3374, 2954, 2869, 1549, 1508, 1473, 1409, 1368, 1305, 1268, 1225, 1202, 1161, 1134, 1102, 1078, 1056 $cm^{-1}$; $^1H$ NMR (400 MHz, $CD_2Cl_2$, TMS): $\delta = 1.62$ (t, $J = 4.9$ Hz, 1H), 1.77–1.90 (m, 2H), 2.44 (s, 6H), 2.47 (s, 6H), 3.02–3.09 (m, 2H), 3.77 (dd, $J = 5.7/10.9$ Hz, 2H), 6.09 (s, 2H). $^{13}C$ NMR (100 MHz, $CD_2Cl_2$, TMS): $\delta = 14.6$ (4C, NC$\underline{C}H_3$), 16.7 (C$\underline{C}H_2$), 25.5 ($\underline{C}H_2CH_2O$), 34.8 ($CH_2\underline{C}H_2O$), 62.7 ($\underline{C}H_2O$), 122.0 (2C, C$\underline{C}$HC), 131.8 (2C, N$\underline{C}$C) 141.3 (2C, NC$\underline{C}$CH), 146.9 (NC$\underline{C}CH_2$), 154.2 (N$\underline{C}$CH) ppm; $^{19}F$ NMR (470 MHz, $CD_2Cl_2$): $\delta = -146.1$ to $-146.7$ (m) ppm; $^{11}B$ NMR (160 MHz, $CD_2Cl_2$): $\delta = -2.25$ (t, $J = 33.0$ Hz, H) ppm; M ($C_{16}H_{21}BF_2N_2O$) = 306.17. MS (CI, $CH_5^+$) m/z (%): 307.15 (17, $[M+H]^+$), 287.15 (100); HRMS (EI+): $M^+$ calc. for $C_{16}H_{21}BF_2N_2O$, 306.1710; found: 306.1718.

**Benzyl 4-hydroxy-4-(2-methoxyphenyl)piperidine-1-carboxylate (22)** 2-Bromanisole (6.0 µl, 4.82 mmol) was added to Mg turnings (680 mg, 28.0 mmol) covered with dry THF (6.0 ml) and stirred vigorously at room temperature. After the Grignard reaction was finished, the reaction mixture was stirred for another 30 minutes. To this reaction mixture *N*-benzyloxycarbonyl-4-piperidone (**20**, 1.00 g, 4.29 mmol), solved in dry THF (3.00 ml) was added dropwise, and the mixture was stirred for 1 h at room temperature. The excess Mg turnings were removed by filtration through cotton wool, the reaction was quenched with addition of 2 N HCl (7.00 mL), and extracted three times with $Et_2O$. The $Et_2O$ extract was washed with brine, dried over $MgSO_4$, filtered, and the solvent was removed. The remaining residue was purified by flash-chromatography (*n*-pentane/EtOAc 3:1, 1% $NEt_3$).

1.10 g (76%); yellow solid; mp 101–104 °C; DC: $R_f = 0.38$ (EtOAc/*n*-pentane = 1:3, 1% $NEt_3$); IR (KBr) $\nu_{max}$ 3448, 3076, 3034, 3009, 2998, 2959, 2934, 2916, 2839, 2025, 1981, 1963, 1945, 1907, 1879, 1822, 1665, 1598, 1571, 1527, 1488, 1477, 1438, 1395, 1366, 1352, 1322, 1274, 1250, 1199, 1182, 1162, 1146, 1104, 1081, 1033 $cm^{-1}$; $^1H$ NMR (400 MHz, DMSO-D6, TMS): $\delta = 1.40$ (d, $J = 13.3$ Hz, 2H), 2.37 (td, $J = 4.6/13.3$ Hz, 2H), 3.10–3.31 (m, 2H), 3.72 (s, 3H), 3.89 (dd, $J = 12.3/4.2$ Hz, 2H), 5.00 (s, 1H), 5.06–5.17 (m, 2H), 6.90–6.99 (m, 2H), 7.18–7.25 (m, 1H), 7.28–7.43 (m, 5H), 7.58 (dd, $J = 1.7/7.7$ Hz, 1H) ppm; $^{13}C$ NMR (100 MHz, DMSO-D6): $\delta = 34.2$ (2C, $NCH_2\underline{C}H_2C$), 40.0 (2C, N$\underline{C}H_2CH_2C$), 55.2 ($H_3\underline{C}O$), 65.8 (C$\underline{C}H_2O$), 70.1 ($CH_2\underline{C}CH_2$), 115.7 ($CC_{ar}C_{ar}\underline{C}_{ar}H$), 120.1 ($C_{ar}C_{ar}HC_{ar}H\underline{C}_{ar}H$), 126.3 ($CC_{ar}\underline{C}_{ar}H$), 127.3 ($C_{ar}\underline{C}_{ar}HC_{ar}H$-$C_{ar}H$), 127.7 ($CC_{ar}C_{ar}HC_{ar}H\underline{C}_{ar}HC_{ar}HC_{ar}$), 127.9 (2C, $CC_{ar}C_{ar}H\underline{C}_{ar}H$), 128.3 (2C, $C_{ar}C_{ar}H\underline{C}_{ar}HC_{ar}H$), 135.9 ($CH_2\underline{C}C_{ar}$), 137.2 ($OCH_2\underline{C}_{ar}$), 154.5 (O*C*N), 156.0 ($H_3CO\underline{C}_{ar}$) ppm; M ($C_{20}H_{23}NO_4$) = 341.16 MS (FAB, NBA) *m/z* (%): 342.5 ($MH^+$); HRMS (FAB, NBA): $MH^+$ calc. for $C_{20}H_{24}NO_4$, 342.1700; found: 342.1711.

