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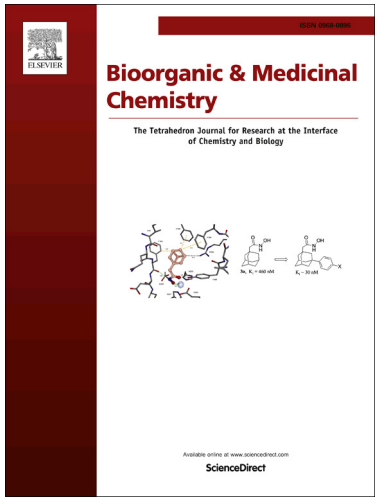

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BN/CC Isosterism in Borazaronaphthalenes towards Phosphodiesterase 10A (PDE10A) Inhibitors

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KEYWORDS: Borazaronaphthalenes, PDE10A Inhibitors, Antipsychotics

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ABBREVIATIONS

cAMP, cyclic adenosine monophosphate; cGMP, cyclic guanosine monophosphate; Boc, *tert*-butyloxycarbonyl; THF, tetrahydrofuran; DMF, dimethylformamide; CPME, cyclopentyl methyl ether; TFA, trifluoroacetic acid; EDCI, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide; HOBt, hydroxybenzotriazole; TMS, trimethylsilyl; PMB, *para*-methoxybenzyl ether.

ABSTRACT: The application of BN/CC isosterism is explored as a method of expanding the scope of core scaffolds in biologically active compounds. The viability of potential drug candidates incorporating BN-heteroaromatic moieties was investigated through the synthesis of BN-substituted analogs to known phosphodiesterase (PDE10A) inhibitors, namely MP10 and a selection of N–methylanilide analogues. These in some cases revealed unexpectedly potent and relatively stable derivatives, providing further support for the potential of BN-incorporation in medicinal chemistry.

Although boron plays an important role in synthetic organic chemistry, it is not commonly used in medicinal chemistry and seldom found in natural products. Few chemists today appreciate the unique properties and potential of boron incorporation into heterocyclic aromatic scaffolds.[1]

A promising method of introducing boron in heterocycles is by taking advantage of the isosteric and isoelectronic relationship between the CC and BN fragments[2], which has also been employed in the synthesis of various Hückel-aromatic scaffolds[3a-c] (Figure 1).

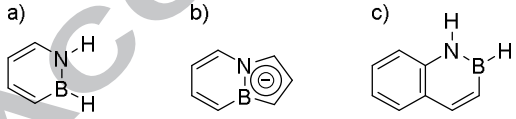


Figure 1. (a) 1,2-Azaborine (1,2-dihydro-1,2-azaborine)[3a] (b) BN-indenyl analog (3a,7a-azaborindenyl anion)[3b] (c) 2,1-borazaronaphthalene (1,2-dihydrobenzo[*e*]-1,2-azaborine)[3c].

The investigation of borazaronaphthalenes for therapeutic applications was largely abandoned following Dewar's pioneering attempts in 1964. Dosing only a very limited range of BN-containing derivatives (Figure 2), these initial trials proved immediately fatal to the lab mice.[4]

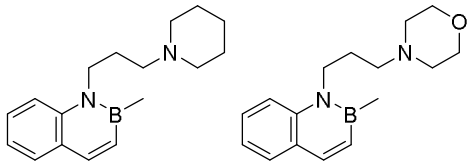


Figure 2. Two borazaronaphthalene derivatives tested by Dewar in mice.[4]

Only two instances of 1,2-azaborine derivatives have been reported to interact with biological systems thus far.[5] The first reported case describes the binding of both the *N*-ethyl- and the parent 1,2-azaborine inside the cavity of T4 lysozyme[5a] while the second demonstrates the potential of *N*- and *B*-ethyl-1,2-azaborine to act as strong inhibitors of ethylbenzene dehydrogenase (EbDH)[5b]. With the exception of Dewar's trials in 1964, these are to our knowledge, the only reports of borazaronaphthalenes exhibiting biological activity.

Recent studies have shown that phosphodiesterase (PDE) enzyme inhibition in the brain could have significant therapeutic benefits including anti-psychotic, and pro-cognitive effects.[6] In particular, PDE10A modulators have attracted particular attention for the treatment of Parkinson's Disease,

Huntington's Disease, schizophrenia, and obsessive compulsive disorder (OCD).[7]

In 2009, research at Pfizer led to the identification of an *N*-methylpyrazol series of which MP10 (**1a**), exhibited subnanomolar PDE10A inhibition (IC_{50} = 0.37 nM) with >1000-fold selectivity over other PDE's.[8a] This compound has since been used ubiquitously as the benchmark comparison with regard to PDE10A inhibition. More recently however, an *N*-methylanilide analog (**1b**) has also shown promising results towards potential PDE inhibition (Figure 3).[8b]

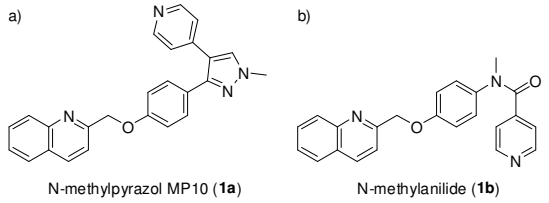


Figure 3. (a) Pfizer's MP10 (**1a**)[8a] and (b) Lundbeck's *N*-methylanilide (**1b**)[8b].

Key to these compounds' activity is their ability to adopt a favorable geometry and form strong interactions with the binding pocket of the target enzyme. The catalytic active site of many PDE's was found to possess several structural features critical to the enzyme's function (Figure 4). In PDE10A a flexible glutamine residue (Gln-726) can rotate to form hydrogen bonds to either natural substrate: cAMP or cGMP. Furthermore, a hydrophilic region containing two metal centers functions to bind the phosphate groups of the aforementioned nucleotides.[8c] The PDE10A active site was also found to possess a unique lipophilic binding pocket, not normally accessible in other PDE's.[8a,d] Here, a well-positioned, nearby tyrosine residue (Tyr-693) is able to accommodate and anchor a guest molecule via H-bond interactions.

Evidence for MP10's selectivity and affinity for PDE10A was subsequently revealed by co-crystal structure analysis, and could be rationalized based on the substrate's binding mode and structure activity relationship (SAR). These highlighted the critical interaction between the quinoline moiety of MP10 and Tyr-693 in the lipophilic selectivity pocket of PDE10A.[8a] Employing a similar binding mode, the recent N-methylanilide lead compound, was also identified as an efficient and selective inhibitor of PDE10A, yet considered to lack potency compared to MP10.

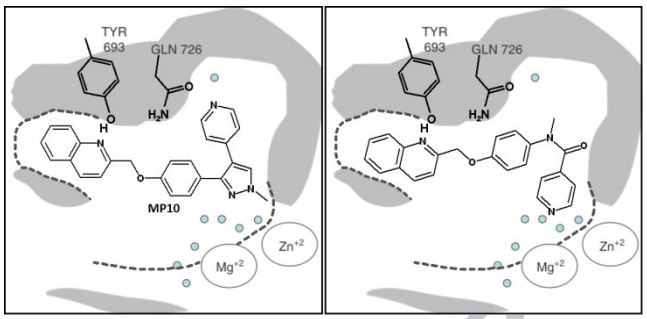


Figure 4. Illustration of MP10 (**1a**) and *N*-methylanilide (**1b**) binding modes in the PDE10A active site.[8a,b]

Studies have indicated that the PDE10A lipophilic pocket is an important site for ligand binding and that modification of the group occupying this space would be expected to alter the potency of the compounds with regard to PDE10A inhibition. Literature to date has identified the quinoline moiety as one of the more potent variants, which has been rationalized in part by its availability to act as an H-bond acceptor, allowing a strong interaction with the nearby Tyr-693 residue.[8a,b] Although not specifically reported, it was hypothesized that the corresponding naphthalene-substituted analogs to these compounds would present a lack of activity towards PDE10A inhibition.

Borazaronaphthalenes, although isosteric and isoelectronic with their naphthalene analogs, do present a significantly more polarized bond, and partial protic character in the NH moiety (Figure 5).[3a] With regard to their physical properties, the borazaronaphthalenes were expected to behave more like the naphthalene analogs in this biological system. The goal of this investigation was to gain a better understanding of the extent that the similarity in their physical properties would translate to similarities in their biological interactions; such as for example, the possibility of added interactions as a result of increased polarization.

