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Boron-containing capsaicinoids†

Jennifer A. Melanson,^a Maxim F. Landry,^a Martin Lanteigne,^b Katherine McQuillan,^b Hebelin Correa,^b Russell G. Kerr^b and Stephen A. Westcott^a

This study reports on the preparation of eight new boron-containing capsaicinoids bearing long aliphatic chains, as an expansion of our previous studies to include tertiary amide derivatives into our substrate scope. Our boron-moiety, a pinacolboronate ester (Bpin) fragment, has been incorporated in two locations: as an aryl substituent of the capsaicinoid produced by the reductive amination of veratraldehyde, or at the terminal end of an aliphatic substituent using an iridium catalyzed hydroboration reaction. We report that most compounds in our series show moderate antimicrobial and cytotoxic activity, surpassing activities noted in our previous study.

Introduction

Organoboron compounds are beginning to receive well-warranted attention in the pharmaceutical industry, including five drugs recently approved by the FDA (Fig. 1): Bortezomib **1** (Velcade, injected cancer therapy),^{1,2} Crisaborole **2** (Eucrisa, topical eczema treatment),³ Ixazomib **3** (Ninlaro, oral cancer therapy),^{4–6} Tavorole **4** (Kerydin, topical anti-fungal),^{7,8} and Vaborbactam **5** (in combination with Meropenem as Vabomere, injected broad-spectrum antibiotic).^{9–11} Indeed, organoboron compounds display a wide variety of marketable pharmaceutical activities.^{12,13}

Our group has a long-standing interest in developing bioactive organoboron compounds,^{14–34} including boron-containing capsaicinoids.^{35,36} Capsaicin (**6**, Fig. 2) is the colourless, hydrophobic, crystalline compound³⁷ that is responsible for the characteristic spicy “heat” flavouring of the chili fruits of the *Capsicum* genus. Capsaicin has many uses beyond the kitchen, including as an anticancer, antifungal, or antibacterial agent, as an insect or animal repellent, as an analgesic, and even in weight loss aid.³⁸ Capsaicinoids are natural products that are structurally related to capsaicin, which also tend to display many of the same marketable properties.

To this extent, our initial study³⁵ focused on the synthesis and biological activity of select capsaicinoids that bear either a long aliphatic moiety or incorporate boron as a substituent on

a phenyl group. These compounds were screened against *Mycobacterium tuberculosis* H37Ra, and it was found that substrates bearing long aliphatic chains (Fig. 2, **7a/b**) demonstrated greater bioactivity.³⁵ In addition, our boron-containing capsaicinoid (Fig. 2, **7c**) showed comparable bioactivity to our boron-omitted lipophilic substrates.³⁵ Our second study shows cases two boron-capsaicinoids bearing either a short or a long aliphatic tail, with the boron moiety attached to the terminal end of this tail (Fig. 2, **8a/b**).³⁶ Both compounds demonstrated antibacterial activity against vancomycin-resistant *Enterococcus*, and the more lipophilic compound (Fig. 2, **8b**) displayed broader antimicrobial activity.³⁶ Based on the results of both studies,^{35,36} we have chosen to expand the substrate scope to

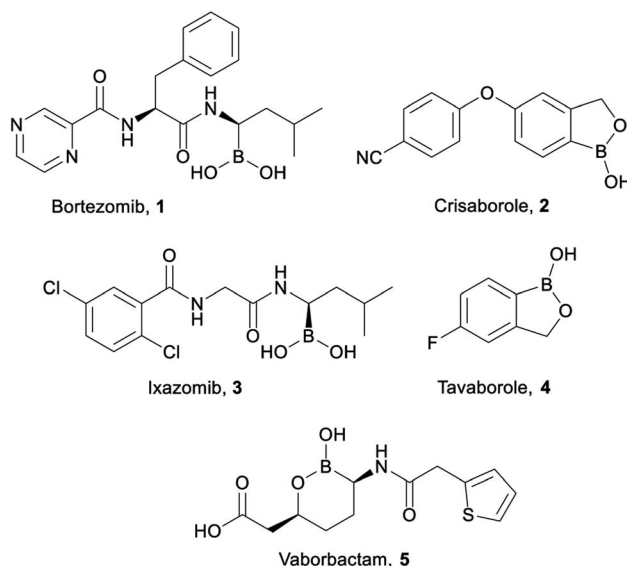


Fig. 1 FDA approved organoboron compounds.

^aDepartment of Chemistry and Biochemistry, Mount Allison University, Sackville, NB E4L 1G8, Canada. E-mail: swestcott@mta.ca; jamelanson@mta.ca; mflandry@mta.ca

^bNautilus Biosciences CRODA Canada Inc., Duffy Research Centre, Charlottetown, PE C1A 4P3, Canada. E-mail: martin.lanteigne@croda.com; katherine.mcquillan@croda.com; hebelin.correa@croda.com

^cDepartment of Chemistry, University of Prince Edward Island, Charlottetown, PE C1A 4P3, Canada. E-mail: rkerr@upei.ca

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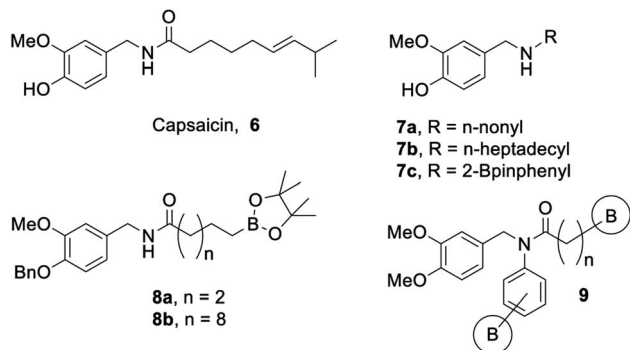


Fig. 2 Capsaicin and biologically active capsaicinoids.

include boron-containing capsaicinoids featuring tertiary amides that bear a long aliphatic tail (Fig. 2, **9**).

Results and discussion

Chemistry

Veratraldehyde (Scheme 1, **10**) is the methylated derivative of vanillin and is used commercially as a fragrant and flavourant,³⁹ as well as a starting material in the synthesis of some pharmaceuticals (e.g., Tiapamil,^{40–42} and Verazide^{43,44}). In our previous study,³⁵ we chose vanillin as our starting aldehyde, but its use requires additional protection and deprotection steps for the compound to be suitable in the methodology employed. Consequently, we decided to use **10** as a replacement.

In our current study, we have shown that the amidation of the boro-aryl amine substrates (**19**, **20**) employed a saturated aliphatic acyl chloride to provide the final tertiary amide capsaicinoid (**23–26**) in good yield without further manipulation.

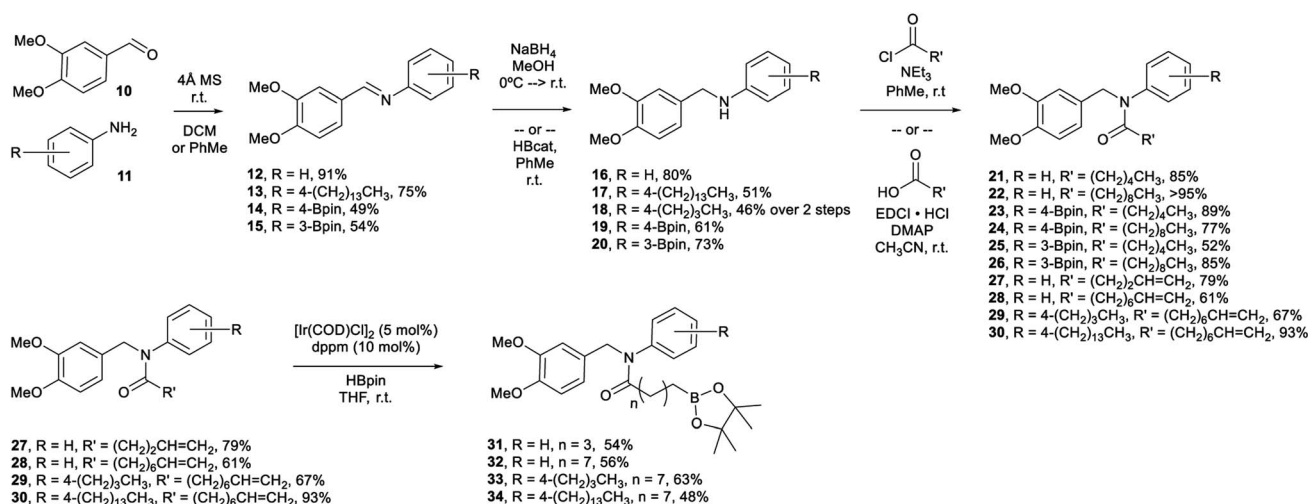
We have also prepared eight boron-containing capsaicinoids (Scheme 1, **23–26/31–34**) in 3–4 steps from **10**, as well as two substrates that do not contain a boron moiety (Scheme 1, **21/22**) using the same methodology. We have prepared these

substrates by a divergent synthesis, beginning with the reductive amination of **10** and either a desboro or boro-aryl primary amine (**11**). Our desboro-aryl amine substrates either were unsubstituted (**16**) or bore aliphatic chains (**17**, **18**). We have previously found that increasing the length of aliphatic substituents on our boron-containing capsaicinoids provided greater antimicrobial activity,³⁶ and so functionalization at this position provided an opportunity to further tune the lipophilicity of the capsaicinoid. Amines **16–18** were isolated in modest to good yield.