## Biological evaluation

### MS Binding Assay

The MS Binding Assays were performed with mGAT1 membrane preparations obtained from a stable HEK293 cell line and NO711 as non-labeled marker in competitive binding experiments as described previously (Zepperitz et al. 2006).

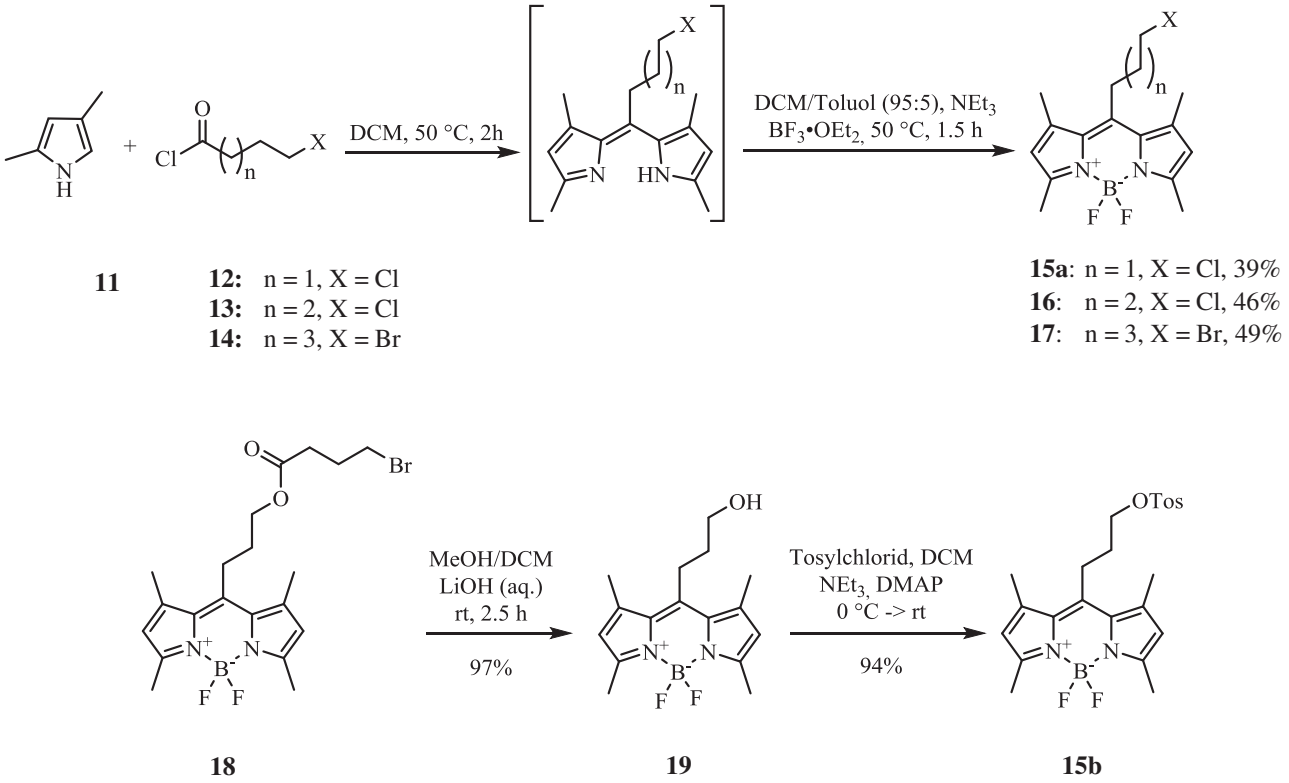
### GABA uptake assay

The [$^3$H]GABA uptake assays were performed in a 96-well plate format with intact HEK293 cells stably expressing mGAT1, mGAT2, mGAT3, and mGAT4, respectively, as described earlier (Kragler et al. 2008).

## Results and discussion

### Synthesis of the ligands

In general, as indicated above, fluorescent GAT inhibitors should be accessed by reaction of selected cyclic amines **7a-l** with the corresponding BODIPY dyes with an alkyl residue in *meso*-position provided with a terminal leaving group. The required BODIPY dyes with ω-halo-alkyl-chains of different lengths, i.e. with a propyl, butyl, or pentyl residue originating from the *meso*-position were synthesized in the form of their chlorides [**15a** and **16** (Groom et al. 2016)] or bromides (**17**). These syntheses were accomplished by following the general method shown in Scheme 1. In the first step, 2,4-dimethylpyrrole (**11**) was subjected to an acid catalyzed condensation reaction with acid chlorides **12–14** to give the corresponding




**Scheme 1** : Synthesis of the BODIYs **15–17** and **15b**

dipyrromethene intermediate which without prior isolation was transformed into the required BODIPY dyes **15a, 16–17** in moderate yields of 39 to 49% upon complexation with trifluoroboron etherate under basic conditions. Alternative synthetic procedures reported previously for compounds **15a** and **16** gave, in contrast to our synthesis, lower yields and inseparable product mixtures, respectively (Esfandiari et al. 2010; Kamkaew and Burgess 2013). In the course of the synthesis of the new fluorescent ligands, nucleophilic substitution reaction of propylchloride derivative BODIPY **15a** with cyclic amines were found to give low yields only. To overcome this problem, the chloride function in **15b** should be replaced by a tosyloxy moiety which is known to be a better leaving group resulting in *meso*-propyl BODIPY dye **15b**. For the synthesis of **15b**, BODIPY **18** prepared according to literature (Simonin et al. 2012) was subjected to basic hydrolysis (LiOH) to give **19** in almost quantitative yields. Here, the usage of LiOH was found to be essential since the application of bases with different counter ions such as sodium or potassium leads to the destruction of the boron complex (Smithen et al. 2012). Compound **19** was finally treated with tosylchloride in the presence of DMAP and $NEt_3$ to give **15b** in a very good yield (94%, Scheme 1).