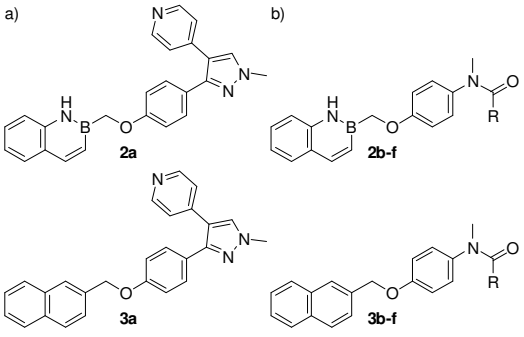
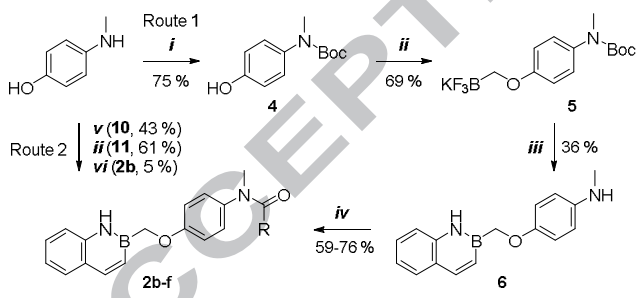


Figure 5. BN- and napthyl-substituted analogs to (a) Pfizer's MP10 (**2a**, **3a**) and (b) Lundbeck's *N*-methylanilide series (**2b-f**, **3b-f**). See Table 1.

Thus, in an effort to probe the viability of BN-substituted compounds in the context of biological systems, and at the same time gain insight into PDE inhibition, the synthesis and characterization of BN-substituted analogs of MP10 and *N*-methylanilide analogs (**2a-f**, Figure 5) was undertaken.

The synthesis and functionalization of borazaronaphthalene scaffolds has been successfully achieved by several groups including Dewar[3c,4,9], Paetzold[10], Ashe[11], and Liu[12]. In a recent development, a one-pot versatile synthesis to 1,2-disubstituted 2,1-borazaronaphthalenes without the use of metal catalysts, under mild conditions, and using inexpensive starting materials was reported by Molander[13a]. Together with the work presented here, rapid progress towards borazaronaphthalene functionalization and derivatization confirms the emerging interest in this field.[13] Employing these techniques, optimization towards the synthesis of the borazaronaphthalene targets was achieved by two routes (Scheme 1). Route 1 presents a general and synthetically convergent four-step protocol which led to the facile synthesis of compound series **2b-f** while route 2 supports the possibility of early derivatization via a linear approach.

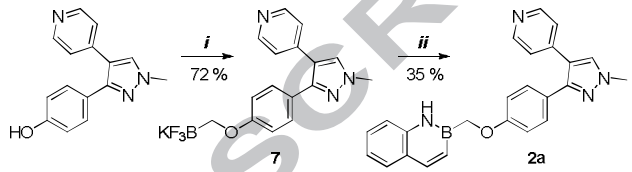
Scheme 1. General protocol towards 2b-f.[a]



[a] Reagents and Conditions: i) Boc anhydride, pyridine, THF/MeCN (5:1), 70 °C, 20 h. ii) NaH, DMF, 120 °C, 1 h; KF_3BCH_2Br, 120 °C, 16 h. iii) 2-aminostyrene, Et_3N, $SiCl_4$, toluene/CPME (1:1), 100 °C, 24 h; TFA, 80 °C, 5 h. iv) EDCI, HOBt, carboxylic acid **b-f**, Et_3N, THF, 16 h. v) Isonicotinoyl chloride, Et_3N, THF, 50 °C, 23 h. vi) 2-aminostyrene, Et_3N, $SiCl_4$, toluene/CPME (1:1), 80 °C, 22 h.

Via route 1, selective Boc-protection of 4-(methylamino)phenol allowed for successful O-alkylation and incorporation of the trifluoroborate functionality to yield the potassium trifluoroborate salt **5**. Subsequent borazaronaphthalene formation, followed by deprotection furnished **6**. Lastly, a standard HOBt-catalyzed amide coupling led to the synthesis of compounds **2b-f**. An analogous strategy was also applied towards the synthesis of **2a** (Scheme 2).

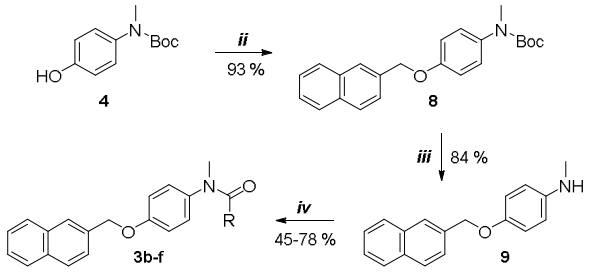
Scheme 2. Synthesis of BN-MP10 (2a).[a]



[a] Reagents and Conditions: i) NaH, DMF, 120 °C, 1 h; KF_3BCH_2Br, 120 °C, 16 h. ii) 2-aminostyrene, Et_3N, $SiCl_4$, MeCN/CPME (3:1), 80 °C, 6 h, then 40 °C, 3 d.

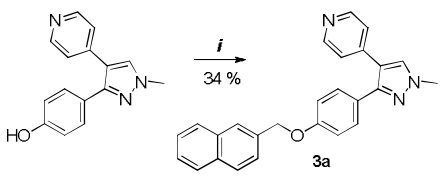
For a more comprehensive analysis of results the napthyl-substituted derivatives of compounds **2a-f** were also targeted. Similar methods were employed towards the synthesis of the naphthyl *N*-methylanilide analogs **3b-f** (Scheme3) and naphthyl MP10 **3a** (Scheme 4).

Scheme 3. General protocol towards 3b-f.[a]



[a] Reagents and Conditions: ii) 2-(bromomethyl)naphthalene, K_2CO_3, MeCN, 20 h. iii) TFA, CH_2Cl_2, 30 °C, 15 min. iv) EDCI, HOBt, carboxylic acid **b-f**, Et_3N, THF, 3 d.

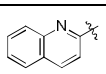
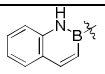
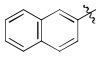
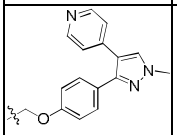
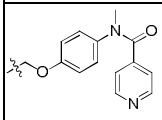
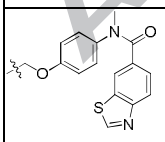
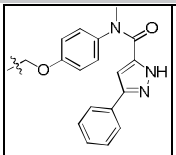
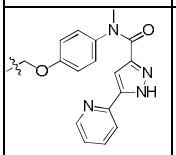
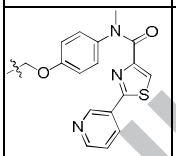
Scheme 4. Synthesis of Naphthyl-MP10 (3a).[a]



[a] Reagents and Conditions: i) 2-(bromomethyl)naphthalene, NaH, MeCN, 60 °C, 30 min.

In agreement with literature and the hypotheses proposed, in vitro studies showed that the quinolinyl-substituted derivatives (**1a-f**)[8] in general exhibited the highest potencies towards PDE10A, whereas the naphthyl analogs (**3a-f**) showed the least activity. Due to the isosteric and isoelectronic relationship with the naphthyl derivatives, it was hypothesized and generally confirmed that the borazaronaphthyl analogs (**2a-d**) presented similar inactivity. Compounds **2e** and **2f** however, exhibited a surprisingly high affinity for PDE10A, comparable to that of the corresponding quinolinyl compounds (Table 1). Docking studies of compounds **2e** and **2f** did not provide evidence for the unexpected high affinity for PDE10A.

Table 1. Metabolic stability, lipophilicity, and PDE10A potency as a function of naphthyl-, quinolinyl-, or borazaronaphthyl-substitution.

			
	**1a** (MP10) IC_{50} = 2.6 cLogP = 3.84 Clint = 1.9	**2a** 48 % inh. cLogP = 4.44 Clint = 2.5	**3a** 25 % inh. cLogP = 5.13 Clint = 5
	**1b** IC_{50} = 250 cLogP = 2.85 Clint = 0.9	**2b** 11 % inh. cLogP = 3.44 Clint = 6.9	**3b** 2 % at 2 μM cLogP = 4.14 Clint = 4.5
	**1c** IC_{50} = 31 cLogP = 4.17 Clint = 1.9	**2c** 45 % inh. cLogP = 4.76 Clint = 4.4	**3c** 5 % inh. cLogP = 5.45 Clint = 2.9
	**1d** IC_{50} = 24 cLogP = 4.78 Clint = 1.3	**2d** IC_{50} = 1800 cLogP = 5.38 Clint = 0.34	**3d** 3 % inh. cLogP = 6.07 Clint = 0.41
	**1e** IC_{50} = 12 cLogP = 3.58 Clint = 2.1	**2e** IC_{50} = 64 cLogP = 4.18 Clint = 1.5	**3e** 4 % inh. cLogP = 4.87 Clint = 1.8
	**1f** IC_{50} = 170 cLogP = 2.35 Clint = >17	**2f** IC_{50} = 330 cLogP = 3.95 Clint = >17	**3f** 2 % inh. cLogP = 4.64 Clint = >17

[a] Metabolic Stability as a measure of microsomal intrinsic clearance (Clint) in L/kg/h; Lipophilicity as calculated LogP (cLogP); PDE10A potency measured as 50 % inhibitory concentration (IC_{50}) in nM or given as percent inhibition at 10 μM. Data for the quinolinyl series (**1a-f**) are literature values.[8]

As good metabolic stability leads to lower clearance compounds, in the search for better drug candidates, these have the potential benefits of reducing the dose quantity and frequency. A common strategy used to estimate and reduce clearance is based on the empirical correlation between lower lipophilicity and lower clearance.[14] Although a subject of debate[15], it was of interest to investigate this trend, hypothesizing a decrease in metabolic stability with **1 a-f > 2 a-f > 3 a-f**.