The desboro-aryl amine substrates were subjected to EDCI-assisted amidation using terminally unsaturated aliphatic acids to provide intermediates (**27–30**) towards the final tertiary amide capsaicinoids (**31–34**). These intermediates were subjected to metal-catalyzed hydroboration, employing $[\text{IrCl}(\text{cod})(\text{dppm})]^{45}$ and pinacolborane (HBpin, pin = 1,2- $\text{O}_2\text{C}_2\text{Me}_4$) at room temperature. The postulated catalytic cycle is anticipated to proceed *via* the generally accepted Ir(I/III) pathway,⁴⁶ whereby loss of the cod ligand opens up coordination sites for the subsequent B–H bond activation step. Coordination of the alkene followed by insertion into either the Ir–H (shown) or the Ir–B bond would generate an iridium alkylboronate ester intermediate. Reductive elimination would afford the expected linear product. This methodology was successful in generating the amide capsaicinoids **31–34** in modest yields.

Biology

Our 8 boron-containing capsaicinoids were evaluated for antimicrobial and cytotoxic activities. Antimicrobial assays were performed using methicillin-resistant *Staphylococcus aureus* MRSA 310, vancomycin-resistant *Enterococcus faecium* VRE 379, *Staphylococcus warneri* (ATCC 17917), *Proteus vulgaris* (ATCC 12454), *Pseudomonas aeruginosa* (ATCC 14210), and *Candida albicans* (ATCC 14035). Compound **25** showed moderate activity against MRSA, VRE, and *S. warneri*, whereas compound **31** showed a low activity against MRSA and *S. warneri* and compound **32** was only active against MRSA (Table 1).



Scheme 1 Synthesis of boron-containing capsaicinoids.



Table 1 Antimicrobial activities^a

| Compound (μM) | MRSA | | VRE | | <i>S. warneri</i> | |
|----------------------------|------------------|----------------------------|------------------|----------------------------|-------------------|----------------------------|
| | MIC90 | IC ₅₀ | MIC90 | IC ₅₀ | MIC90 | IC ₅₀ |
| 25 | 136.9 | 70.6 \pm 6.6 | 273.8 | 91.6 \pm 6.8 | 136.9 | 78.3 \pm 39.8 |
| 26 | 15.3 | 13.2 \pm 0.0 | Inactive | Inactive | Inactive | Inactive |
| 31 | Inactive | 120.6 \pm 2.0 | Inactive | Inactive | 282.3 | 135.0 \pm 15.4 |
| 32 | Inactive | 153.9 \pm 37.1 | Inactive | Inactive | Inactive | Inactive |
| Control | 1.4 ^a | 0.5 \pm 0.1 ^a | 2.4 ^b | 1.2 \pm 0.1 ^b | 0.3 ^a | 0.3 \pm 0.1 ^a |
| 8a* | Inactive | 107.1 | Inactive | Inactive | — | — |
| 8b* | Inactive | 244.7 | Inactive | 276.7 | — | — |
| Phenylboronic acid* | Inactive | 169.6 | Inactive | Inactive | — | — |
| Capsaicin* | Inactive | Inactive | Inactive | Inactive | — | — |

^a Inhibition at concentrations above 300 μM was considered inactive. Controls: (a) Vancomycin, (b) Rifampicin. Reported activity is the average \pm SD. *Data collected in previous study, inhibition above 400 μM was considered inactive; activity against *S. warneri* was not previously studied.³⁶

Interestingly, compound **26** was also selectively active against the MRSA pathogen and was able to be administered at the lowest dosage in the antimicrobial series to achieve 90% growth inhibition at a concentration of 15.3 μM (compared to the control antibiotic Vancomycin that demonstrates MIC90 of MRSA at 1.4 μM). Compounds **23**, **24**, **33**, and **34** were inactive against all tested pathogens. None of the boron-containing capsaicinoids showed activity against *P. aeruginosa*, *P. vulgaris*, and *C. albicans*.

In addition to the antimicrobial study, our boron-containing capsaicinoid series was also submitted to cytotoxic assays using human foreskin BJ fibroblast cells (ATCC CRL-2522), green monkey kidney cells Vero (ATCC CCL-81), human breast adenocarcinoma cells (ATCC HTB-26 MDA-MB 231 and MCF7. ATCC HTB-22), and human colorectal carcinoma cells (HCT116 ATCC CCL-247). Compounds **23**, **25**, and **31** showed a selective but low to moderate activity against the three cancer cell lines tested. Compounds **24**, **26**, **32**, and **33** demonstrated unselective cytotoxic effects across all cell lines, with compound **33** being the most cytotoxic compound of our study. In addition to being broadly cytotoxic, compound **33** showed notable activity against MCF7 (with an IC₅₀ of 3.4 μM). The most lipophilic capsaicinoid, compound **34**, was found to be inactive against all screened cell lines (Table 2).

Conclusions

As a result of this study, we have synthesized fourteen capsaicinoids in 3–4 steps from commercially available veratraldehyde in modest to good yield. Most compounds demonstrated low to moderate activity in cytotoxicity assays, but compound **33** displayed the most notable activity against MCF7. Unfortunately, **33** was also found to be cytotoxic against normal cell lines. Compounds **23**, **25**, and **31** were found to be selectively cytotoxic against cancer cell lines, but the activity displayed was very modest. In our antimicrobial studies, notable antibacterial activity was displayed from compound **26** against MRSA. Although the compound does not best the industry standard, it does outperform our previously published substrates.³⁶ We feel that the antimicrobial and cytotoxic assays warrant additional examination of capsaicinoids bearing boron-moieties to further tailor bioactivity. Further studies are in progress and will be reported in due course.

Experimental

Materials and methods

Reagents and solvents were obtained from Sigma-Aldrich, Strem Chemicals, TCI Chemicals, or Alfa Aesar. Where

Table 2 Cytotoxicity activities^a

| Compound (IC ₅₀ μM) | Normal cell lines | | Cancer cell lines | | |
|--|-------------------|------------------|--------------------------------|----------------|------------------|
| | Vero | BJ | HCT | HTB | MCF7 |
| 23 | Inactive | Inactive | 117.7 \pm 4.9 | 85.8 \pm 7.1 | Inactive |
| 24 | 26.9 \pm 4.4 | 36.1 \pm 0.8 | 33.8 \pm 2.1 | 25.2 \pm 1.3 | 24.1 \pm 3.8 |
| 25 | Inactive | Inactive | 136.7 \pm 12.0 | 76.1 \pm 3.4 | 117.7 \pm 19.5 |
| 26 | 47.2 \pm 6.7 | 38.6 \pm 1.0 | 44.3 \pm 10.5 | 31.5 \pm 2.7 | 35.7 \pm 16.2 |
| 31 | Inactive | Inactive | 125.9 \pm 16.5 | 58.0 \pm 3.5 | 108.3 \pm 30.9 |
| 32 | 77.1 \pm 8.4 | 111.7 \pm 10.0 | 80.1 \pm 3.9 | 42.6 \pm 1.8 | 68.5 \pm 15.1 |
| 33 | 20.9 \pm 1.2 | 24.2 \pm 0.2 | 20.3 \pm 0.7 | 21.2 \pm 3.5 | 3.4 \pm 2.2 |
| Doxorubicin | >14.7 | >14.7 | <1.2 \times 10 ^{−4} | 0.4 \pm 0.2 | 0.2 \pm 0.2 |

^a Inhibition at concentrations above 300 μM was considered inactive. Reported activity is the average \pm SD.



specified, manipulations under an inert atmosphere were performed in a MB Unilab glove box produced by MBraun or using standard Schlenk techniques. NMR spectra were recorded on a JEOL JNM-GSX400 FT NMR (^1H : 400 MHz; ^{11}B : 128 MHz; ^{13}C : 100 MHz) spectrometer. ^1H , $^{13}\text{C}\{^1\text{H}\}$, and $^{11}\text{B}\{^1\text{H}\}$ NMR chemical shifts (δ /ppm) are referenced to Me_4Si , Me_4Si , and $\text{BF}_3 \cdot \text{OEt}_2$, respectively. Chemical shifts (δ) are reported in ppm [relative to residual solvent peaks (^1H and ^{13}C) or external $\text{BF}_3 \cdot \text{OEt}_2$ (^{11}B)]. Multiplicities are reported as singlet (s), doublet (d), triplet (t), quartet (q), quintet (quint), or multiplet (m), with broad (br) or apparent (a) added as a prefix where necessary, and coupling constants (J) reported in hertz. Melting points were measured uncorrected with a Stuart SMP30 apparatus. High resolution mass spectrometry was performed at DalChem Mass Spec Laboratory (Dalhousie University, Halifax, NS).

General procedure 1

Synthesis of diarylimines. A solution of 3,4-dimethoxybenzaldehyde (1 equiv.) in DCM [0.6 M] was added to an Erlenmeyer flask equipped with a layer of 4 Å MS, after which the prescribed aniline substrate (1–1.5 equiv.) was added and the vessel was sealed. The resulting solution was reacted at ambient temperature (20 °C) for 4 days before decanting to remove the 4 Å MS and concentrating the reaction mixture *in vacuo*. The resulting oil/solid was dissolved in hot EtOH and then allowed to cool to RT. The precipitate was filtered and washed with hexanes, and then recrystallized from EtOH to afford the desired product as a colourless, crystalline solid.

General procedure 2

Synthesis of BPin substituted diarylimines. A solution of 3,4-dimethoxybenzaldehyde (1 equiv.) in PhMe [0.2 M] was added to an Erlenmeyer flask equipped with a layer of 4 Å MS under an inert atmosphere (glove box) after which the prescribed BPin substituted aniline substrate (1 equiv.) was added and the vessel was sealed. The resulting solution reacted at ambient temperature (20 °C) for 2 weeks before decanting to remove the 4 Å MS and concentrating the reaction mixture *in vacuo*. The resulting crude oil/solid was dissolved in hot EtOH and then allowed to cool to RT. The precipitate was filtered and washed with hexanes, and then recrystallized from EtOH to afford the desired product as a colourless, crystalline solid.