For the construction of the target compounds, the fluorescent ligands **8a-m–10a-m**, in addition, the cyclic amine moieties **7a-l** shown in Fig. 2 were required. The cyclic amines **7a-g** as well as **7j** and **7l** were commercially available. Compound **7i** was synthesized as described in literature (Haradahira et al. 2002) and for the synthesis of its analogue **7h** with a 2-methoxy substituted phenyl residue, the same synthetic pathway was used, but (4-methyoxyphenyl)magnesiumbromide was replaced by (2-methoxyphenyl)magnesium bromide (**21**). Hence, the carbobenzoxy protected piperidone **20** was treated with Grignard reagent **21** resulting after aqueous workup in the addition product **22** which upon hydrogenerative removal of the protective group ($H_2$, Pd-C) gave the secondary cyclic amine **7h** in quantitative yield (Scheme 2). The synthesis of cyclic amine **7j** started from the *N*-Boc protected piperidine derivative **23** that had been accessed by a method described in a patent (Castelhano et al. 2002). For the removal of the *N*-Boc protective group from **23**, the reported reaction conditions were slightly varied (Castelhano et al. 2002). Instead of the described sulfuric acid in methanol hydrochloric acid in diethyl ether was used (Scheme 2). Upon this modification, the yield for the cleavage product **7j** increased

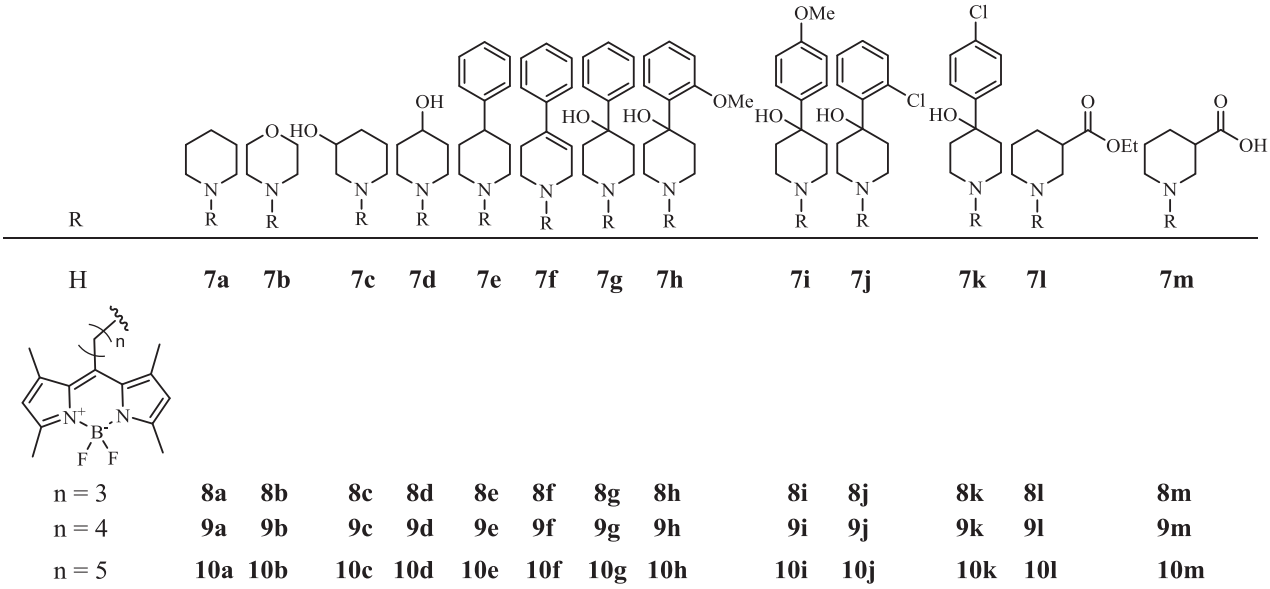
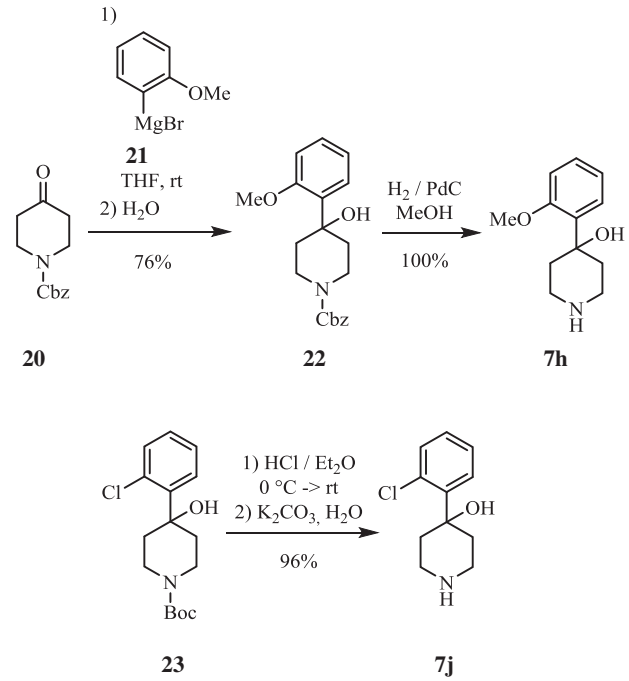



**Fig. 2** Structures of the used cyclic amines (**7a–m**) and the new BODIPY dyes **8a–m**, **9a–m**, and **10a–m**

from 52 to 96%, whereas the reaction time decreased from 3.5 days to 20 h (Scheme 2).