Results however, do not show a systematic trend between metabolic stability and lipophilicity with the compounds described. Although the quinoline derivatives presented the highest metabolic stabilities, borazaronaphthalenes **2d** and **2e** did show metabolic stabilities comparable to their quinolinyl analogs. This suggests that it is not only lipophilicity driving metabolism and that a better understanding of structure-clearance relationships for the chemotype in question may

be a more effective strategy to delivering low clearance compounds.

With regard to the compounds' ability to inhibit PDE10A, no systematic trend is readily apparent. As expected, the naphthalene analogues (**3a-f**) show little inhibitory activity, and although the borazaronaphthalenes (**2a-d**) in general fall far below the activities of the quinoline derivatives (**1a-d**), their potencies as inhibitors are marginally better than that of the corresponding naphthalene analogues. Compounds **2e** and **2f** however, were found to be relatively potent compared to the corresponding naphthalene analogues **3e** and **3f**. Initial thoughts were that these results could possibly be explained by an interaction between the pyridine group and the water molecules associated with the metal ions. This would be supported by the diminished potency observed in **2d**. However, affinity data obtained for compounds **3e** and **3f** suggests that the pyridine group alone is not a cause of potency gain. Furthermore, the results also indicate that a more favorable interaction between the borazaronaphthalene moiety in **2e** and **2f** exists in the lipophilic selectivity pocket of PDE10A, when compared to that of the corresponding naphthalene analogues **3e** and **3f**.

In conclusion, the potential of several borazaronaphthyl-substituted compounds as potent, metabolically stable, and thus biologically viable candidates for further studies is revealed. These results suggest that although affinity for the enzyme's active site is diminished, a certain degree of interaction between these compounds and the PDE10A active site persists. Assuming a similar binding mode as for the known analogs, the relatively high activity of compounds **2e** and **2f** might be attributable to a favorable interaction between the BN moiety and the Tyr-693 residue, in addition to interactions between the pyridinyl moieties and the hydrophilic region of the enzymatic active site. In view of the prevalence and importance of naphthalene and quinoline moieties in medicinal chemistry, this study further supports the potential of borazaronaphthalenes and their use as naphthalene and quinoline bioisosteres.

EXPERIMENTAL

General Procedures and Materials.

Unless otherwise stated, all solvents and reagents were obtained from commercial suppliers and used without further purification. All reactions involving dry solvents or air-sensitive agents were performed under a nitrogen or argon atmosphere and glassware was dried prior to use. Solvents were dried according to standard procedures. Reactions were monitored by analytical LC-MS which was conducted on a Waters Acquity UPLC-MS, equipped with an Acquity UPLC BEH C18 1.7 µm; 2.1 x 50 mm column at a temperature of 60 °C. A three-component solvent system, A = H_2O/TFA (99.5:0.5) and B = MeCN/H_2O/TFA (94.965:5:0.035) was applied with a linear gradient, A:B = 90:10 to 0:100 in 1.0 min, eluting at rate of 1.2 mL/min. Compound detection and visualization was achieved via internal PDA (254 nm) and ELSD detectors. APPI+ was used as the ionization method. Flash chromatography was performed using either a CombiFlash Rf System (Teledyne Isco, Inc.) on GraceResolv columns or a Flashmaster II (Argonaut) on ISOLUTE Flash Si II columns. Eluent systems are given in volume/volume concentrations. NMR spectra were recorded on a 500 MHz Bruker Avance AV500 instrument or on a 600 MHz Bruker Avance Ultrashield 600 plus instrument. The samples were prepared as $CDCl_3$ solutions using TMS/$CDCl_3$ as internal standards, or DMSO-d_6 solutions. Chemical shifts (δ) are given in parts per million (ppm), and coupling constants (*J*) are given in Hertz (Hz). The following abbreviations are used: br = broad, s = singlet, d = doublet, dd = doublet of doublet, ddd = doublet of doublet of doublets, t = triplet, q = quartet, m = multiplet. The synthesis and properties of compounds **1a-f** have been reported in previous litterature.[8] 2-Vinylaniline[13a] and potassium trifluoro(phenoxymethyl)borate[13f] were synthesized according to literature procedure. 4-(1-methyl-4-(pyridin-4-yl)-1H-pyrazol-3-yl)phenol can be synthesized according to literature procedure[8a] or purchased from Ambinter.

tert-Butyl(4-hydroxyphenyl)(methyl)carbamate (4)

A solution of 4-(methylamino)phenol hemisulfate (10.33 g, 30.0 mmol) in THF (250 mL), MeCN (50 mL), and pyridine (4.75 g, 4.83 mL, 60.0 mmol) was treated with di-*tert*-butyl dicarbonate (13.75 g, 63.0 mmol) and heated to 70 °C for 21 h. The mixture was concentrated *in vacuo* to 1/3 the volume, then diluted with Et_2O (400 mL) and washed with sat. aq. NH_4Cl (2 x 400 mL) then brine (400 mL). The organic phase was isolated, dried over Na_2SO_4, filtered, and the solvent was

removed *in vacuo*. The residue was purified by gradient column chromatography (SiO_2, flash, 0-100 % EtOAc/heptane) to isolate the title compound, *tert*-butyl (4-hydroxyphenyl)(methyl)carbamate (**4**) after solvent removal, as a white solid (4.99 g, 22.4 mmol, 75 %). ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.38 (s, 1H), 7.03 – 7.00 (m, 2H), 6.71 – 6.68 (m, 2H), 3.08 (s, 3H), 1.35 (s, 9H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 155.04, 154.16, 135.02, 126.92, 115.05, 78.97, 37.49, 28.01. GC-MS (EI+, EtOH, m/z) found 168 [M-(*t*-Bu)+H]$^+$ calculated 168.1 [M-(*t*-Bu)+H]$^+$. LC-MS (APPI+, H_2O/MeCN/TFA, m/z) found 168 [M-(*t*-Bu)+H]$^+$ calculated 168.1 [M-(*t*-Bu)+H]$^+$, rt (PDA) 0.59 min.

_N_-(4-hydroxyphenyl)-_N_-methylisonicotinamide (10)

To a suspension of *N*-methyl-p-aminophenol sulfate (6.89 g, 20.0 mmol) and isonicotinoyl chloride hydrochloride (7.12 g, 40.0 mmol)) in THF (120 mL) at 0 °C, was added Et_3N (12.14 g, 16.74 mL, 120 mmol) dropwise over 5 min. The mixture was then heated to 50 °C for 23 h, after which it was cooled to RT, concentrated *in vacuo* and the crude residue purified by gradient column chromatography (SiO_2, flash, 0-100 % (10 % MeOH/5 % Et_3N/EtOAc)/EtOAc) to yield the title compound, *N*-(4-hydroxyphenyl)-*N*-methylisonicotinamide (**10**) after solvent removal, as a pale yellow solid (1.95 g, 8.54 mmol, 43 %). ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.58 (s, 1H), 8.42 (d, *J* = 5.5 Hz, 2H), 7.15 (d, *J* = 5.5 Hz, 2H), 7.00 (d, *J* = 8.5 Hz, 2H), 6.60 (d, *J* = 8.5 Hz, 2H), 3.30 (s, 3H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 167.56, 156.29, 149.33, 144.34, 134.75, 128.72, 122.16, 115.69, 37.57. LC-MS (APPI+, H_2O/MeCN/TFA, m/z) found 229 [M+H]$^+$ calculated 229.1 [M+H]$^+$, rt (PDA) 0.21 min.