Synthesis of 1-(3,4-dimethoxyphenyl)-N-phenylmethanimine (12). General procedure 1 was followed using aniline (1.10 mL, 12.0 mmol) and 3,4-dimethoxybenzaldehyde (2.00 g, 12.0 mmol) to give the title compound as a colourless solid. Yield: 2.63 g (91%). MP (EtOH) 75.7–78.0 °C; ^1H NMR (400 MHz, in $\text{CDCl}_3\text{-d}_1$): δ 8.35 (s, 1H), 7.62 (br d, 1H), 7.40–7.36 (m, 2H), 7.29 (at, 1H), 7.23–7.19 (m, 3H), 6.91 (br d, 1H), 3.97 (br d, 3H), 3.92 (br d, 3H) ppm; ^{13}C NMR (100 MHz, in $\text{CDCl}_3\text{-d}_1$): δ 159.9, 152.3, 152.0, 149.4, 129.6, 129.2, 125.6, 124.5, 120.9, 110.4, 108.8, 56.0 ppm. Comparable to literature.⁴⁷

Synthesis of 1-(3,4-dimethoxyphenyl)-N-(4-tetradecylphenyl) methanimine (13). General procedure 1 was followed using 4-tetradecylaniline (1.74 g, 6.02 mmol) and 3,4-dimethoxybenzaldehyde (1.00 g, 6.02 mmol) to give the title compound as a colourless solid. Yield: 1.97 g (75%). MP (EtOH) 68.0–68.8 °C; FT-IR (neat): ν_{max} 2914 (s), 2848 (m), 1624 (w), 1595 (m), 1580 (m), 1512 (s), 1270 (s), 1144 (m) cm^{-1} ; ^1H NMR (400 MHz, in

$\text{CDCl}_3\text{-d}_1$): δ 8.38 (s, 1H), 7.61 (s, 1H), 7.28 (d, 1H, $J = 8.2$ Hz), 7.19 (d, 2H, $J = 8.3$ Hz), 7.14 (d, 2H, $J = 8.3$ Hz), 6.93 (d, 1H, $J = 8.2$ Hz), 3.99 (s, 3H), 3.95 (s, 3H), 2.61 (t, 2H, $J = 7.7$ Hz), 1.66–1.59 (m, 2H), 1.31–1.26 (m, 22H), 0.88 (t, 3H, $J = 6.8$ Hz) ppm; ^{13}C NMR (100 MHz, in $\text{CDCl}_3\text{-d}_1$): δ 159.2, 152.0, 149.9, 149.5, 140.7, 129.9, 129.2, 124.4, 120.9, 110.5, 108.9, 56.1, 35.6, 32.1, 31.7, 29.82, 29.75, 29.7, 29.5, 29.4, 22.8, 14.3 ppm; HRMS (ESI) calc'd for $\text{C}_{29}\text{H}_{44}\text{NO}_2^+ [\text{M} + \text{H}]^+$ 438.3367, found 438.3349.

Synthesis of 1-(3,4-dimethoxyphenyl)-N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl) methanimine (14). General procedure 2 was followed using 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (1.12 g, 5.11 mmol) and 3,4-dimethoxybenzaldehyde (0.850 g, 5.11 mmol) to give the title compound as a colourless solid. Yield: 0.918 g (49%). MP (EtOH) 114.0–114.2 °C; FT-IR (neat): ν_{max} 2976 (w), 2934 (w), 1626 (w), 1593 (m), 1580 (m), 1267 (s), 1135 (s) cm^{-1} ; ^1H NMR (400 MHz, in $\text{CDCl}_3\text{-d}_1$): δ 8.35 (s, 1H), 7.84 (d, 2H, $J = 8.3$ Hz), 7.61 (d, 1H, $J = 1.8$ Hz), 7.31 (dd, 1H, $J = 8.2, 1.8$ Hz), 7.17 (d, 2H, $J = 8.3$ Hz), 6.93 (d, 1H, $J = 8.2$ Hz), 3.99 (s, 3H), 3.95 (s, 3H), 1.35 (s, 12H) ppm; ^{13}C NMR (100 MHz, in $\text{CDCl}_3\text{-d}_1$): δ 160.4, 155.0, 152.2, 149.6, 136.0, 129.6, 124.8, 120.4, 110.5, 109.0, 83.9, 56.1, 25.0 ppm; ^{11}B NMR (128 MHz, in $\text{CDCl}_3\text{-d}_1$): δ 30.4 ppm; HRMS (ESI) calc'd for $\text{C}_{21}\text{H}_{27}\text{BNO}_4^+ [\text{M} + \text{H}]^+$ 368.2028, found 368.2014.

Synthesis of 1-(3,4-dimethoxyphenyl)-N-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl) methanimine (15). General procedure 2 was followed using 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (1.12 g, 5.11 mmol) and 3,4-dimethoxybenzaldehyde (0.850 g, 5.11 mmol) to give the title compound as a colourless solid. Yield: 1.01 g (54%). MP (EtOH) 124.0–124.5 °C; FT-IR (neat): ν_{max} 2982 (w), 2930 (w), 1619 (m), 1567 (m), 1266 (m), 1135 (s) cm^{-1} ; ^1H NMR (400 MHz, in $\text{CDCl}_3\text{-d}_1$): δ 8.41 (s, 1H), 7.67–7.65 (m, 1H), 7.62 (br s, 2H), 7.40 (at, 1H), 7.35–7.29 (m, 2H), 6.93 (d, 1H, $J = 8.2$ Hz), 3.98 (s, 3H), 3.95 (s, 3H), 1.36 (s, 12H) ppm; ^{13}C NMR (100 MHz, in $\text{CDCl}_3\text{-d}_1$): δ 160.0, 152.0, 151.7, 149.5, 132.1, 129.8, 128.7, 126.2, 124.9, 124.5, 110.5, 108.9, 84.0, 56.1, 25.0 ppm; ^{11}B NMR (128 MHz, in $\text{CDCl}_3\text{-d}_1$): δ 30.1 ppm; HRMS (ESI) calc'd for $\text{C}_{21}\text{H}_{27}\text{BNO}_4^+ [\text{M} + \text{H}]^+$ 368.2028, found 368.2029.

General procedure 3

Synthesis of diarylamines. A stirring solution of diarylimine (1 equiv.) in MeOH [0.25 M] cooled to 0 °C, and NaBH_4 (2.5 equiv.) was slowly added over 5–10 minutes (portion wise). The reaction gradually increased from 0 °C to ambient temperature and was stirred overnight before the solvent was removed *in vacuo*. The crude oil was partitioned between EtOAc and water, extracted with EtOAc, and the organic fractions were dried over MgSO_4 , filtered, and concentrated *in vacuo*. The resulting oil/solid was dissolved in hot EtOH and then allowed to cool to RT. The precipitate was filtered and washed with hexanes, and then recrystallized from EtOH to afford the desired product as a colourless, crystalline solid.

General procedure 4

Synthesis of diarylamines. A solution of HBCat (2 equiv.) in PhMe [1.5 M] was added to a stirring solution of diarylimine (1 equiv.) in PhMe [0.3 M] and was stirred for 48 hours before the solvent was removed *in vacuo*. The crude oil was partitioned between DCM and water, extracted with DCM, and the organic



fractions were dried over MgSO_4 , filtered, and concentrated *in vacuo*. The resulting oil/solid was dissolved in hot EtOH and then allowed to cool to RT. The precipitate was filtered and washed with hexanes, and then recrystallized from EtOH to afford the desired product as a colourless, crystalline solid.

Synthesis of *N*-(3,4-dimethoxybenzyl)phenylamine (16). General procedure 3 was followed using **12** (1.00 g, 4.14 mmol) to give the title compound as a colourless solid. Yield: 0.804 g (80%). MP (EtOH) 78.6–79.7 °C; ^1H NMR (400 MHz, in $\text{CDCl}_3\text{-d}_1$): δ 7.21–7.15 (m, 2H), 6.93–6.91 (m, 2H), 6.85–6.82 (m, 1H), 6.75–6.70 (m, 1H), 6.65 (br d, 2H), 4.25 (s, 2H), 3.96 (br s, 1H), 3.874 (s, 3H), 3.867 (s, 3H) ppm; ^{13}C NMR (100 MHz, in $\text{CDCl}_3\text{-d}_1$): δ 149.2, 148.3, 148.3, 132.0, 129.4, 119.8, 117.7, 113.0, 111.2, 110.8, 56.0, 48.3 ppm. Comparable to literature.⁴⁸

Synthesis of 4-tetradecyl-*N*-(3,4-dimethoxybenzyl)aniline (17). General procedure 3 was followed using **13** (1.70 g, 3.88 mmol) to give the title compound as a colourless solid. Yield: 0.869 g (51%). MP (EtOH) 73.5–74.9 °C; FT-IR (neat): ν_{max} 3374 (m), 2919 (s), 2849 (s), 1614 (m), 1513 (s), 1464 (s), 1259 (s), 1231 (s), 1139 (s) cm^{-1} ; ^1H NMR (400 MHz, in $\text{CDCl}_3\text{-d}_1$): δ 7.00 (d, 2H, $J = 8.3$ Hz), 6.92 (ad, 2H), 6.84 (d, 1H, $J = 8.7$ Hz), 6.60 (d, 2H, $J = 8.3$ Hz), 4.23 (s, 2H), 3.88–3.87 (m, 6H), 2.49 (t, 2H, $J = 7.7$ Hz), 1.60–1.51 (m, 2H), 1.37–1.21 (m, 22H), 0.88 (t, 3H) ppm; ^{13}C NMR (100 MHz, in $\text{CDCl}_3\text{-d}_1$): δ 149.2, 148.3, 132.4, 132.2, 129.3, 119.9, 113.1, 111.2, 110.9, 56.1, 56.0, 48.8, 35.2, 32.1, 32.0, 29.83, 29.80, 29.78, 29.7, 29.51, 29.46, 22.8, 14.3 ppm; HRMS (ESI) calc'd for $\text{C}_{29}\text{H}_{46}\text{NO}_2^+ [\text{M} + \text{H}]^+$ 440.3523, found 440.3539.