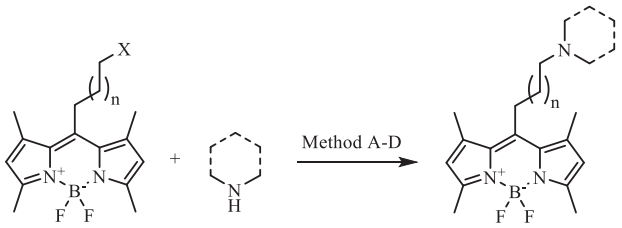
The first potential BODIPY derived GAT inhibitors were synthesized by reacting **15a** with four different amines, **7a**, **7b**, **7h**, and **7i**, respectively, in the presence of $K_2CO_3$ and KI, for an in situ Finkelstein reaction in acetone under microwave heating. The reaction resulted in low to good yields varying from 32% (**8a**), 54% (**8b**), 44% (**8h**) to 70% (**8i**), respectively (Table 1, method A, entry 1, 5, 23, and 26). Due to low yields observed in some cases, the BODIPY dye derived tosylate **15b** should be used instead of the chloro derivative **15a** for the subsequent reactions with remaining amines **7c–g** and **7j–l**. For comparative purposes, the first reaction of tosyl derivative **15b** was performed with piperidine (**7a**) in acetonitrile at 50 °C of which 3 equivalents were employed for the neutralization of acid formed during the reaction. As compared to the alkylation reaction with the chloro derivative **15a**, the yield with tosylate **15b** rose from 32 to 80% (compare Table 1, entry 1 and 2) indicating that the lower yields that had been obtained with **15a** are due to the lower reactivity of the latter. Here and in all subsequent alkylation reactions, acetonitrile instead of acetone was used as solvent due to better solubility of the reactants as for example of **15b**. Hence, the synthesis of target compounds **8c–g** and **8j–l** was accomplished by reacting the remaining amines **7c–g** and **7j–l** with tosylate **15b** under standard conditions resulting in good yields of 75–88% (Table 1, method B, entry 8, 11, 14, 17, 20, 29, 32, and 35). In case of the synthesis of the florescent ligands with a butyl spacer **9a–l**, BODIPY **16** exhibiting chloride as leaving group worked well as alkylating agent. Upon reaction with 1.4 equivalents of the corresponding amines




**Scheme 2** Synthesis of Amine **7h** and **7j**

**7a–l** in acetonitrile at 80 °C in the presence of $K_2CO_3$ and KI in acetonitrile (Table 1, method D), good yields ranging from 74 to 91% for **9a–l** could be achieved (Table 1, method D, entry 3, 6, 9, 12, 15, 18, 21, 24, 27, 30, 33, and 36). The ligands with a pentyl spacer **10a–l** were synthesized by reaction of BODIPY **17** with 1.4 equivalents of the corresponding amines **7a–l** in acetonitrile at 80 °C in the presence of $K_2CO_3$ (Table 1, method C). Though KI was

**Table 1** Synthesis of the fluorescent ligands for mGAT1–mGAT4




| Entry | BODIPY | Amine | Product | Yield [%] |
|---|---|---|---|---|
| 1 | **15a**[a] | **7a** | **8a** | 32 |
| 2 | **15b**[b] | - " - | **8a** | 80 |
| 3 | **16**[c] | - " - | **9a** | 86 |
| 4 | **17**[d] | - " - | **10a** | 78 |
| 5 | **15a**[a] | **7b** | **8b** | 54 |
| 6 | **16**[c] | - " - | **9b** | 78 |
| 7 | **17**[d] | - " - | **10b** | 82 |
| 8 | **15b**[b] | **7c** | **8c** | 81 |
| 9 | **16**[c] | - " - | **9c** | 81 |
| 10 | **17**[d] | - " - | **10c** | 58 |
| 11 | **15b**[b] | **7d** | **8d** | 82 |
| 12 | **16**[c] | - " - | **9d** | 74 |
| 13 | **17**[d] | - " - | **10d** | 80 |
| 14 | **15b**[b] | 7e | **8e** | 88 |
| 15 | **16**[c] | - " - | **9e** | 86 |
| 16 | **17**[d] | - " - | **10e** | 87 |
| 17 | **15b**[b] | **7f** | **8f** | 75 |
| 18 | **16**[c] | - " - | **9f** | 40 |
| 19 | **17**[d] | - " - | **10f** | 72 |
| 20 | **15b**[b] | **7g** | **8g** | 87 |
| 21 | **16**[c] | - " - | **9g** | 78 |
| 22 | **17**[d] | - " - | **10g** | 87 |
| 23 | **15a**[a] | **7h** | **8h** | 44 |
| 24 | **16**[c] | - " - | **9h** | 81 |
| 25 | **17**[d] | - " - | **10h** | 73 |
| 26 | **15a**[a] | **7i** | **8i** | 70 |
| 27 | **16**[c] | - " - | **9i** | 74 |
| 28 | **17**[d] | - " - | **10i** | 56 |
| 29 | **15b**[b] | **7j** | **8j** | 75 |
| 30 | **16**[c] | - " - | **9j** | 91 |
| 31 | **17**[d] | - " - | **10j** | 83 |
| 32 | **15a**[b] | **7k** | **8k** | 88 |
| 33 | **16**[c] | - " - | **9k** | 82 |
| 34 | **17**[d] | - " - | **10k** | 77 |
| 35 | **15b**[b] | **7l** | **8l** | 79 |
| 36 | **16**[c] | - " - | **9l** | 80 |
| 37 | **17**[d] | - " - | **10l** | 95 |