Potassium trifluoro((4-(_N_-methylisonicotinamido)-phenoxy)methyl)borate (11)

To a solution of *N*-(4-hydroxyphenyl)-*N*-methylisonicotinamide (**10**) (0.433 g, 1.90 mmol) in DMF (20 mL) under Ar atmosphere, was added sodium hydride (0.076 g, 1.90 mmol, 60 % dispersion in mineral oil) in one portion. The mixture was heated to 120 °C and stirred for 1 h. Potassium bromomethyltrifluoroborate (0.317 g, 1.58 mmol) was then added in one portion at RT, and the reaction was heated back to 120 °C overnight. The mixture was then cooled to RT and quenched using sat. aq. potassium bifluoride (5 mL, 22.5 mmol, 4.5 M). The mixture was stirred for 30 min before it was concentrated to dryness *in vacuo*. The crude solid was loaded onto a filter and washed with hot acetone (200 mL). The filtrate was concentrated *in vacuo* onto celite, loaded onto a new filter, and washed with CH_2Cl_2 (100 mL). 5 % MeOH/ CH_2Cl_2 (200 mL) was then used to elute the title compound, (**11**) which was isolated after solvent removal, as a pale yellow solid (0.334 g, 0.959 mmol, 61 %). mp = 104-110 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.42 (d, *J* = 5.7 Hz, 2H), 7.15 (d, *J* = 5.7 Hz, 2H), 7.02 (d, *J* = 8.8 Hz, 2H), 6.69 (d, *J* = 8.8 Hz, 2H), 3.32 (s, 3H), 2.89 – 2.83 (m, 2H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 167.50, 160.92, 149.35, 144.26, 134.47, 128.28, 122.17, 114.20, 37.66. *note: B-CH_2 ^{13}C signal not observed. IR (ATR, neat) 3052, 2911, 1636, 1552, 1509, 1442, 1414, 1383, 1286, 1269, 1245, 1089, 1067, 1020, 979, 837, 756, 731, 693, 642 cm^{-1}. LC-MS (APPI+, H_2O/MeCN/TFA, m/z) found 287 [$C_{14}H_{16}BN_2O_4$]$^+$ calculated 287.1 [$C_{14}H_{16}BN_2O_4$]$^+$, rt (PDA) 0.24 min. HRMS (MALDI+ FT-ICR, dithranol): found 291.11125 [M-KF+H]$^+$ calculated 291.11109 [M-KF+H]$^+$. Elemental Analysis Calc. ($C_{14}H_{13}BF_3KN_2O_2$): C, 48.30; H, 3.76; N, 8.05; Found: C, 48.39; H, 3.83; N, 8.15.

_N_-(4-(benzo[*e*][1,2]azaborinin-2(1H)-ylmethoxy)phenyl)-_N_-methylisonicotinamide (2b)

Route 2: To an oven-dried microwave vial equipped with a stirrer bar was added potassium trifluoroborate salt (**11**) (0.104 g, 0.300 mmol) under Ar atmosphere. To this, dry CPME (1 mL) and toluene (1 mL) were added, followed by dry, degassed 2-vinylaniline (0.043 g, 0.042 mL, 0.360 mmol), perchlorosilane (0.051 g, 0.034 mL, 0.300 mmol), then Et_3N (0.046 g, 0.063 mL, 0.450 mmol). The vial was heated to 80 °C for 22 h on an aluminum block. The reaction mixture was then diluted with CH_2Cl_2 (5 mL) and passed through a small celite plug eluting with CH_2Cl_2 (50 mL). The eluent was concentrated *in vacuo* and the residue purified by gradient column chromatography (SiO_2, flash, 0-100 % (10 % MeOH/5 % Et_3N/ EtOAc)/EtOAc) to elute the title compound (**2b**) which was isolated, after solvent removal, as a pale yellow solid (5.2 mg, 0.014 mmol, 5 %). mp = 143-146 °C. ^{1}H NMR (600 MHz,

$CDCl_3$) δ 8.45 (d, *J* = 5.5 Hz, 2H), 8.33 (s, 1H), 8.05 (d, *J* = 11.5 Hz, 1H), 7.64 (d, *J* = 7.7 Hz, 1H), 7.45 (ddd, *J* = 8.3, 7.3, 1.4 Hz, 1H), 7.33 (d, *J* = 8.1 Hz, 1H), 7.20 (ddd, *J* = 8.0, 7.1, 1.0 Hz, 1H), 7.14 (d, *J* = 5.5 Hz, 2H), 6.98 (d, *J* = 8.8 Hz, 2H), 6.93 (d, *J* = 8.8 Hz, 2H), 6.77 (dd, *J* = 11.5, 1.6 Hz, 1H), 4.27 (s, 2H), 3.48 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 168.45, 159.58, 149.75, 145.63, 143.93, 139.70, 136.37, 129.72, 128.62, 128.31, 126.17 (br), 125.66, 122.70, 121.36, 118.26, 115.26, 61.59 (br), 38.47. ^{11}B NMR (160 MHz, $CDCl_3$) δ 35.11 (br). IR (ATR, neat) 3390, 3306, 3043, 2880, 2825, 1641, 1615, 1595, 1565, 1508, 1437, 1378, 1291, 1265, 1243, 1207, 1171, 1147, 1133, 1107, 1067, 1022, 997, 886, 835, 803, 758, 734, 701, 680, 631 cm^{-1}. LC-MS (APPI+, H_2O/MeCN/TFA, m/z) found 370 $[M+H]^+$ calculated 370.2 $[M+H]^+$, rt (PDA) 0.65 min. HRMS (ESI+, DMSO) found 370.1727 $[M+H]^+$ calculated 370.1721 $[M+H]^+$; found 443.2622 $[M+Et_2NH_2]^+$ calculated 443.2613 $[M+Et_2NH_2]^+$. Elemental Analysis Calc. ($C_{22}H_{20}BN_3O_2$): C, 71.57; H, 5.46; N, 11.38; Found: C, 71.55; H, 5.57; N, 11.20.

Potassium ((4-((tert-butoxycarbonyl)(methyl)amino)phenoxy)methyl)trifluoroborate (5)

To a solution of *tert*-butyl (4-hydroxyphenyl)(methyl)carbamate (**4**) (4.93 g, 22.1 mmol) in DMF (150 mL) was added sodium hydride (0.883 g, 22.1 mmol, 60 % dispersion in mineral oil) and the mixture was heated to 120 °C for 1 h. Potassium bromomethyltrifluoroborate (3.70 g, 18.4 mmol) was then added in one portion at RT, and the reaction was heated back to 120 °C overnight. The mixture was then cooled to RT, quenched using sat. aq. potassium bifluoride (50 mL, 225 mmol, 4.5 M) and stirred for a further 30 min before it was concentrated to dryness *in vacuo*. The residue was loaded onto a filter and washed with acetone (100 mL). The filtrate was concentrated *in vacuo* to approx. 10 mL, and the product was precipitated out of solution by slow addition into heptane (400 mL). The fine suspension was then filtered and the title compound (**5**) was isolated as a white powder (4.38 g, 12.8 mmol, 69 %). mp = 140-146 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.06 – 7.02 (m, 2H), 6.80 – 6.76 (m, 2H), 3.09 (s, 3H), 2.93 (q, $^3J_{FH}$ = 5.0 Hz, 2H), 1.35 (s, 9H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 159.81, 154.22, 134.75, 126.56, 113.58, 78.91, 37.53, 28.03. *note: B-CH_2 ^{13}C signal not observed. IR (ATR, neat) 2977, 2904, 2847, 1695, 1608, 1512, 1479, 1444, 1365, 1291, 1244, 1157, 1105, 1009, 976, 836, 798, 768, 745, 647, 600 cm^{-1}. LC-MS (APPI+, H_2O/MeCN/TFA, m/z) found 226 $[C_9H_{13}BNO_5]^+$ calculated 226.1 $[C_9H_{13}BNO_5]^+$, rt (PDA) 0.57 min. HRMS (MALDI+ FT-ICR, dithranol): found 382.05994 $[M+K]^+$ calculated 382.06005 $[M+K]^+$.

4-(Benzo[*e*][1,2]azaborinin-2(1H)-ylmethoxy)-*N*-methylaniline (6)