Synthesis of 4-butyl-*N*-(3,4-dimethoxybenzyl)aniline (18; 2 step procedure). A solution of 3,4-dimethoxybenzaldehyde (1 g, 6.018 mmol) in DCM (10 mL) was added to an Erlenmeyer flask equipped with a layer of 4 Å MS, after which 4-butylaniline (2.00 mL, 12.0 mmol) was added and the vessel was sealed. The resulting solution reacted at room temperature (20 °C) for 1 week before decanting to remove the 4 Å MS and concentrating the solvent *in vacuo*. The resulting oil/solid was then dissolved in MeOH (24 mL) and cooled to 0 °C, and NaBH_4 (0.524 g, 15.0 mmol) was added portion wise. The reaction gradually increased from 0 °C to ambient temperature and was stirred overnight before the solvent was removed *in vacuo*. The crude concentration was partitioned between EtOAc and water, extracted with EtOAc, and the organic fractions were dried over MgSO_4 , filtered, and concentrated *in vacuo*. Precipitation and recrystallization from EtOH provided the title compound as a colourless crystalline solid. Yield: 0.824 g (46% isolated yield over 2 steps). MP (EtOH) 70.3–72.6 °C; FT-IR (neat): ν_{max} 3375 (m), 2958–2835 (w), 1616 (m), 1514 (s), 1258 (m), 1232 (s), 1138 (s) cm^{-1} ; ^1H NMR (400 MHz, in $\text{CDCl}_3\text{-d}_1$): δ 7.02–7.00 (m, 2H), 6.93–6.92 (m, 2H), 6.85–6.83 (m, 1H), 6.60 (ad, 2H), 4.24 (s, 2H), 3.88 (ad, 6H) 2.51 (at, 2H), 1.59–1.51 (m, 2H), 1.39–1.30 (m, 2H), 0.94–0.90 (m, 3H) ppm; ^{13}C NMR (100 MHz, in $\text{CDCl}_3\text{-d}_1$): δ 149.2, 148.2, 146.3, 132.25, 132.22, 129.2, 119.8, 113.0, 111.2, 110.9, 56.0, 55.9, 48.7, 34.8, 34.1, 22.4, 14.1 ppm; HRMS (ESI) calc'd for $\text{C}_{19}\text{H}_{26}\text{NO}_2^+ [\text{M} + \text{H}]^+$ 300.1958, found 300.1969.

Synthesis of 3,4-dimethoxy-*N*-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-benzenemethanamine (19). General procedure 4 was followed using **14** (0.340 g, 0.930 mmol) to give the title compound as a colourless solid. Yield: 0.210 g (61%).

MP (EtOH) 179.1–180.4 °C; FT-IR (neat): ν_{max} 3377 (m), 2980 (w), 2938 (w), 2838 (w), 1602 (s), 1512 (m), 1264 (s), 1138 (s) cm^{-1} ; ^1H NMR (400 MHz, in $\text{CDCl}_3\text{-d}_1$): δ 7.64 (d, 2H, $J = 8.1$ Hz), 6.91–6.89 (m, 2H), 6.83 (d, 1H, $J = 7.8$ Hz), 6.62 (d, 2H, $J = 8.1$ Hz), 4.29 (s, 2H), 4.17 (s, 1H), 3.87 (s, 3H), 3.86 (s, 3H), 1.32 (s, 12H) ppm; ^{13}C NMR (100 MHz, in $\text{CDCl}_3\text{-d}_1$): δ 150.8, 149.3, 148.4, 136.5, 131.6, 119.8, 112.0, 111.3, 110.8, 83.4, 56.1, 56.0, 47.8, 25.0 ppm; ^{11}B NMR (128 MHz, in $\text{CDCl}_3\text{-d}_1$): δ 30.0 ppm; HRMS (ESI) calc'd for $\text{C}_{21}\text{H}_{28}\text{BNNaO}_4^+ [\text{M} + \text{Na}]^+$ 392.2004, found 392.1995.

Synthesis of 3,4-dimethoxy-*N*-[3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-benzenemethanamine (20). General procedure 4 was followed using **15** (0.550 g, 1.50 mmol) to give the title compound as a colourless solid. Yield: 0.405 g (73%). MP (EtOH) 119.1–121.5 °C; FT-IR (neat): ν_{max} 3415 (br), 29.75 (w), 2931 (w), 1602 (m), 1512 (m), 1247 (s), 1142 (s) cm^{-1} ; ^1H NMR (400 MHz, in $\text{CDCl}_3\text{-d}_1$): δ 7.22–7.17 (m, 2H), 7.14–7.14 (1H, m), 6.91–6.89 (m, 2H), 6.84–6.82 (m, 1H), 6.74–6.71 (m, 1H), 4.28 (s, 2H), 3.92 (s, 1H), 3.88 (s, 3H), 3.87 (s, 3H), 1.33 (s, 12H) ppm; ^{13}C NMR (100 MHz, in $\text{CDCl}_3\text{-d}_1$): δ 149.2, 148.3, 147.7, 132.1, 128.9, 124.1, 119.8, 119.3, 115.7, 110.9, 83.8, 56.0, 55.9, 48.4, 25.0 ppm; ^{11}B NMR (128 MHz, in $\text{CDCl}_3\text{-d}_1$): δ 30.5 ppm; HRMS (ESI) calc'd for $\text{C}_{21}\text{H}_{28}\text{BNNaO}_4^+ [\text{M} + \text{Na}]^+$ 392.2004, found 392.2011.

General procedure 5

Synthesis of diarylamides from acid chlorides. A solution of the prescribed acyl chloride (1 equiv.) in PhMe [0.1–0.4 M] was added to a stirring solution of amine (1 equiv.) in PhMe [0.2–0.7 M], followed by the addition of a solution of NEt_3 (1.1 equiv.) in PhMe [0.2–0.8 M]. The resulting mixture was stirred under inert atmosphere for 20–24 h before a white precipitate was removed by filtration. The mother liquor was concentrated to produce a colourless solid that was recrystallized from EtOH (unless otherwise specified).

Synthesis of *N*-(3,4-dimethoxyphenylmethyl)-*N*-(phenyl)-hexanamide (21). General procedure 5 was following using a solution of **16** (0.530 g, 2.20 mmol) in toluene (5 mL), of hexanoyl chloride (0.290 g, 2.20 mmol) in toluene (3 mL), and of Et_3N (0.240 g, 2.40 mmol) in toluene (3 mL). The reaction was allowed to proceed under inert atmosphere for 20 h. A white precipitate was collected by suction filtration and solvent was removed from the filtrate under vacuum yielding a clear oil that solidified while refrigerated at 5 °C for a week. Yield: 0.640 g (85%). MP (EtOH) 31.5–33.8 °C; FT-IR (neat): ν_{max} 2999 (w), 2952 (m), 2868 (w), 1650 (s), 1588 (m), 1511 (s), 1258 (s), 1137 (s) cm^{-1} ; ^1H NMR (400 MHz, in $\text{CDCl}_3\text{-d}_1$): δ 7.33–7.27 (m, 3H), 6.94–6.92 (m, 2H), 6.77 (d, 1H, $J = 1.8$ Hz), 6.71 (d, 1H, $J = 8.2$ Hz), 6.64 (dd, 1H, $J = 8.2, 1.8$ Hz), 4.80 (s, 2H), 3.84 (s, 3H), 3.79 (s, 3H), 2.03 (t, 2H, $J = 7.5$ Hz), 1.58 (quint, 2H, $J = 7.5$ Hz), 1.23–1.13 (m, 4H), 0.81 (t, 3H, $J = 6.9$ Hz) ppm; ^{13}C NMR (100 MHz, in $\text{CDCl}_3\text{-d}_1$): δ 173.1, 148.8, 148.3, 142.5, 130.5, 129.5, 128.7, 128.0, 121.5, 112.1, 110.7, 55.9, 52.7, 34.4, 31.5, 25.4, 22.5, 14.0 ppm; HRMS (ESI) calc'd for $\text{C}_{21}\text{H}_{27}\text{NNaO}_5^+ [\text{M} + \text{Na}]^+$ 364.1883, found 364.1873.