[a]Method A: 1.4 eq. of 7a-l, acetone, $K_2CO_3$, KI, 100 °C (Microwave)

[b]Method B: 3.0 eq. of 7a-l, acetonitrile, 50 °C

[c]Method D: 1.4 eq. of 7a-l, acetonitrile, $K_2CO_3$, KI, 80 °C

[d]Method C: 1.4 eq. of 7a-l, acetonitrile, $K_2CO_3$, 80 °C

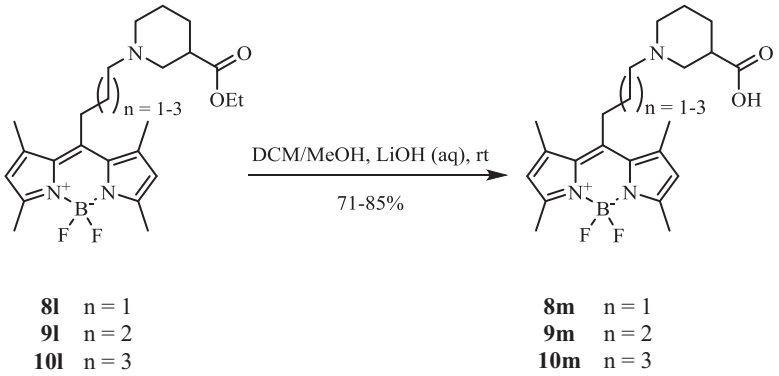
omitted in this case because of the presence of bromide as leaving group in **17**, yields amounted to satisfying 56–95% (Table 1, entry 4, 7, 10, 13, 16, 19, 22, 25, 28, 31, 34, and 37).

To obtain compounds **8m–10m** exhibiting a free nipecotic acid function for the biological testing, the ester function in **8l**, **9l**, and **10l** had to be hydrolyzed which was accomplished under basic conditions using LiOH in $H_2O$ providing the target compounds in yields of 71–85% (Scheme 3). Again, LiOH was used as base to avoid decomposition of the boron complex otherwise observed when sodium or potassium containing bases were employed (Smithen et al. 2012).

## Biological evaluation

For the synthesized fluorescent ligands **8a–k**, **8m**, **9a–m**, and **10a–m**, the binding affinities for mGAT1 were determined in MS Binding Assays with NO711 as MS marker (Zepperitz et al. 2006). In addition, these compounds were characterized with regard to their inhibitory potency at the GABA transporter subtypes mGAT1–mGAT4 using a standardized [$^3$H]GABA uptake assay which is based on HEK cell lines, stably expressing the individual GATs (Kragler et al. 2008). If NO711 binding in MS Binding Assays or [$^3$H]GABA uptake in [$^3$H]GABA uptake assays was decreased by at least 50% at a concentration of 100 µM, affinities ($pK_i$ values) or the inhibitory potencies ($pIC_{50}$ values) were determined in additional experiments. When compounds were not able to decrease NO711 binding or to reduce [$^3$H]GABA uptake to a value below 50% due to low potency at the test concentration of 100 µM, only the percentage of remaining NO711 binding and [$^3$H]GABA uptake, respectively, is given. In the following discussion, remaining NO711 binding ≥ 50% or [$^3$H]GABA uptake ≥ 50% given in Table 2 will be considered as being equal to a $pK_i \leq 4$ and $pIC_{50} \leq 4$, respectively.

All tested compounds showed weak to mediocre inhibitory potencies at the GABA transporters mGAT1–mGAT4 (Table 2). In comparison to the lead structures Tiagabine (**1**) and SKF 89976-A (**2**), both known mGAT1 selective inhibitors, the potencies at mGAT1 ($pIC_{50}$ values) of the new test compounds are low. Compound NNC 05-2090 (**3**) has been reported in literature as mGAT2 selective and NNC 05-2045 (**4**) has been reported in literature displaying some selectivity for mGAT2 and to a low extent for mGAT4 (Thomsen et al. 1997). According to own test results, their potencies at mGAT1–mGAT4 are, however, either rather similar for all four GATs (**3**) or for mGAT2–mGAT4 (**4**), with a slight preference for the latter as compared to mGAT1. Also, the $pIC_{50}$ values of the new test compounds at mGAT1–mGAT4 are quite similar, which might be owed to the fact that these compounds show



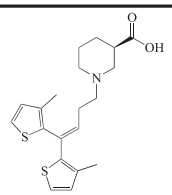
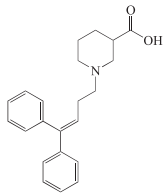
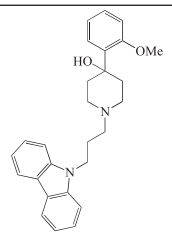
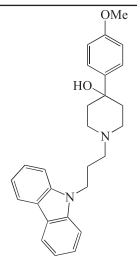
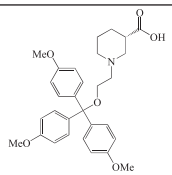
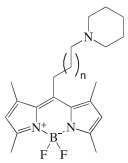
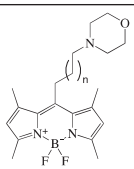