To an oven-dried flask equipped with a stirrer bar and reflux condenser was added potassium trifluoroborate salt (**5**) (6.00 g, 17.5 mmol) under Ar atmosphere and suspended 1:1 toluene/CPME (50 mL). To this mixture were consecutively added 2-vinylaniline (2.50 g, 2.47 mL, 21.0 mmol), perchlorosilane (2.97 g, 2.00 mL, 17.5 mmol), then Et_3N (2.65 g, 3.66 mL, 26.2 mmol). The reaction was heated to 100 °C for 24 h then cooled back down to RT. The mixture was treated with TFA (2.99 g, 2.00 mL, 26.2 mmol) and heated to 80 °C for 3 h, after which another two aliquots of TFA (2.99 g, 2.00 mL, 26.2 mmol) were added at 1 h intervals. The reaction was then cooled RT, quenched with a solution of Et_3N (15 mL) in MeOH (50 mL), and the volatiles were removed *in vacuo*. The crude residue was diluted with EtOAc (100 mL), washed with sat. aq. $NaHCO_3$ (3 x 100 mL) and finally brine (100 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered, and the solvent was removed *in vacuo*. The residue was further purified by gradient column chromatography (SiO_2, flash, 0-100 % EtOAc/heptane) to isolate the title compound (**6**), after solvent removal, as a white powder (1.65 g, 6.24 mmol, 36 %). mp = 96-99 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.44 (s, 1H), 8.04 (d, *J* = 11.5 Hz, 1H), 7.67 – 7.61 (m, 1H), 7.44 (ddd, *J* = 8.3, 7.2, 1.4 Hz, 1H), 7.34 (d, *J* = 8.1 Hz, 1H), 7.19 (ddd, *J* = 7.9, 7.2, 1.0 Hz, 1H), 7.00 – 6.96 (m, 2H), 6.79 (dd, *J* = 11.5, 1.7 Hz, 1H), 6.67 – 6.62 (m, 2H), 4.29 (s, 2H), 3.47 (s, br, 1H), 2.83 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 153.22, 145.27, 143.62, 139.90, 129.62, 128.44, 126.50 (br), 125.64, 121.08, 118.29, 115.44, 113.86, 61.86 (br), 31.83. ^{11}B NMR (160 MHz, $CDCl_3$) δ 35.79 (br). IR (ATR, neat) 3390, 3024, 2875, 2810, 1725, 1615, 1593, 1563, 1511, 1436, 1390, 1345, 1281, 1232, 1133, 1104, 1057, 999, 941, 882, 818, 760, 705

cm^{-1}. LC-MS (APPI+, H_2O/MeCN/TFA, m/z) found 265 $[M+H]^+$ calculated 265.2 $[M+H]^+$, rt (PDA) 0.58 min. HRMS (MALDI+ FT-ICR, dithranol): found 265.15067 $[M+H]^+$ calculated 265.15067 $[M+H]^+$. Elemental Analysis Calc. ($C_{16}H_{17}BN_2O$): C, 72.76; H, 6.49; N, 10.61; Found: C, 72.64; H, 6.59; N, 10.54.

***N*-(4-(benzo[*e*][1,2]azaborinin-2(1H)-ylmethoxy)phenyl)-*N*-methylamides (2b-f)**

Route 1: To a suspension of *N*-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI) (100 mg, 0.520 mmol) in THF (5 mL) under Ar atmosphere were added 1-hydroxybenzotriazole (HOBt) (60 mg, 0.440 mmol) and the corresponding carboxylic acid (**b-f**) (0.400 mmol). After 30 min, 4-(benzo[*e*][1,2]azaborinin-2(1H)-ylmethoxy)-*N*-methylaniline (**6**) (106 mg, 0.400 mmol) followed by Et_3N (121 mg, 167 µL, 1.20 mmol) were added at 0 °C and the mixture was allowed to warm to RT overnight (16 h). The crude mixture was then diluted with EtOAc (25 mL) and washed with sat. aq. NH_4Cl (3 x 25 mL) then brine (25 mL). The organic phase was isolated and dried over Na_2SO_4, filtered, and the solvent was removed *in vacuo*. The crude residue was further purified by gradient column chromatography (SiO_2, flash, 0-100 % EtOAc/heptane) to isolate the title compounds (**2b-f**) after solvent removal.

***N*-(4-(benzo[*e*][1,2]azaborinin-2(1H)-ylmethoxy)phenyl)-*N*-methylisonicotinamide (2b)**

Route 1: Obtained as a white solid (111 mg, 75 %). Characterization reported above.

***N*-(4-(benzo[*e*][1,2]azaborinin-2(1H)-ylmethoxy)phenyl)-*N*-methylbenzo[*d*]thiazole-6-carboxamide (2c)**

Obtained as a white solid (121 mg, 71 %). mp = 64-71 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.99 (s, 1H), 8.32 (s, 1H), 8.06 – 8.05 (m, 1H), 8.03 (d, *J* = 11.5 Hz, 1H), 7.88 (d, *J* = 8.4 Hz, 1H), 7.63 (d, *J* = 7.6 Hz, 1H), 7.44 (ddd, *J* = 8.4, 7.2, 1.4 Hz, 1H), 7.39 (d, *J* = 8.2 Hz, 1H), 7.31 (d, *J* = 8.1 Hz, 1H), 7.19 (ddd, *J* = 8.0, 7.2, 1.0 Hz, 1H), 7.02 (d, *J* = 8.0 Hz, 2H), 6.91 (d, *J* = 8.4 Hz, 2H), 6.75 (dd, *J* = 11.5, 1.7 Hz, 1H), 4.25 (s, 2H), 3.52 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 170.06, 159.08, 155.81, 153.63, 145.57, 139.71, 137.47, 133.81, 133.44, 129.70, 128.59, 128.20, 126.94, 126.21 (br), 125.65, 123.08, 122.76, 121.31, 118.25, 115.15, 61.53 (br), 38.93. ^{11}B NMR (160 MHz, $CDCl_3$) δ 35.30 (br). IR (ATR, neat) 3388, 3302, 3056, 2878, 2823, 1632, 1615, 1594, 1564, 1507, 1436, 1391, 1368, 1291, 1240, 1206, 1171, 1155, 1146, 1132, 1106, 1067, 1020, 996, 910, 885, 865, 833, 801, 759, 730, 719, 700, 653 cm^{-1}. LC-MS (APPI+, H_2O/MeCN/TFA, m/z) found 426 $[M+H]^+$ calculated 426.1 $[M+H]^+$, rt (PDA) 0.82 min. HRMS (ESI+, DMSO) found 499.2348 $[M+Et_2NH_2]^+$ calculated 499.2334 $[M+Et_2NH_2]^+$. Elemental Analysis Calc. ($C_{24}H_{20}BN_3O_2S$): C, 67.78; H, 4.74; N, 9.88; Found: C, 67.55; H, 4.83; N, 9.71.

***N*-(4-(benzo[*e*][1,2]azaborinin-2(1H)-ylmethoxy)phenyl)-*N*-methyl-3-phenyl-1H-pyrazole-5-carboxamide (2d)**

Obtained as a white solid (103 mg, 59 %). Compound crystallizes with heptane upon concentration from EtOAc/heptane solution. mp = 186-192 °C ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.99 (s, 1H), 8.44 (s, 1H), 8.08 (d, *J* = 11.5 Hz, 1H), 7.67 (d, *J* = 7.6 Hz, 1H), 7.52 (d, *J* = 7.4 Hz, 2H), 7.46 (ddd, *J* = 8.3, 7.2, 1.4 Hz, 1H), 7.38 (d, *J* = 8.0 Hz, 1H), 7.32 – 7.29 (m, 2H), 7.25 – 7.21 (m, 3H), 7.20 – 7.17 (m, 2H), 6.83 (dd, *J* = 11.5, 1.8 Hz, 1H), 5.32 (s, 1H), 4.42 (s, 2H), 3.46 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 160.84, 145.72, 139.74, 135.72, 129.76, 129.12, 128.73, 128.68, 128.09, 126.23 (br), 125.68, 121.42, 118.31, 115.75, 104.82, 61.85 (br), 38.80. *note: 5 ^{13}C signals not observed; EtOAc and heptane impurities present. ^{11}B NMR (160 MHz, $CDCl_3$) δ 35.09 (br). IR (ATR, neat) 3279, 3062, 3025, 2922, 2360, 2021, 1964, 1737, 1626, 1616, 1567, 1508, 1438, 1396, 1292, 1245, 1194, 1170, 1155, 1133, 1107, 1074, 1042, 994, 960, 886, 833, 798, 757, 736, 695, 648, 614 cm^{-1}. LC-MS (APPI+, H_2O/MeCN/TFA, m/z) found 435 $[M+H]^+$ calculated 435.2 $[M+H]^+$, rt (PDA) 0.88 min. HRMS (ESI+, DMSO) found 435.1987 $[M+H]^+$ calculated 435.1987 $[M+H]^+$.

***N*-(4-(benzo[*e*][1,2]azaborinin-2(1H)-ylmethoxy)phenyl)-*N*-methyl-5-(pyridin-2-yl)-1H-pyrazole-3-carboxamide (2e)**

Obtained as a white solid (124 mg, 71 %). mp = 174-182 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 11.39 (s, 1H), 8.55 – 8.38

(m, 2H), 8.07 (d, *J* = 11.5 Hz, 1H), 7.72 (s, 1H), 7.68 – 7.62 (m, 2H), 7.47 – 7.42 (m, 1H), 7.37 (d, *J* = 8.1 Hz, 1H), 7.25 – 7.19 (m, 3H), 7.14 (d, *J* = 7.7 Hz, 3H), 6.82 (dd, *J* = 11.5, 1.6 Hz, 1H), 5.86 (s, 1H), 4.38 (s, 2H), 3.47 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 149.54, 145.62, 139.77, 136.74, 129.72, 128.82, 128.62, 126.27 (br), 125.68, 122.83, 121.34, 120.21, 118.32, 115.69, 61.72 (br), 38.92. *note: 7 ^{13}C signals not observed. ^{11}B NMR (160 MHz, $CDCl_3$) δ 35.17 (br). IR (ATR, neat) 3390, 3233, 3052, 2925, 2875, 2360, 1615, 1594, 1565, 1508, 1432, 1395, 1360, 1282, 1243, 1207, 1170, 1147, 1133, 995, 963, 886, 837, 789, 760, 734, 650 cm^{-1}. LC-MS (APPI+, H_2O/MeCN/TFA, m/z) found 436 $[M+H]^+$ calculated 436.2 $[M+H]^+$, rt (PDA) 0.69 min. HRMS (ESI+, DMSO) found 436.1950 $[M+H]^+$ calculated 436.1939 $[M+H]^+$; found 509.2828 $[M+Et_2NH_2]^+$ calculated 509.2831 $[M+Et_2NH_2]^+$. Elemental Analysis Calc. ($C_{25}H_{22}BN_5O_2$): C, 68.98; H, 5.09; N, 16.09; Found: C, 69.05; H, 5.16; N, 15.91.