Synthesis of *N*-(3,4-dimethoxyphenylmethyl)-*N*-(phenyl)-decanamide (22). General procedure 5 was following using a solution of **16** (0.090 g, 0.37 mmol) in toluene (5 mL), of



decanoyl chloride (0.080 g, 0.39 mmol) in toluene (2 mL), and of Et₃N (0.040 g, 0.42 mmol) in toluene (2 mL). The reaction was allowed to proceed under inert atmosphere for 20 h. A white precipitate was collected by suction filtration and solvent was removed from the filtrate under vacuum yielding a clear oil. Yield: 0.14 g (>95%). FT-IR (neat): ν_{\max} 2923 (m), 2852 (m), 1652 (m), 1593 (m), 1514 (m), 1259 (s), 1139 (m) cm⁻¹; ¹H NMR (400 MHz, in CDCl₃-d₁): δ 7.34–7.29 (m, 3H), 6.93 (d, 2H, J = 7.9 Hz), 6.76 (s, 1H), 6.71 (d, 1H, J = 8.2 Hz), 6.65 (d, 1H, J = 8.2 Hz), 4.80 (s, 2H), 3.84 (s, 3H), 3.79 (s, 3H), 2.03 (t, 2H, J = 7.5 Hz), 1.57 (t, 2H, J = 6.7 Hz), 1.28–1.17 (m, 12H), 0.85 (t, 3H, J = 6.9 Hz) ppm; ¹³C NMR (100 MHz, in CDCl₃-d₁): δ 173.1, 148.8, 148.3, 130.5, 129.6, 128.7, 128.0, 121.5, 112.2, 110.7, 55.9, 52.7, 34.5, 32.0, 29.51, 29.46, 29.3, 25.7, 22.8, 14.2 ppm; HRMS (ESI) calc'd for C₂₅H₃₅NNaO₅⁺ [M + Na]⁺ 420.2509, found 420.2509.

Synthesis of *N*-(3,4-dimethoxyphenylmethyl)-*N*-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-hexanamide (23). General procedure 5 was following using a solution of **19** (0.260 g, 0.700 mmol) in toluene (10 mL), of hexanoyl chloride (0.090 g, 0.70 mmol) in toluene (4 mL), and of Et₃N (0.080 g, 0.79 mmol) in toluene (4 mL). The reaction was allowed to proceed under inert atmosphere for 24 h. A white precipitate was collected by suction filtration and solvent was removed from the filtrate under vacuum yielding a colourless solid. Yield: 0.29 g (89%). MP (EtOH) 51.5–53.5 °C; FT-IR (neat): ν_{\max} 2949 (m), 2859 (w), 1646 (s), 1603 (s), 1511 (m), 1253 (m), 1136 (s) cm⁻¹; ¹H NMR (400 MHz, in CDCl₃-d₁): δ 7.75 (d, 2H, J = 8.0 Hz), 6.94 (d, 2H, J = 8.0 Hz), 6.79 (s, 1H), 6.69 (d, 1H, J = 8.1 Hz), 6.61 (d, 1H, J = 8.1 Hz), 4.80 (s, 2H), 3.83 (s, 3H), 3.79 (s, 3H), 2.03 (t, 2H, J = 7.4 Hz), 1.57 (quintet, 2H, J = 7.4 Hz), 1.34 (s, 12H), 1.25–1.11 (m, 4H), 0.81 (t, 3H, J = 7.0 Hz) ppm; ¹³C NMR (100 MHz, in CDCl₃-d₁): δ 173.0, 148.9, 148.3, 145.2, 136.0, 130.4, 127.9, 121.5, 112.1, 110.7, 84.2, 55.93, 55.90, 52.7, 34.5, 31.5, 25.4, 25.0, 22.5, 14.0 ppm; ¹¹B NMR (128 MHz, in CDCl₃-d₁): δ 30.4 ppm; HRMS (ESI) calc'd for C₂₇H₃₈BNNaO₅⁺ [M + Na]⁺ 490.2735, found 490.2747.

Synthesis of *N*-(3,4-dimethoxyphenylmethyl)-*N*-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-decanamide (24). General procedure 5 was following using a solution of **19** (0.210 g, 0.570 mmol) in toluene (5 mL), of decanoyl chloride (0.110 g, 0.580 mmol) in toluene (2 mL), and of Et₃N (0.060 g, 0.59 mmol) in toluene (2 mL). The reaction was allowed to proceed under inert atmosphere for 24 h. A white precipitate was collected by suction filtration and solvent was removed from the filtrate under vacuum yielding a colourless solid. Yield: 0.23 g (77%). MP (EtOH) 58.1–59.8 °C; FT-IR (neat): ν_{\max} 2924 (m), 2853 (w), 1656 (m), 1604 (m), 1514 (m), 1260 (s), 1140 (s) cm⁻¹; ¹H NMR (400 MHz, in CDCl₃-d₁): δ 7.75 (d, 2H, J = 8.1), 6.95 (d, 2H, J = 8.1 Hz), 6.79 (d, 1H, J = 1.8 Hz), 6.69 (d, 1H, J = 8.2 Hz), 6.61 (dd, 1H, J = 8.2, 1.8 Hz), 4.80 (s, 2H), 3.84 (s, 3H), 3.80 (s, 3H), 2.03 (t, 2H, J = 7.5 Hz), 1.56 (quint, 2H, J = 7.0 Hz), 1.34 (s, 12H), 1.26–1.17 (m, 12H), 0.85 (t, 3H, J = 7.0 Hz) ppm; ¹³C NMR (100 MHz, in CDCl₃-d₁): δ 173.0, 148.9, 148.4, 145.2, 136.0, 130.4, 128.0, 121.5, 112.1, 110.7, 84.2, 55.95, 55.92, 52.7, 34.6, 32.0, 29.53, 29.48, 29.4, 25.7, 25.0, 22.8, 14.3 ppm; ¹¹B NMR (128 MHz, in CDCl₃-d₁): δ 32.4 ppm; HRMS (ESI) calc'd for C₃₁H₄₆BNNaO₅⁺ [M + Na]⁺ 546.3361, found 546.3368.

Synthesis of *N*-(3,4-dimethoxyphenylmethyl)-*N*-[3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-hexanamide (25). General procedure 5 was following using a solution of **20** (0.230 g, 0.620 mmol) in toluene (3 mL), of hexanoyl chloride (0.090 g, 0.70 mmol) in toluene (2 mL), and of Et₃N (0.090 g, 0.89 mmol) in toluene (2 mL). The reaction was allowed to proceed under inert atmosphere for 24 h. A white precipitate was collected by suction filtration and solvent was removed from the filtrate under vacuum yielding a pale yellow solid. Yield: 0.15 g (52%). MP (EtOH) 58.0–60.2 °C; FT-IR (neat): ν_{\max} 2931 (m), 1652 (m), 1592 (w), 1514 (m), 1260 (s), 1140 (s) cm⁻¹; ¹H NMR (400 MHz, in CDCl₃-d₁): δ 7.73 (d, 1H, J = 7.4 Hz), 7.49 (s, 1H), 7.29 (at, 1H), 6.92 (d, 1H, J = 7.9 Hz), 6.76 (s, 1H), 6.71 (d, 1H, J = 8.1 Hz), 6.69 (d, 1H, J = 8.1 Hz), 4.80 (s, 2H), 3.84 (s, 3H), 3.79 (s, 3H), 2.02 (t, 2H, J = 7.5 Hz), 1.61–1.54 (m, 4H), 1.34 (s, 12H), 1.23–1.13 (m, 4H), 0.81 (t, 3H, J = 6.9 Hz) ppm; ¹³C NMR (100 MHz, in CDCl₃-d₁): δ 173.1, 148.8, 148.3, 142.2, 134.5, 134.2, 131.8, 130.5, 128.9, 121.6, 112.2, 110.8, 84.3, 55.9, 52.8, 34.5, 31.6, 25.4, 25.0, 22.6, 14.1 ppm; ¹¹B NMR (128 MHz, in CDCl₃-d₁): δ 30.5 ppm; HRMS (ESI) calc'd for C₂₇H₃₈BNNaO₅⁺ [M + Na]⁺ 490.2735, found 490.2750.

Synthesis of *N*-(3,4-dimethoxyphenylmethyl)-*N*-[3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-decanamide (26). General procedure 5 was following using a solution of **20** (0.300 g, 0.810 mmol) in toluene (10 mL), of decanoyl chloride (0.150 g, 0.790 mmol) in toluene (2 mL), and of Et₃N (0.090 g, 0.89 mmol) in toluene (2 mL). The reaction was allowed to proceed under inert atmosphere for 24 h. A white precipitate was collected by suction filtration and solvent was removed from the filtrate under vacuum yielding the title compound as a yellow oil. Yield: 0.36 g (85%). FT-IR (neat): ν_{\max} 2924 (m), 2853 (w), 1655 (m), 1592 (w), 1514 (m), 1261 (s), 1140 (s) cm⁻¹; ¹H NMR (400 MHz, in CDCl₃-d₁): δ 7.73 (d, 1H, J = 7.4 Hz), 7.49 (s, 1H), 7.31–7.27 (m, 1H), 6.92 (ddd, 1H, J = 7.9, 2.0, 1.1 Hz), 6.76 (d, 1H, J = 2.0 Hz), 6.72–6.65 (m, 2H), 4.80 (s, 2H), 3.84 (s, 3H), 3.79 (s, 3H), 2.01 (t, 2H, J = 7.5 Hz), 1.59–1.53 (m, 2H), 1.34 (s, 12H), 1.28–1.17 (m, 12H), 0.85 (t, 3H, J = 7.0 Hz) ppm; ¹³C NMR (100 MHz, in CDCl₃-d₁): δ 173.1, 148.8, 148.3, 142.2, 134.5, 134.2, 131.8, 130.5, 128.9, 121.6, 112.3, 110.7, 84.3, 55.9, 52.8, 34.6, 32.0, 29.5, 29.4, 25.7, 25.0, 22.8, 14.2 ppm; ¹¹B NMR (128 MHz, in CDCl₃-d₁): δ 30.3 ppm; HRMS (ESI) calc'd for C₃₁H₄₆BNNaO₅⁺ [M + Na]⁺ 546.3361, found 546.3366.