**8l** n = 1
**9l** n = 2
**10l** n = 3

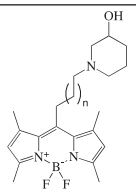
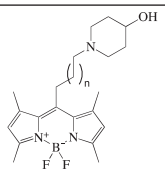
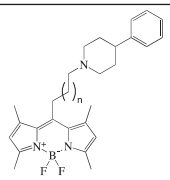
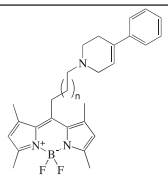
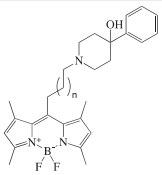
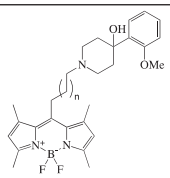
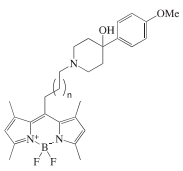
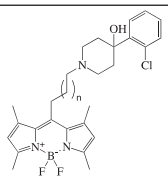
**8m** n = 1
**9m** n = 2
**10m** n = 3

**Scheme 3** Hydrolysis of the ester function in BODIPY **8**–**10l** using LiOH (aq.) to obtain the nipecotic acid derivatives **8**–**10m**

some structural similarities to these two compounds. Interestingly with regard to SNAP-5114 (**5**), a mGAT4 selective compound, some of our test compounds reach $pIC_{50}$ values that are just half a log unit lower at mGAT4 than that of the reference compounds. For compounds **8a, 9a**, and **10a** (Table 2, entry 6), with a pure piperidine ring as polar head, which can be seen as starting point of the series of compounds presented in this paper, inhibitory potencies ranging from $pIC_{50} \leq 4.0$ to almost 5.0 at the transporter subtypes mGAT1–mGAT4 can be observed. Thereby, the test results suggest that a spacer length of five carbon atoms seems to be favorable for the inhibitory potency since compound **10a** has $pIC_{50}$ values > 4.00 at all subtypes, mGAT1–mGAT4, and a $pIC_{50}$ value close to 5.00 at mGAT2 and neither **8a** nor **9a** reach similar high values. Yet, none of these three compounds show a distinct preference towards one of the transporter subtypes (Table 1, entry 6). For a morpholine ring containing compounds **8b**, **9b**, and **10b** (Table 2, entry 7) only barely measurable inhibitory potencies at mGAT1–mGAT4 can be observed. Yet again, compound **10b** with the pentyl spacer has the highest inhibitory potencies of these a morpholine ring containing compounds. For the next series of compounds **8c**, **9c**, and **10c** as well as **8d**, **9d**, and **10d** (Table 2, entry 8 and 9) with a hydroxyl group in 3- or 4-position of the piperidine core, the measured $pIC_{50}$ values are in the range of $pIC_{50} \leq 4.00$ to 4.69. For these compounds, the previously made observation that a pentyl linker is more favorable for the inhibitory potency is no longer apparent. Also, a preference for one of the four transporter subtypes was not noticeable for any of these compounds. With the steric more demanding yet more lipophilic amines **8e**, **9e**, and **10e** as well as **8f**, **9f**, and **10f** (Table 2, entry 10 and 11) exhibiting a phenyl residue at the piperidine ring, again only weak to mediocre inhibitory potencies with no notable subtype selectivity are observed. For compounds **8g**, **9g**, and **10g** exhibiting not only a phenyl group, but also an additional hydroxyl group in 4-position of the piperidine ring, the test results improved. Compound **8g** with a spacer length of three carbon atoms displays $pIC_{50}$ values ranging from 4.41–4.86 for all transporter subtypes (Table 2, entry 12, n = 1). Also compound **9g** with a one carbon atom extended linker has $pIC_{50}$ values close to 5.00 at both mGAT2 and mGAT3 (Table 2, entry 12, n = 2). And furthermore, compound **10g** with a pentyl linker exhibited $pIC_{50}$ values around 5.00 at mGAT2 and mGAT4 (Table 2, entry 12, n = 3). Yet still no distinct preference towards one GAT subtype can be observed. For the compounds **8h**, **9h**, and **10h** with the cyclic amine subunit identical to that of NNC05-2090 (**3**), we found moderate $pIC_{50}$ values at all transporter subtypes ranging from 4.72 to 5.20 (Table 2, entry 13). Although we could not detect subtype selectivity for one of the transporters mGAT1–mGAT4, but for mGAT2–4, we could again observe that a longer linker is more favorable for higher potencies. The compounds with the methoxy group in 4-position of the phenyl ring attached to the piperidine moiety, compounds **8i**, **9i**, and **10i** (Table 2, entry 14) show comparable $pIC_{50}$ values for mGAT2–4 in the individual linker series, whereby the inhibitory potencies increase with increasing spacer length, leading to $pIC_{50}$ values around 5 for **10i**. Compounds **8j**, **9j**, and **10j** with a phenyl group, and also a chloride in 4-position of the phenyl ring attached to the piperidine ring have some of the best $pIC_{50}$ values at mGAT1–mGAT4 of the compounds presented in this study (Table 2, entry 15). Compound **8j** with only a propyl linker reached $pIC_{50}$ values close to 5.00 for mGAT1 and even higher $pIC_{50}$ values for mGAT2. At mGAT3 and mGAT4, the $pIC_{50}$ were lower with $pIC_{50} = 4.79$ at mGAT3 and $pIC_{50} = 4.83$ at mGAT4 (Table 2, entry 15, n = 1). Compound **9j** with the butyl linker has $pIC_{50}$ values close to or higher than 5.00 for all four transporter subtypes (Table 2, entry 15, n = 2). For compound **10j** with the pentyl linker, we found the highest measured $pIC_{50}$ values in this study at mGAT2–4, ranging from $5.12 \pm 0.08$ to $5.35 \pm 0.04$. Only at mGAT1, the measured $pIC_{50}$ value was less than 5.00 ($pIC_{50} = 4.90$, Table 2, entry 15, n = 3). As for the compounds with the methoxy groups, also the position of the chloride from the 2-position to the 4-position of the phenyl ring has been altered. For the compounds with a methoxy group and a butyl or pentyl spacer, i.e. compounds **9h**, **9i**,