***N*-(4-(benzo[*e*][1,2]azaborinin-2(1H)-ylmethoxy)phenyl)-*N*-methyl-2-(pyridin-3-yl)thiazole-4-carboxamide (2f)**

Obtained as a pale yellow solid (132 mg, 73 %). mp = 192-200 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.86 (s, 1H), 8.57 (d, *J* = 3.7 Hz, 1H), 8.41 (s, 1H), 8.04 (d, *J* = 11.5 Hz, 1H), 7.92 (d, *J* = 7.3 Hz, 1H), 7.64 (d, *J* = 7.7 Hz, 1H), 7.61 (s, 1H), 7.44 (ddd, *J* = 8.3, 7.2, 1.4 Hz, 1H), 7.33 (d, *J* = 8.1 Hz, 1H), 7.28 – 7.24 (m, 1H), 7.20 (ddd, *J* = 8.0, 7.1, 1.0 Hz, 1H), 7.13 (d, *J* = 7.9 Hz, 2H), 7.03 (d, *J* = 8.3 Hz, 2H), 6.78 (dd, *J* = 11.5, 1.6 Hz, 1H), 4.31 (s, 2H), 3.51 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 163.38, 163.11, 159.62, 151.65, 151.08, 147.83, 145.56, 139.76, 137.60, 133.79, 129.69, 129.23, 128.58, 128.32, 126.29 (br), 125.66, 124.47, 123.71, 121.30, 118.28, 114.94, 61.69 (br), 38.83. *note: residual EtOAc solvent impurity present.^{11}B NMR (160 MHz, $CDCl_3$) δ 35.31 (br). IR (ATR, neat) 3373, 2875, 2360, 2338, 1630, 1612, 1563, 1507, 1437, 1419, 1367, 1271, 1237, 1130, 1007, 978, 882, 836, 817, 806, 768, 738, 706, 640 cm^{-1}. LC-MS (APPI+, H_2O/MeCN/TFA, m/z) found 453 $[M+H]^+$ calculated 453.2 $[M+H]^+$, rt (PDA) 0.74 min. HRMS (ESI+, DMSO) found 453.1544 $[M+H]^+$ calculated 453.1551 $[M+H]^+$; found 526.2434 $[M+Et_2NH_2]^+$ calculated 526.2443 $[M+Et_2NH_2]^+$. Elemental Analysis Calc. ($C_{25}H_{21}BN_4O_2S$): C, 66.38; H, 4.68; N, 12.39; Found: C, 65.92; H, 4.79; N, 12.15.

Potassium trifluoro((4-(1-methyl-4-(pyridin-4-yl)-1H-pyrazol-3-yl)phenoxy)methyl)borate (7)

To a solution of 4-(1-methyl-4-(pyridin-4-yl)-1H-pyrazol-3-yl)phenol (1.00 g, 4.00 mmol) in dry, degassed DMF (50 mL) under Ar atmosphere was added sodium hydride (0.160 g, 4.00 mmol, 60 % dispersion in mineral oil) in one portion. The mixture was heated to 120 °C and stirred for 1 h. Potassium bromomethyltrifluoroborate (0.669 g, 3.33 mmol) was then added in one portion at RT, and the reaction was heated back to 120 °C overnight. The mixture was then cooled to RT and quenched using sat. aq. potassium bifluoride (10 mL, 45.0 mmol, 4.5 M), allowing to stir for 30 min before the mixture was concentrated to dryness *in vacuo*. The crude solid was loaded onto a filter and washed with hot acetone (200 mL). The filtrate was concentrated *in vacuo* onto celite which was then loaded onto a filter and washed with CH_2Cl_2 (200 mL). 5% MeOH/ CH_2Cl_2 (300 mL) was used to elute the title compound (**7**), which was isolated after solvent removal, as a pale yellow powder (0.894 g, 2.41 mmol, 72 %). mp = 124-130 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.44 – 8.42 (m, 2H), 8.14 (s, 1H), 7.22 – 7.18 (m, 4H), 6.90 – 6.78 (m, 2H), 3.89 (s, 3H), 3.02 – 2.89 (m, 2H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 161.98, 149.68, 148.60, 141.13, 131.81, 129.17, 123.53, 121.91, 116.34, 113.89, 38.74. *note: B-CH_2 ^{13}C signal not observed. IR (ATR, neat) 3050, 2922, 1681, 1640, 1604, 1545, 1527, 1440, 1418, 1347, 1316, 1278, 1243, 1206, 1177, 1090, 1026, 987, 972, 835, 819, 733, 702, 670, 660, 641 cm^{-1}. LC-MS (APPI+, H_2O/MeCN/TFA, m/z) found 314 $[(M-KF)+H]^+$ calculated 314.1 $[(M-KF)+H]^+$, rt (PDA) 0.27 min. HRMS (MALDI+ FT-ICR, dithranol): found 314.12746 $[M-KF+H]^+$ calculated 314.12708 $[M-KF+H]^+$.

2-((4-(1-Methyl-4-(pyridin-4-yl)-1H-pyrazol-3-yl)phenoxy)methyl)-1,2-dihydrobenzo[*e*][1,2]azaborinine (2a)

In an oven-dried microwave vial equipped with a stirrer bar, potassium trifluoroborate salt (**7**) (148 mg, 0.400 mmol) was suspended in a mixture of dry CPME (0.8 mL) and MeCN (1.6 mL) under Ar atmosphere. The mixture was solubilized by heating to 80 °C. To this hot stirring mixture, 2-vinylaniline (57 mg, 57 µL, 0.480 mmol), followed by Et_3N (243 mg, 335 µL, 2.40 mmol) and lastly perchlorosilane (68 mg, 46 µL,

0.400 mmol) were added. After stirring for 6 h at 80 °C, additional 2-vinylaniline (29 mg, 28 µL, 0.240 mmol) was added, followed by perchlorosilane (34 mg, 23 µL, 0.200 mmol) 1 h later. The mixture was then stirred for 3 days at 40 °C, after which it was quenched with a solution of Et_3N (243 mg, 335 µL, 2.40 mmol) in MeOH (2 mL). The volatiles were then removed *in vacuo* and the residue dissolved in EtOAc (25 mL). The organic phase was washed with 1 M NaOH (2 x 25 mL) and brine (25 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by gradient column chromatography (SiO_2, flash, 0-100 % EtOAc/heptane) to isolate the title compound (**2a**), after solvent removal, as a pale beige solid (55 mg, 35 %). mp = 76-78 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.48 (d, *J* = 5.5 Hz, 2H), 8.43 (s, 1H), 8.06 (d, *J* = 11.5 Hz, 1H), 7.65 (d, *J* = 7.8 Hz, 1H), 7.59 (s, 1H), 7.47 – 7.40 (m, 3H), 7.36 (d, *J* = 8.0 Hz, 1H), 7.22 – 7.17 (m, 3H), 7.08 (d, *J* = 8.5 Hz, 2H), 6.81 (d, *J* = 11.5 Hz, 1H), 4.37 (s, 2H), 3.99 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 160.64, 150.08, 149.66, 145.48, 141.48, 139.81, 130.64, 129.87, 129.68, 128.55, 126.37 (br), 125.67, 125.22, 122.69, 121.23, 118.32, 117.89, 114.62, 61.29 (br), 39.33. ^{11}B NMR (160 MHz, $CDCl_3$) δ 35.35 (br). IR (ATR, neat) 3389, 3252, 3029, 2939, 2874, 1601, 1564, 1525, 1498, 1438, 1417, 1345, 1302, 1280, 1264, 1240, 1177, 1155, 1146, 1133, 1109, 1087, 999, 977, 942, 885, 833, 813, 761, 737, 704, 669, 659, 627 cm^{-1}. LC-MS (APPI+, H_2O/MeCN/TFA, m/z) found 393 $[M+H]^+$ calculated 393.2 $[M+H]^+$, rt (PDA) 0.62 min. HRMS (MALDI+ FT-ICR, dithranol): found 393.18787 $[M+H]^+$ calculated 393.18812 $[M+H]^+$.