General procedure 6

Synthesis of diarylamides from carboxylic acids. A solution of diarylamine (1 equiv.), alkenoic acid (1.2–2 equiv.), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide HCl (EDCI·HCl, 1.2–2 equiv.), and 4-dimethylaminopyridine (DMAP, 1.5–2 equiv.) in CH₃CN [0.1–0.2 M] was stirred under an inert atmosphere for 24–48 h before a white precipitate was removed by filtration and the mother liquor was diluted with EtOAc. The resulting solution was then extracted with 2 M HCl, then H₂O, then brine. The organic layer was dried over MgSO₄, filtered and concentrated *in vacuo*, before dissolving in CHCl₃ and filtering through a Dowex plug. The mother liquor was concentrated once more to provide the product as a yellow oil.



Synthesis of *N*-(3,4-dimethoxybenzyl)-*N*-phenylpent-4-enamide (27). General procedure 6 was followed using **16** (0.600 g, 2.47 mmol), 4-pentenoic acid (0.296 g, 2.96 mmol), EDCI·HCl (0.567 g, 2.96 mmol), and DMAP (0.452 g, 3.70 mmol) in CH₃CN (15 mL) to give the title compound as a yellow oil. Yield: 0.517 g (79%). FT-IR (neat): ν_{\max} 3070 (w), 2934 (w), 2834 (w), 1651 (s), 1593 (m), 1513 (s), 1259 (s), 1235 (s), 1155 (m), 1138 (s) cm⁻¹; ¹H NMR (400 MHz, in CDCl₃-d₁): δ 7.34–7.29 (m, 3H), 6.95–6.93 (m, 2H), 6.76 (s, 1H), 6.71 (d, 1H, J = 8.1 Hz), 6.64 (d, 1H, J = 8.1 Hz), 5.76–5.67 (m, 1H), 4.92 (at, 2H), 4.80 (s, 2H), 3.84 (s, 3H), 3.78 (s, 3H), 2.35 (q, 2H, J = 7.0 Hz), 2.13 (t, 2H, J = 7.4 Hz) ppm; ¹³C NMR (100 MHz, in CDCl₃-d₁): δ 172.1, 148.8, 148.3, 142.3, 137.6, 130.3, 129.6, 128.7, 128.1, 121.5, 115.2, 112.1, 110.7, 55.9, 52.8, 33.8, 29.6 ppm; HRMS (ESI) calc'd for C₂₀H₂₃NNaO₃⁺ [M + Na]⁺ 348.1570, found 348.1575.

Synthesis of *N*-(3,4-dimethoxybenzyl)-*N*-phenylnon-8-enamide (28). General procedure 6 was followed using **16** (0.600 g, 2.47 mmol), 8-nonenoic acid (0.462 g, 2.96 mmol), EDCI·HCl (0.567 g, 2.96 mmol), and DMAP (0.452 g, 3.70 mmol) in CH₃CN (15 mL) to give the title compound as a yellow oil. Yield: 0.484 g (61%). FT-IR (neat): ν_{\max} 3075 (w), 2926 (m), 2853 (w), 1652 (s), 1593 (m), 1513 (m), 1259 (s), 1236 (s), 1156 (m), 1139 (m) cm⁻¹; ¹H NMR (400 MHz, in CDCl₃-d₁): δ 7.34–7.27 (m, 3H), 6.93 (dd, 2H, J = 7.6, 1.7 Hz), 6.76 (d, 1H, 1.4 Hz), 6.71 (d, 1H, J = 8.1 Hz), 6.64 (dd, 1H, J = 8.1, 1.4 Hz), 5.82–5.70 (m, 1H), 4.97–4.88 (m, 2H), 4.80 (s, 2H), 3.84 (s, 3H), 3.78 (s, 3H), 2.03 (t, 2H, J = 7.5 Hz), 1.97 (q, 2H, J = 7.1 Hz), 1.57 (quintet, 2H, J = 7.1 Hz), 1.31–1.17 (m, 6H) ppm; ¹³C NMR (100 MHz, in CDCl₃-d₁): δ 173.1, 148.8, 148.3, 142.5, 139.2, 130.4, 129.5, 128.7, 128.0, 121.4, 114.3, 112.1, 110.7, 55.9, 52.7, 34.4, 33.8, 29.2, 28.9, 28.8, 25.6 ppm; HRMS (ESI) calc'd for C₂₄H₃₁NNaO₃⁺ [M + Na]⁺ 404.2196, found 404.2191.

Synthesis of *N*-(4-butylphenyl)-*N*-(3,4-dimethoxybenzyl)non-8-enamide (29). General procedure 6 was followed using **18** (0.200 g, 0.668 mmol), 8-nonenoic acid (0.209 g, 1.34 mmol), EDCI·HCl (0.256 g, 1.34 mmol), and DMAP (0.150 g, 1.47 mmol) in CH₃CN (5 mL) to give the title compound as a yellow oil. Yield: 0.196 g (67%). FT-IR (neat): ν_{\max} 3075 (w), 2927 (m), 2855 (w), 1652 (s), 1606 (w), 1510 (s), 1259 (s), 1236 (s), 1156 (m), 1139 (m) cm⁻¹; ¹H NMR (400 MHz, in CDCl₃-d₁): δ 7.11 (d, 2H, J = 8.1 Hz), 6.82 (d, 2H, J = 8.1 Hz), 6.75–6.72 (m, 2H), 6.68 (d, 2H, J = 8.2 Hz), 5.82–5.71 (m, 1H), 4.97–4.89 (m, 2H), 4.78 (s, 2H), 3.85 (s, 3H), 3.79 (s, 3H), 2.60 (t, 2H, J = 7.7 Hz), 2.04 (t, 2H, J = 7.4 Hz), 1.98 (q, 2H, J = 7.1 Hz), 1.62–1.55 (m, 5H), 1.39–1.25 (m, 5H), 1.19 (s, 4H), 0.93 (td, 3H, J = 7.3, 2.0 Hz) ppm; ¹³C NMR (100 MHz, in CDCl₃-d₁): δ 173.2, 148.7, 148.2, 142.8, 140.0, 139.2, 130.6, 129.4, 128.3, 121.4, 114.3, 112.2, 110.7, 55.90, 55.86, 52.7, 35.3, 34.4, 33.8, 33.6, 29.2, 28.9, 28.8, 25.6, 22.4, 14.1 ppm; HRMS (ESI) calc'd for C₂₈H₃₉NNaO₃⁺ [M + Na]⁺ 460.2822, found 460.2824.

Synthesis of *N*-(3,4-dimethoxybenzyl)-*N*-(4-tetradecylphenyl)non-8-enamide (30). General procedure 6 was followed using **17** (0.200 g, 0.455 mmol), 8-nonenoic acid (0.157 g, 0.910 mmol), EDCI·HCl (0.174 g, 0.910 mmol), and DMAP (0.122 g, 1.00 mmol) in CH₃CN (5 mL) to give the title compound as a yellow oil. Yield: 0.238 g (93%). FT-IR (neat): ν_{\max} 3375 (m),

2997–2838 (w), 1635 (w), 1601 (m), 1509 (m), 1238 (m), 1171 (m) cm⁻¹; ¹H NMR (400 MHz, in CDCl₃-d₁): δ 7.10 (d, 2H, J = 8.1 Hz), 6.82 (d, 2H, J = 8.1 Hz), 6.75 (s, 1H), 6.72 (d, 1H, J = 8.2 Hz), 6.67 (d, 1H, J = 8.2 Hz), 5.81–5.70 (m, 1H), 4.97–4.92 (m, 1H), 4.97–4.88 (m, 1H), 4.78 (s, 2H), 3.84 (s, 3H), 3.78 (s, 3H), 2.58 (t, 2H, J = 7.5 Hz), 2.03 (t, 2H, J = 7.5 Hz), 1.97 (q, 2H, J = 7.0 Hz), 1.58 (q, 4H, J = 7.0 Hz), 1.40–1.18 (m, 30H), 0.89–0.85 (m, 3H) ppm; ¹³C NMR (100 MHz, in CDCl₃-d₁): δ 173.2, 148.7, 148.2, 142.8, 140.0, 139.1, 130.6, 129.4, 128.3, 121.4, 114.3, 112.2, 110.7, 55.9, 55.8, 52.7, 35.6, 34.3, 33.8, 32.0, 31.4, 29.8, 29.74, 29.69, 29.6, 29.5, 29.4, 29.2, 28.9, 28.8, 25.6, 22.8, 14.2 ppm; HRMS (ESI) calc'd for C₃₈H₅₉NNaO₃⁺ [M + Na]⁺ 600.4387, found 600.4377.

General procedure 7

Hydroboration of diarylalkenamides. A solution of [Ir(COD)Cl]₂ (5 mol%) and bis(diphenylphosphino)methane (dppm, 10 mol%) in THF under an inert atmosphere for 10 min before adding a solution of diarylalkenamide (1 equiv.) in THF, followed by a solution of HBPIn (1.5–2.4 equiv.) in THF. The resulting reaction mixture was stirred for 24 h before removing the solvent *in vacuo*. The crude mixture was dissolved as a concentrated solution in 1 : 1 EtOH/hexanes, and was refrigerated at 5 °C until a white precipitate forms. The precipitate was removed *via* filtration using a celite plug, and the mother liquor was concentrated to provide the crude material as an oil. The crude material was purified *via* short silica plug (eluent – 100% EtOAc), which provided the product as a yellow oil upon concentration of the fractions containing the product.