**Table 2** GABA-uptake inhibition

| Entry | Structure | # | Binding assay $pK_i \pm SEM^a$ | Uptake assay $pIC_{50} \pm SEM^b$ | | | |
|---|---|---|---|---|---|---|---|
| | | | mGAT1 | mGAT1 | mGAT2 | mGAT3 | mGAT4 |
| 1 |  | **1**[c] | **7.43±0.11** | **6.88±0.12** | 50% | 64% | 73% |
| 2 |  | **2**[c] | **6.72±0.02** | **6.16±0.05** | 3.43±0.07 | 3.71±0.04 | 3.56±0.06 |
| 3 |  | **3**[c] | 5.21±0.18 | 4.99±0.06 | 5.09±0.06 | 4.93±0.03 | 4.78±0.10 |
| 4 |  | **4**[c] | 4.41±0.04 | 4.35±0.03 | 4.97±0.11 | 4.96±0.06 | 5.35±0.03 |
| 5 |  | **5** | 4.56±0.02 | 4.07±0.09 | 63% | 5.29±0.04 | 5.65±0.02 |
| 6 |  | **8a** n = 1 | 71% | 97% | 4.14 | 64% | 4.20 |
| | | **9a** n = 2 | 61% | 4.32±0.11 | 4.19 | 4.77 | 4.19 |
| | | **10a** n = 3 | 4.20 | 4.63 | **4.95±0.08** | 4.86 | 4.61 |
| 7 |  | **8b** n = 1 | 68% | 67% | 50% | 64% | 51% |
| | | **9b** n = 2 | 52% | 50% | 58% | 62% | 4.10 |
| | | **10b** n = 3 | 4.36 | 4.37 | 4.53 | 4.44 | 4.41 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 8 |  | **8c** n = 1 | 70% | 57% | 4.31 | 4.32 | 4.44 |
| | | **9c** n = 2 | 55% | 4.03 | 4.47±0.15 | 4.26 | 4.56 |
| | | **10c** n = 3 | 45% | 4.28 | 4.56 | 4.53 | 4.60 |
| 9 |  | **8d** n = 1 | 81% | 58% | 50% | 59% | 56% |
| | | **9d** n = 2 | 62% | 4.29 | 4.64±0.12 | 4.42 | 4.38 |
| | | **10d** n = 3 | 47% | 4.23 | 4.41 | 4.69 | 4.39 |
| 10 |  | **8e** n = 1 | 45% | 46% | 4.61 | 4.14 | 4.01 |
| | | **9e** n = 2 | 4.63 | 4.31 | 4.56 | 4.37 | 4.45 |
| | | **10e** n = 3 | 4.15 | 4.48 | 4.77 | 4.46 | 4.55 |
| 11 |  | **8f** n = 1 | -[d] | 4.14 | 53% | 4.11 | 4.49 |
| | | **9f** n = 2 | 60% | 4.38 | 4.49 | 4.08 | 4.77 |
| | | **10f** n = 3 | 51% | 4.40 | 4.89 | 4.29 | 4.83 |
| 12 |  | **8g** n = 1 | 39% | 4.41 | 4.86 | 4.64 | 4.79 |
| | | **9g** n = 2 | 4.69 | 4.70 | 4.94 | 4.92 | 4.79 |
| | | **10g** n = 3 | 4.57 | 4.84 | **5.07±0.09** | 4.87 | **5.09±0.07** |
| 13 |  | **8h** n = 1 | 4.22 | 4.81±0.10 | 4.78 | 4.86 | 4.92 |
| | | **9h** n = 2 | 4.73 | 4.72 | 4.83±0.08 | 5.00±0.04 | 4.99±0.15 |
| | | **10h** n = 3 | 4.25 | 4.91 | **5.11±0.07** | **5.12±0.06** | **5.20±0.06** |
| 14 |  | **8i** n = 1 | 54% | 4.42 | 4.24 | 4.54 | 4.73 |
| | | **9i** n = 2 | 4.38 | 4.75 | 4.57±0.14 | 4.63 | 4.68±0.20 |
| | | **10i** n = 3 | 63% | 4.63 | **5.11±0.05** | 4.94 | **5.15±0.05** |
| 15 |  | **8j** n = 1 | 59% | 4.99 | **5.15±0.09** | 4.79 | 4.83 |
| | | **9j** n = 2 | **5.11±0.08** | **5.07±0.11** | **5.25±0.07** | **5.03±0.05** | **5.05±0.11** |
| | | **10j** n = 3 | **5.27±0.05** | 4.90 | **5.35±0.04** | **5.12±0.08** | **5.25±0.03** |

[a]Results are given as $pK_i \pm$ SEM of three independent experiments, each performed in triplicate. For low $pK_i$ values only one measurement was performed in triplicate, therefore no SEM was calculated or only the percentage of remaining MS Marker Binding at a concentration of 100 µM has been determined

[b]Results of [$^3$H]GABA uptake assays are given as $pIC_{50} \pm$ SEM of three independent experiments, each performed in triplicate. For low $pIC_{50}$ values only one measurement was performed in triplicate, therefore no SEM could be calculated. Percentages represent remaining [$^3$H]GABA uptake in the presence of 100 µM test compound