tert-Butyl methyl(4-(naphthalen-2-ylmethoxy)phenyl)carbamate (8)

To a solution of *tert*-butyl (4-hydroxyphenyl)(methyl)carbamate (**4**) (4.36 g, 19.6 mmol) and 2-(bromomethyl)naphthalene (2.83 g, 12.8 mmol) in MeCN (100 mL) was added potassium carbonate (5.31 g, 38.4 mmol) and the reaction was stirred overnight (20 h). The solvent was then removed *in vacuo*, and the residue dissolved in EtOAc (300 mL). The organic phase was washed with H_2O (2 x 200 mL) and brine (200 mL) then dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was purified by gradient column chromatography (SiO_2, flash, 0-100 % EtOAc/heptane). The title compound (**8**) was isolated, after solvent removal, as a crystalline white solid (4.31 g, 11.9 mmol, 93 %). mp = 119-120 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.90 – 7.83 (m, 4H), 7.54 (dd, *J* = 8.4, 1.5 Hz, 1H), 7.52 – 7.47 (m, 2H), 7.20 – 7.07 (m, 2H), 6.99 – 6.95 (m, 2H), 5.22 (s, 2H), 3.22 (s, 3H), 1.44 (s, 9H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 156.55, 155.23, 137.29, 134.51, 133.39, 133.18, 128.54, 128.06, 127.86, 127.05, 126.46, 126.38, 126.22, 125.38, 114.99, 80.16, 70.49, 37.75, 28.49. IR (ATR, neat) 3053, 2976, 2929, 2361, 1694, 1604, 1585, 1511, 1475, 1456, 1434, 1365, 1294, 1238, 1151, 1109, 1014, 976, 894, 860, 832, 817, 747, 620, cm^{-1}. LC-MS (APPI+, H_2O/MeCN/TFA, m/z) found 308 $[M-(t\text{-Bu})+H]^+$ calculated 308.1 $[M-(t\text{-Bu})+H]^+$, rt (PDA) 0.99 min. HRMS (MALDI+ FT-ICR, dithranol): found 386.17249 $[M+Na]^+$ calculated 386.17266 $[M+Na]^+$.

***N*-methyl-4-(naphthalen-2-ylmethoxy)aniline (9)**

To a solution of *tert*-butyl methyl(4-(naphthalen-2-ylmethoxy)phenyl)carbamate (**8**) (3.64 g, 10.0 mmol) in CH_2Cl_2 (100 mL) was added TFA (29.8 g, 20 mL, 261 mmol) and the mixture was heated to 30 °C for 15 min. The volatiles were then removed *in vacuo* and the residue was purified by gradient column chromatography (SiO_2, flash, 0 - 100% EtOAc/heptane). The title compound (**9**) was isolated, after solvent removal, as a white solid (2.21 g, 8.38 mmol, 84 %). mp = 68-72 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.89 – 7.82 (m, 4H), 7.55 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.51 – 7.46 (m, 2H), 6.93 – 6.90 (m, 2H), 6.61 – 6.57 (m, 2H), 5.17 (s, 2H), 2.81 (s, 3H). *note: NH ^{1}H signal not observed. ^{13}C NMR (151 MHz, $CDCl_3$) δ 151.35, 144.08, 135.26, 133.43, 133.12, 128.40, 128.07, 127.84, 126.37, 126.26, 126.05, 125.54, 116.37, 113.70, 71.19, 31.70. IR (ATR, neat) 3393, 3052, 2868, 2807, 1632, 1601, 1508, 1467, 1372, 1296, 1223, 1178, 1149, 1123, 1104, 1016, 951, 900, 854, 813, 737, 642, 621 cm^{-1}. LC-MS (APPI+, H_2O/MeCN/TFA, m/z) found 264 $[M+H]^+$ calculated 264.1 $[M+H]^+$, rt (PDA) 0.55 min. HRMS (MALDI+ FT-ICR, dithranol): found 264.13832 $[M+H]^+$ calculated 264.13829 $[M+H]^+$. Elemental Analysis Calc. ($C_{18}H_{17}NO$): C, 82.10; H, 6.51; N, 5.32; Found: C, 81.97; H, 6.59; N, 5.25.

***N*-methyl-*N*-(4-(naphthalen-2-ylmethoxy)phenyl)carboxamides (3b-f)**

To a suspension of *N*-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI) (0.100 g, 0.520 mmol) in THF (4 mL), were added 1-hydroxybenzotriazole (HOBt) (0.059 g, 0.440 mmol) and the corresponding carboxylic acid (**b-f**) (0.400 mmol). After 30 min, a solution of *N*-methyl-4-(naphthalen-2-ylmethoxy)aniline (**9**) (0.105 g, 0.400 mmol) and Et_3N (0.121 g, 0.167 mL, 1.20 mmol) in THF (1 mL) was added and the mixture was stirred over 3 d. The reaction was then diluted with CH_2Cl_2 (10 mL) and the resulting solution was concentrated *in vacuo* onto celite. The residue was purified by gradient column chromatography (SiO_2, flash, 0-100 % EtOAc/heptane) to isolate the title compounds (**3b-f**) after solvent removal.

***N*-methyl-*N*-(4-(naphthalen-2-ylmethoxy)phenyl)isonicotinamide (3b)**

Obtained as a white solid (115 mg, 0.312 mmol, 78 %). mp = 163-165 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.45 (d, *J* = 5.0 Hz, 2H), 7.88 – 7.81 (m, 4H), 7.52 – 7.47 (m, 3H), 7.12 (d, *J* = 5.1 Hz, 2H), 6.95 (d, *J* = 8.6 Hz, 2H), 6.86 (d, *J* = 8.6 Hz, 2H), 5.16 (s, 2H), 3.46 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 168.42, 157.80, 149.77, 143.83, 136.85, 133.90, 133.35, 133.23, 128.66, 128.36, 128.05, 127.90, 126.58, 126.52, 126.39, 125.29, 122.68, 115.79, 70.50, 38.44. IR (ATR, neat) 3051, 2935, 1645, 1598, 1552, 1509, 1466, 1430, 1408, 1376, 1300, 1287, 1240, 1176, 1108, 1067, 1022, 894, 834, 816, 755, 690, 644, 620 cm^{-1}. LC-MS (APPI+, H_2O/MeCN/TFA, m/z) found 369 $[M+H]^+$ calculated 369.2 $[M+H]^+$, rt (PDA) 0.63 min. HRMS (MALDI+ FT-ICR, dithranol): found 369.15970 $[M+H]^+$ calculated 369.15975 $[M+H]^+$. Elemental Analysis Calc. ($C_{24}H_{20}N_2O_2$): C, 78.24; H, 5.47; N, 7.60; Found: C, 78.15; H, 5.41; N, 7.68.

***N*-methyl-*N*-(4-(naphthalen-2-ylmethoxy)phenyl)benzo[*d*]thiazole-6-carboxamide (3c)**

Obtained as a white solid (108 mg, 0.253 mmol, 63 %). mp = 56-60 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.00 (s, 1H), 8.03 (s, 1H), 7.90 – 7.79 (m, 5H), 7.51 – 7.45 (m, 3H), 7.37 (d, *J* = 8.0 Hz, 1H), 6.98 (d, *J* = 8.1 Hz, 2H), 6.84 (d, *J* = 8.6 Hz, 2H), 5.14 (s, 2H), 3.50 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 170.02, 157.28, 155.86, 153.65, 137.94, 134.03, 133.69, 133.46, 133.34, 133.20, 128.60, 128.23, 128.05, 127.88, 126.92, 126.51, 126.47, 126.33, 125.28, 123.08, 122.79, 115.68, 70.42, 38.90. IR (ATR, neat) 3055, 2930, 1636, 1509, 1469, 1442, 1426, 1395, 1366, 1293, 1239, 1177, 1108, 1021, 954, 909, 890, 865, 836, 816, 767, 752, 619 cm^{-1}. LC-MS (APPI+, H_2O/MeCN/TFA, m/z) found 425 $[M+H]^+$ calculated 425.1 $[M+H]^+$, rt (PDA) 0.82 min. HRMS (MALDI+ FT-ICR, dithranol): found 425.13174 $[M+H]^+$ calculated 425.13183 $[M+H]^+$. Elemental Analysis Calc. ($C_{26}H_{20}N_2O_2S$): C, 73.56; H, 4.75; N, 6.60; Found: C, 73.66; H, 4.83; N, 6.54.