Synthesis of *N*-(3,4-dimethoxybenzyl)-*N*-phenyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pentanamide (31). General procedure 7 was followed using [Ir(COD)Cl]₂ (0.014 g, 0.021 mmol) and dppm (0.016 g, 0.041 mmol) in THF (2 mL), **27** (0.100 g, 0.411 mmol) in THF (1 mL), and HBPIn (0.140 mL, 0.986 mmol) in THF (1 mL) to provide the product as a yellow oil. Yield: 0.073 g (54%). FT-IR (neat): ν_{\max} 2976–2932 (w), 2250 (w), 1651 (m), 1594 (m), 1371 (m), 1236 (m), 1141 (s) cm⁻¹; ¹H NMR (400 MHz, in CDCl₃-d₁): δ 7.32–7.27 (m, 3H), 6.93–6.91 (m, 2H), 6.75 (d, 1H, J = 1.6 Hz), 6.70 (d, 1H, J = 8.2 Hz), 6.63 (dd, 1H, J = 8.2, 1.6 Hz), 4.78 (s, 2H), 3.83 (s, 3H), 3.78 (s, 3H), 2.03 (t, 2H, J = 7.6 Hz), 1.58 (dt, 2H, J = 15.3, 7.8 Hz), 1.28 (t, 2H, J = 7.8 Hz), 1.22–1.19 (m, 12H), 0.66 (t, 2H, J = 8.0 Hz) ppm; ¹³C NMR (100 MHz, in CDCl₃-d₁): δ 173.0, 148.8, 148.3, 142.5, 130.4, 129.5, 128.6, 127.9, 121.4, 112.1, 110.7, 83.0, 55.88, 55.86, 52.7, 34.4, 28.3, 24.9, 24.8, 23.9 ppm; ¹¹B NMR (100 MHz, in CDCl₃-d₁): δ 33.5 ppm; HRMS (ESI) calc'd for C₂₆H₃₆BNNaO₅⁺ [M + Na]⁺ 476.2579, found 476.2574.

Synthesis of *N*-(3,4-dimethoxybenzyl)-*N*-phenyl-9-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nonanamide (32). General procedure 7 was followed using [Ir(COD)Cl]₂ (0.011 g, 0.016 mmol) and dppm (0.012 g, 0.031 mmol) in THF (2 mL), **28** (0.100 g, 0.311 mmol) in THF (1 mL), and HBPIn (0.068 g, 0.47 mmol) in THF (1 mL) to provide the product as a yellow oil. Yield: 0.089 g (56%). FT-IR (neat): ν_{\max} 2976–2583 (m), 1652 (m), 1594 (m), 1514 (m), 1371 (m), 1260 (s), 1237 (s), 1141 (s) cm⁻¹; ¹H NMR (400 MHz, in CDCl₃-d₁): δ 7.34–7.29 (m, 3H), 6.93 (ad, 2H), 6.76 (br s, 1H), 6.71 (d, 1H, J = 8.1 Hz), 6.65 (d, 1H, J = 8.1), 4.80 (s, 2H), 3.84 (s, 3H), 3.79 (s, 3H), 2.02 (t, 2H, J = 7.4 Hz), 1.56



(br s, 2H), 1.38–1.30 (m, 2H), 1.21–1.16 (m, 20H), 0.73 (t, 2H, $J = 7.8$ Hz) ppm; ^{13}C NMR (100 MHz, in $\text{CDCl}_3\text{-d}_1$): δ 173.1, 148.8, 148.3, 142.5, 130.4, 129.5, 128.6, 127.9, 121.4, 112.1, 110.7, 82.9, 55.9, 52.7, 34.5, 32.5, 29.4, 29.34, 29.31, 25.7, 24.9, 24.0, 11.6 ppm; ^{11}B NMR (100 MHz, in $\text{CDCl}_3\text{-d}_1$): δ 33.5 ppm; HRMS (ESI) calc'd for $\text{C}_{30}\text{H}_{44}\text{BNNaO}_5^+ [\text{M} + \text{Na}]^+$ 532.3205, found 532.3194.

Synthesis of *N*-(4-butylphenyl)-*N*-(3,4-dimethoxybenzyl)-9-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nonamide (33). General procedure 7 was followed using $[\text{Ir}(\text{COD})\text{Cl}]_2$ (0.008 g, 0.01 mmol) and dppm (0.008 g, 0.02 mmol) in THF (2 mL), **29** (0.100 g, 0.229 mmol) in THF (1 mL), and HBPIn (0.080 mL, 0.550 mmol) in THF (1 mL) to provide the product as a yellow oil. Yield: 0.08 g (63%). FT-IR (neat): ν_{max} 2925 (m), 2854 (w), 1652 (m), 1607 (w), 1592 (w), 1511 (s), 1371 (m), 1260 (s), 1237 (s), 1141 (s) cm^{-1} ; ^1H NMR (400 MHz, in $\text{CDCl}_3\text{-d}_1$): δ 7.10 (d, 2H, $J = 8.1$ Hz), 6.81 (d, 2H, $J = 8.1$ Hz), 6.75 (br s, 1H), 6.72 (d, 1H, $J = 8.2$), 6.67 (d, 1H, $J = 8.2$ Hz), 4.77 (s, 2H), 3.84 (s, 3H), 3.78 (s, 3H), 2.59 (t, 2H, $J = 7.7$ Hz), 2.02 (t, 2H, $J = 7.5$ Hz), 1.62–1.52 (m, 4H), 1.38–1.29 (m, 4H), 1.21–1.16 (m, 20H), 0.92 (td, 3H, $J = 7.3$), 0.73 (t, 2H, $J = 7.8$ Hz) ppm; ^{13}C NMR (100 MHz, in $\text{CDCl}_3\text{-d}_1$): δ 173.3, 148.8, 148.2, 142.7, 140.1, 130.7, 129.4, 128.3, 121.4, 112.2, 110.7, 82.9, 55.92, 55.88, 52.7, 35.3, 34.4, 33.6, 32.5, 29.41, 29.36, 25.8, 24.9, 24.1, 22.5, 14.1, 11.3 ppm; ^{11}B NMR (100 MHz, in $\text{CDCl}_3\text{-d}_1$): δ 33.3 ppm; HRMS (ESI) calc'd for $\text{C}_{34}\text{H}_{52}\text{BNNaO}_5^+ [\text{M} + \text{Na}]^+$ 588.3831, found 588.3821.

Synthesis of *N*-(3,4-dimethoxybenzyl)-*N*-(4-tetradecylphenyl)-9-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nonamide (34). General procedure 7 was followed using $[\text{Ir}(\text{COD})\text{Cl}]_2$ (0.006 g, 0.009 mmol) and dppm (0.007 g, 0.02 mmol) in THF (2 mL), **30** (0.100 g, 0.177 mmol) in THF (1 mL), and HBPIn (0.034 g, 0.27 mmol) in THF (1 mL) to provide the product as a yellow oil. Yield: 0.06 g (48%). FT-IR (neat): ν_{max} 2922 (s), 2852 (s), 1656 (s), 1607 (w), 1592 (w), 1511 (s), 1378 (s), 1260 (s), 1237 (s), 1142 (s) cm^{-1} ; ^1H NMR (400 MHz, in $\text{CDCl}_3\text{-d}_1$): δ 7.10 (d, 2H, $J = 8.1$ Hz), 6.82 (d, 2H, $J = 8.1$ Hz), 6.75 (d, 1H, $J = 1.7$ Hz), 6.72 (d, 1H, $J = 8.2$ Hz), 6.67 (dd, 1H, $J = 8.2, 1.7$ Hz), 4.77 (2, s), 3.85 (s, 3H), 3.78 (s, 3H), 2.58 (t, 2H, $J = 7.8$ Hz), 2.02 (t, 2H, $J = 7.5$ Hz), 1.64–1.52 (m, 4H), 1.30–1.16 (m, 44H), 0.87 (t, 3H, $J = 6.8$ Hz), 0.73 (t, 2H, $J = 7.8$ Hz) ppm; ^{13}C NMR (100 MHz, in $\text{CDCl}_3\text{-d}_1$): δ 173.3, 148.7, 148.2, 142.8, 140.1, 130.6, 129.4, 128.3, 121.4, 112.2, 110.7, 82.9, 55.9, 55.8, 52.7, 35.6, 34.4, 32.5, 32.0, 31.4, 29.79, 29.76, 29.7, 29.6, 29.5, 29.43, 29.39, 29.3, 25.7, 24.9, 24.1, 22.8, 14.2, 11.3 ppm; ^{11}B NMR (100 MHz, in $\text{CDCl}_3\text{-d}_1$): δ 33.9 ppm; HRMS (ESI) calc'd for $\text{C}_{44}\text{H}_{72}\text{BNNaO}_5^+ [\text{M} + \text{Na}]^+$ 728.5396, found 728.5369.