[c]$pIC_{50}$ values were determined using the same standard assay as for all tested compounds (Kragler et al. 2008)

[d]not determined [e]tested as hydrochloride

**10h**, and **10i**, it had been found that the position of the methoxy group (2- and 4-position) has just little influence on the $pIC_{50}$ values (Table 2, entry 13 and 14). For compounds **8k**, **9k**, and **10k** with a chloride instead of a methoxy group (Table 2, entry 16), the position of the chloride has some impact on the uptake inhibition as compared to the inhibitory activity of regioisomers **8j**, **9j**, and **10j**. Compound **8k** with a chloride in 4-position of the phenyl ring and a propyl linker reached $pIC_{50}$ values slightly higher than 5.00 just for mGAT2 and mGAT4 (Table 2, entry 16, n = 1), which is still close to the values observed for **8j**. Compound **9k** with the butyl linker has clearly decreased $pIC_{50}$ values compared to compound **9j** with $pIC_{50}$ values ranging from $pIC_{50} \leq 4.00$ to 4.85 (Table 2, entry 15 and 16, n = 2). Compound **10k** with a pentyl linker has an almost identical $pIC_{50}$ of $5.30 \pm 0.07$ as **10j** ($pIC_{50} = 5.35 \pm 0.04$) at mGAT2 and for the other transporter subtypes mGAT1 and mGAT3–mGAT4 $pIC_{50}$ values of 4.96 for mGAT1 and values close to 5.00, but yet less than the values measured for its analogue with the chloride in 2-position, compound **10j** (Table 2, entry 15 and 16, n = 3). The biological evaluation of **9l** and **10l**, both ester precursors of nipecotic acid, resulted in $pIC_{50}$ values > 4.5 at mGAT1–mGAT4 with the highest $pIC_{50}$ value of $5.05 \pm 0.2$ exhibited by compound **10l** at mGAT3 (Table 2, entry 17, n = 3). Fluorescence ligands **9m–10m** characterized by a nipecotic acid subunit (Table 2, entry 18, n = 1, 2 and 3) as e.g. in Tiagabine (**1**) showed, independent from the length of the linker, no noticeable inhibitory potency at any of the transporter subtypes mGAT1–mGAT4 (Table 2, entry 18). In summary, it can be concluded by the obtained data that in general longer spacers and the usage of more lipophilic and sterically more demanding cyclic amines are favorable for higher $pIC_{50}$ values, when a BODIPY core is used as a substitute for the aromatic domain found in most common GAT inhibitors such as **1–5** that consist of two or more aryl rings or a carbazole unit.

In addition to the $pIC_{50}$ values, also the binding affinities of the synthesized compounds at mGAT1 were determined. Almost all compounds of this study show, independent of the cyclic amine subunit present and the length of the spacer (three to five carbon atoms), low to negligible binding affinities for mGAT1 with $pK_i$ values ranging from below 4.00 to 4.73 (Table 2, entry 6–14 and 16–18). Even compounds **8m**, **9m**, and **10m** with the nipecotic acid as cyclic amine adapted from Tiagabine, which has a $pK_i$ value of 7.43 (Table 2, entry 1) have just weak binding affinities ($pK_i = 4.22$–$4.48$, Table 2, entry 18, n = 1–3). Only exceptions are compounds **9j** and **10j**, respectively, presenting a higher binding affinity towards mGAT1 with $pK_i$ values higher than 5.00 (Table 2, entry 15) representing with compound **8j** the most potent inhibitors at mGAT1 (see Table 2, entry 15, $pIC_{50} = 5.27 \pm 0.05$) in this study.

For all compounds studied, the found $pK_i$ values for mGAT1 in MS Binding Assays were similar or about a half log unit higher than the $pIC_{50}$ values observed in [$^3$H]GABA uptake assays, which is a common phenomenon frequently observed with the used test system (Zepperitz et al. 2006). The data for the binding affinities ($pK_i$) and inhibitory potencies ($pIC_{50}$) are thus fitting very well.

## Conclusion

In conclusion, a series of novel fluorescent ligands delineated from common GAT inhibitors in which the lipophilic domain has been replaced by a BODIPY dye subunit has been synthesized and evaluated for binding affinities at mGAT1 and inhibitory potencies at mGAT1–mGAT4. Overall, the inhibitory potencies of the presented compounds were weak to mediocre, and no distinct selectivity towards one transporter subtype was observed. Still, some of the herein presented compounds show $pIC_{50}$ values of up to 5.35 at different transporter subtypes, whereby highest potencies are observed for mGAT2–4. Additionally, two of the compounds have $pK_i$ values above 5.00 at mGAT1. Although the best inhibitors lack a distinct subtype selectivity, the measured $pIC_{50}$ values and subtype selectivities are in the same range as those of the prototypic inhibitors of mGAT2-mGAT4, i.e. of NNC 05-2090 (**3**), NNC 05-2045 (**4**), and (*S*)-SNAP-5114 (**5**). This study sheds light on the effect that the structure of the amine subunit of the target compounds and the length of the spacer have on the inhibitory potency at the GABA transporter. In particular, a spacer with four to five carbon atoms in combination with a 4-hydroxy-4-phenyl-piperidine moiety carrying a methoxy or chloro substituent at the aromatic residue representing the amino subunit seems to be favorable for reasonable

inhibitory potencies at the GABA transporter. As fluorescence based analysis techniques not necessarily require ligands with high binding affinity to the target, the herein presented fluorescent GAT inhibitors might serve as promising tool compounds or at least as a starting point for the development of such entities for the respective analytical methods.

## Compliance with ethical standards

**Conflict of interest** None of the authors have conflict of interest related to the information described in this paper.

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