***N*-methyl-*N*-(4-(naphthalen-2-ylmethoxy)phenyl)-3-phenyl-1H-pyrazole-5-carboxamide (3d)**

Obtained as a white solid (94 mg, 0.217 mmol, 54 %). mp = 164-166 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.85 (s, 1H), 7.92 (s, 1H), 7.90 – 7.83 (m, 3H), 7.57 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.54 – 7.49 (m, 4H), 7.35 – 7.31 (m, 2H), 7.29 (d, *J* = 7.3 Hz, 1H), 7.23 – 7.20 (m, 2H), 7.13 – 7.10 (m, 2H), 5.31 (s, 2H), 5.29 (s, 1H), 3.43 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 159.00, 133.93, 133.40, 133.27, 129.22, 128.76, 128.14, 128.07, 127.93, 126.57, 126.52, 126.43, 125.70, 125.16, 116.25, 104.79, 70.66, 38.73. *note: 6 ^{13}C signals not observed. IR (ATR, neat) 3207, 3059, 2360, 2334, 1740, 1621, 1509, 1443, 1395, 1357, 1297, 1241, 1173, 1121, 1076, 1009, 988, 955, 894, 836, 816, 757, 694, 668, 622 cm^{-1}. LC-MS (APPI+, H_2O/MeCN/TFA, m/z) found 434 $[M+H]^+$ calculated 434.2 $[M+H]^+$, rt (PDA) 0.88 min. HRMS (MALDI+ FT-ICR, dithranol): found 434.18630 $[M+H]^+$ calculated 434.18630 $[M+H]^+$. Elemental Analysis Calc. ($C_{28}H_{23}N_3O_2$): C, 77.58; H, 5.35; N, 9.69; Found: C, 77.69; H, 5.30; N, 9.54.

***N*-methyl-*N*-(4-(naphthalen-2-ylmethoxy)phenyl)-5-(pyridin-2-yl)-1H-pyrazole-3-carboxamide (3e)**

Obtained as a white solid (78 mg, 0.180 mmol, 45 %). mp = 92-96 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 11.37 (s, 1H), 8.53 (d, *J* = 3.7 Hz, 1H), 7.90 (s, 1H), 7.88 – 7.82 (m, 3H), 7.69 (dt, *J* = 24.5, 7.8 Hz, 2H), 7.55 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.52 – 7.48 (m, 2H), 7.22 – 7.16 (m, 3H), 7.09 – 7.05 (m, 2H), 5.92 (s, 1H), 5.27 (s, 2H), 3.45 (s, 3H). ^{13}C NMR (151 MHz,

$CDCl_3$) δ 158.66, 149.55, 136.78, 134.08, 133.39, 133.23, 128.89, 128.66, 128.08, 127.90, 126.51, 126.48, 126.34, 125.28, 122.89, 120.22, 116.21, 105.85, 70.63, 38.87. *note: 5 ^{13}C signals not observed. IR (ATR, neat) 3195, 3050, 2931, 1620, 1594, 1568, 1506, 1429, 1394, 1358, 1299, 1280, 1238, 1172, 1121, 1035, 993, 962, 893, 835, 814, 789, 735, 702, 667, 622 cm^{-1}. LC-MS (APPI+, H_2O/MeCN/TFA, m/z) found 435 $[M+H]^+$ calculated 435.2 $[M+H]^+$, rt (PDA) 0.67 min. HRMS (MALDI+ FT-ICR, dithranol): found 435.18149 $[M+H]^+$ calculated 435.18155 $[M+H]^+$. Elemental Analysis Calc. ($C_{27}H_{22}N_4O_2$): C, 74.64; H, 5.10; N, 12.89; Found: C, 74.46; H, 5.03; N, 12.72.

***N*-methyl-*N*-(4-(naphthalen-2-ylmethoxy)phenyl)-2-(pyridin-3-yl)thiazole-4-carboxamide (3f)**

Obtained as a white solid (115 mg, 0.255 mmol, 64 %). mp = 148-154 °C. ^1H NMR (600 MHz, $CDCl_3$) δ 8.86 (s, 1H), 8.60 (d, *J* = 3.8 Hz, 1H), 7.92 – 7.88 (m, 1H), 7.86 – 7.82 (m, 3H), 7.80 (dd, *J* = 5.9, 3.2 Hz, 1H), 7.59 (s, 1H), 7.52 – 7.47 (m, 3H), 7.29 – 7.24 (m, 1H), 7.10 (d, *J* = 7.6 Hz, 2H), 6.96 (d, *J* = 8.2 Hz, 2H), 5.21 (s, 2H), 3.49 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 163.34, 163.11, 157.79, 151.53, 151.08, 147.80, 138.08, 134.17, 133.76, 133.35, 133.18, 129.22, 128.59, 128.35, 128.21, 128.02, 127.88, 126.45, 126.31, 125.25, 124.53, 123.73, 115.49, 70.57, 38.79. IR (ATR, neat) 3053, 2930, 1637, 1586, 1572, 1509, 1467, 1450, 1417, 1369, 1274, 1238, 1172, 1146, 1107, 1024, 1009, 981, 954, 894, 834, 814, 748, 704, 670, 642, 619 cm^{-1}. LC-MS (APPI+, H_2O/MeCN/TFA, m/z) found 452 $[M+H]^+$ calculated 452.1 $[M+H]^+$, rt (PDA) 0.72 min. HRMS (MALDI+ FT-ICR, dithranol): found 452.14277 $[M+H]^+$ calculated 452.14272 $[M+H]^+$. Elemental Analysis Calc. ($C_{27}H_{21}N_3O_2S$): C, 71.82; H, 4.69; N, 9.31; Found: C, 71.93; H, 4.71; N, 9.12.

4-(1-Methyl-3-(4-(naphthalen-2-ylmethoxy)phenyl)-1H-pyrazol-4-yl)pyridine (3a)

To a solution of 4-(1-methyl-4-(pyridin-4-yl)-1H-pyrazol-3-yl)phenol (157 mg, 0.624 mmol) and 2-(bromomethyl)naphthalene (138 mg, 0.624 mmol) in MeCN (3 mL) was added sodium hydride (25 mg, 0.624 mmol, 60 % dispersion in mineral oil) and the reaction was heated to 60 °C for 30 min. The mixture was then diluted with MeOH (10 mL) and CH_2Cl_2 (10 mL) and the solution was concentrated *in vacuo* onto celite. The residue was purified by gradient column chromatography (SiO_2, flash, 0-100 % EtOAc /heptane) to isolate the title compound (**3a**), after solvent removal, as a beige solid (83 mg, 0.211 mmol, 34 %). mp = 144-146 °C. ^1H NMR (600 MHz, $CDCl_3$) δ 8.49 – 8.46 (m, 2H), 7.90 (s, 1H), 7.89 – 7.84 (m, 3H), 7.58 (s, 1H), 7.56 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.51 – 7.47 (m, 2H), 7.42 – 7.39 (m, 2H), 7.19 – 7.16 (m, 2H), 7.03 – 6.99 (m, 2H), 5.25 (s, 2H), 3.98 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 158.89, 150.06, 149.45, 141.40, 134.40, 133.40, 133.19, 130.64, 129.86, 128.54, 128.08, 127.86, 126.56, 126.39, 126.23, 125.79, 125.45, 122.68, 117.90, 115.10, 70.28, 39.32. IR (ATR, neat) 3053, 2938, 2866, 1602, 1577, 1543, 1525, 1510, 1445, 1415, 1346, 1302, 1282, 1238, 1179, 1124, 1109, 1087, 1009, 993, 978, 954, 896, 833, 815, 747, 706, 660, 620 cm^{-1}. LC-MS (APPI+, H_2O/MeCN/TFA, m/z) found 392 $[M+H]^+$ calculated 392.2 $[M+H]^+$, rt (PDA) 0.63 min. HRMS (MALDI+ FT-ICR, dithranol): found 392.17567 $[M+H]^+$ calculated 392.17574 $[M+H]^+$.

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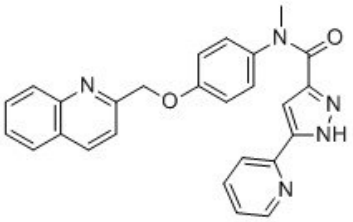
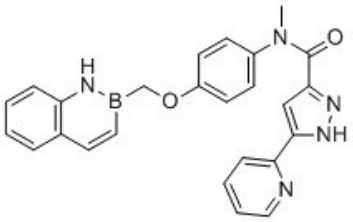
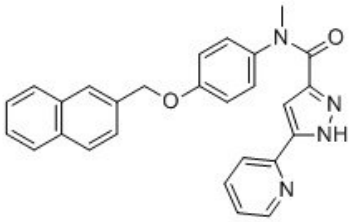


1e
IC_{50} = 12 nM (PDE10A)



2e
IC_{50} = 64 nM (PDE10A)



3e
IC_{50} = 4% @ 10 μM (PDE10A)