Antimicrobial assay

The microorganisms (methicillin-resistant *S. aureus* MRSA 310, vancomycin-resistant *E. faecium* VRE 379, *S. warneri* (ATCC 17917), *P. vulgaris* (ATCC 12454), *P. aeruginosa* (ATCC 14210), and *C. albicans* (ATCC 14035)) were grown overnight on agar media. The following day the cultures were transferred into 0.9% saline water into a sterile glass tube. Using the McFarland reader, the turbidity was determined and further diluted into their respective media. The pure compounds were tested at

seven different concentrations ranging from 2 to 128 $\mu\text{g mL}^{-1}$ in triplicate. Samples were plated into 96 well plates (10 μL in 20% DMSO) and then diluted pathogen (90 μL) was pipetted into the pre-prepared sample plates yielding 5×10^5 cfu mL^{-1} with a final volume of 100 μL . Antibiotics that are active against specific pathogens were used as positive controls. The plates were incubated into a 37 °C incubator for 22 h. Growth of *S. warneri*, *P. vulgaris*, *P. aeruginosa* and *C. albicans* were measured by reading optical density (OD_{600}), or in the case of slow growing microorganisms (MRSA and VRE), PrestoBlue was used to assess metabolic activity by measuring fluorescence (535–560)/(590–615) (excitation/emission) using a Thermo Scientific Variskan Flash plate reader at time zero and then again after incubation of the plates for 22 h at 37 °C. After subtracting the time zero OD_{600} from the final reading, the percentages of microorganism survival relative to vehicle control wells were calculated. Comparable to literature.⁴⁹

Cytotoxicity assay

The cells (human foreskin BJ fibroblast cells (ATCC CRL-2522), green monkey kidney cells Vero (ATCC CCL-81), human breast adenocarcinoma cells (ATCC HTB-26 MDA-MB 231), human breast adenocarcinoma cells (MCF7 ATCC HTB-22), and human colorectal carcinoma cells (HCT116 ATCC CCL-247)) were grown to 80% confluency, the cells were counted, diluted, and plated into treated 96-well cell culture plates. The BJ fibroblast and Vero cells were plated at a cell density of 10 000 cells per well and the HTB26, HCT116 and MCF7 cells were plated at cell density of 5000 cells per well in 90 μL of respective growth medium (without the addition of antibiotics) and incubated for 24 h to allow cells to adhere to the plates before treatment. Pure compounds were tested in triplicate in serial dilutions of seven concentrations ranging from 2 to 128 $\mu\text{g mL}^{-1}$ per well (final well volume of 100 μL , 1% DMSO per well). Each of the cell lines were incubated at 37 °C in a humidified atmosphere of 5% CO_2 ; the BJ fibroblast and Vero cells for 24 h and the HTB-26, HCT116 and MCF7 cells for 72 h. Each plate contained four uninoculated positive controls, four untreated negative controls, and one column containing a concentration range for doxorubicin. Alamar blue was added, 24 h after the treatment, and fluorescence was monitored using a Cytation Gen 5 plate reader using 560 nm Ex/590 Em both at time zero and 4 h after Alamar blue addition. The inferred percentage of cell viability relative to vehicle control wells were calculated after subtracting the time zero emission 590 nm measurement from the final reading and the IC_{50} was determined. Comparable to literature.⁴⁹

Conflicts of interest

There are no conflicts of interest to declare.

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Notes and references

- 1 S. K. Kumar, B. LaPlant, V. Roy, C. B. Reeder, M. Q. Lacy, M. A. Gertz, K. Laumann, M. A. Thompson, T. E. Witzig, F. K. Buadi, C. E. Rivera, J. R. Mikhael, P. L. Bergsagel, P. Kapoor, L. Hwa, R. Fonseca, A. K. Stewart, A. Chanan-Khan, S. V. Rajkumar and A. Dispenzieri, *Blood Canc. J.*, 2015, **5**, e338.
- 2 S. Touchet, F. Carreaux, B. Carboni, A. Bouillon and J.-L. Boucher, *Chem. Soc. Rev.*, 2011, **40**, 3895–3914.
- 3 A. S. Paller, W. L. Tom, M. G. Lebwohl, R. L. Blumenthal, M. Boguniewicz, R. S. Call, L. F. Eichenfield, D. W. Forsha, W. C. Rees, E. L. Simpson, M. C. Spellman, L. F. Stein Gold, A. L. Zaenglein, M. H. Hughes, L. T. Zane and A. A. Hebert, *J. Am. Acad. Dermatol.*, 2016, **75**, 494–503.
- 4 B. Muz, R. N. Ghazarian, M. Ou, M. J. Luderer, H. D. Kusdono and A. K. Azab, *Drug Des., Dev. Ther.*, 2016, **10**, 217–226.
- 5 E. Kupperman, E. C. Lee, Y. Cao, B. Bannerman, M. Fitzgerald, A. Berger, J. Yu, Y. Yang, P. Hales, F. Bruzzese, J. Liu, J. Blank, K. Garcia, C. Tsu, L. Dick, P. Fleming, L. Yu, M. Manfredi, M. Rolfe and J. Bolen, *Cancer Res.*, 2010, **70**, 1970–1980.
- 6 D. Chauhan, Z. Tian, B. Zhou, D. Kuhn, R. Orlowski, N. Raje, P. Richardson and K. C. Anderson, *Clin. Canc. Res.*, 2011, **17**, 5311–5321.
- 7 S. J. Baker, Y.-K. Zhang, T. Akama, A. Lau, H. Zhou, V. Hernandez, W. Mao, M. R. K. Alley, V. Sanders and J. J. Plattner, *J. Med. Chem.*, 2006, **49**, 4447–4450.
- 8 N. Sharma and D. Sharma, *J. Pharmacol. Pharmacother.*, 2015, **6**, 236–239.
- 9 M. Castanheira, P. R. Rhomberg, R. K. Flamm and R. N. Jones, *Antimicrob. Agents Chemother.*, 2016, **60**, 5454–5458.
- 10 O. Lomovskaya, D. Sun, D. Rubio-Aparicio, K. Nelson, R. Tsivkovski, D. C. Griffith and M. N. Dudley, *Antimicrob. Agents Chemother.*, 2017, **61**, e01443-17.
- 11 D. C. Griffith, J. S. Loutit, E. E. Morgan, S. Durso and M. N. Dudley, *Antimicrob. Agents Chemother.*, 2016, **60**, 6326–6332.
- 12 F. Ali, N. S. Hosmane and Y. Zhu, *Molecules*, 2020, **25**, 828 and references therein.
- 13 A. N. Tevyashova and M. V. Chudihov, *Russ. Chem. Rev.*, 2021, **90**, 451–487 and references therein.
- 14 X.-F. He, H. Zhang, C. M. Vogels, A. Decken and S. A. Westcott, *Heteroat. Chem.*, 2004, **15**, 369–375.
- 15 S. A. Westcott, X.-F. He, C. M. Vogels and A. Decken, *Acta Crystallogr., Sect. E: Struct. Rep. Online*, 2004, **60**, o115–o116.
- 16 A. Decken, A. Singh, C. M. Vogels and S. A. Westcott, *Acta Crystallogr., Sect. E: Struct. Rep. Online*, 2002, **58**, o1213–o1214.
- 17 H. Zhang, C. M. Vogels, S. L. Wheaton, F. J. Baerlocher, A. Decken and S. A. Westcott, *Synthesis*, 2005, 2739–2743.
- 18 J. W. Hicks, C. B. Kyle, C. M. Vogels, S. L. Wheaton, F. J. Baerlocher, A. Decken and S. A. Westcott, *Chem. Biodiversity*, 2008, **5**, 2415–2422.
- 19 D. R. Duguay, M. T. Zamora, J. M. Blacquiére, F. E. Appoh, C. M. Vogels, S. L. Wheaton, F. J. Baerlocher, A. Decken and S. A. Westcott, *Cent. Eur. J. Chem.*, 2008, **6**, 562–568.
- 20 F. E. Appoh, S. L. Wheaton, C. M. Vogels, F. J. Baerlocher, A. Decken and S. A. Westcott, *Heteroat. Chem.*, 2009, **20**, 56–63.
- 21 E. A. Gwynne, J. C. Holt, J. R. Dwan, F. E. Appoh, C. M. Vogels, S. L. Wheaton, F. J. Baerlocher, A. Decken and S. A. Westcott, *Helv. Chim. Acta*, 2010, **93**, 1093–1100.
- 22 C. M. Vogels, L. G. Nikolcheva, D. W. Norman, H. A. Spinney, A. Decken, M. O. Baerlocher, F. J. Baerlocher and S. A. Westcott, *Can. J. Chem.*, 2011, **79**, 1115–1123.
- 23 J. A. Mosseler, J. A. Melanson, E. G. Bowes, G. M. Lee, C. M. Vogels, F. J. Baerlocher, A. Decken and S. A. Westcott, *J. Mol. Struct.*, 2011, **1002**, 24–27.
- 24 M. J. Geier, E. G. Bowes, G. M. Lee, H. Li, T. O'Neill, A. Flewelling, C. Vogels, A. Decken, C. A. Gray and S. A. Westcott, *Heteroat. Chem.*, 2013, **24**, 116–123.
- 25 M. I. Webb, N. R. Halcovitch, E. G. Bowes, G. M. Lee, M. J. Geier, C. M. Vogels, T. O'Neill, H. Li, A. J. Flewelling, A. Decken, C. A. Gray and S. A. Westcott, *J. Heterocycl. Chem.*, 2014, **51**, 157–161.
- 26 L. Campbell-Verduyn, E. G. Bowes, H. Li, A. M. Vallée, C. M. Vogels, A. Decken, C. A. Gray and S. A. Westcott, *Heteroat. Chem.*, 2014, **25**, 100–106.
- 27 J. Yang, B. J. Johnson, A. A. Letourneau, C. M. Vogels, A. Decken, F. J. Baerlocher and S. A. Westcott, *Aust. J. Chem.*, 2015, **68**, 366–372.
- 28 M. J. G. Hébert, A. J. Flewelling, T. N. Clark, N. A. Levesque, J. Jean-François, M. E. Surette, C. A. Gray, C. M. Vogels, M. Touaibia and S. A. Westcott, *Int. J. Med. Chem.*, 2015, 418362.
- 29 K. Cormier, R. D. Curry, M. P. Betsch, J. A. Goguen, C. M. Vogels, A. Decken, S. Turcotte and S. A. Westcott, *J. Heterocycl. Chem.*, 2016, **53**, 1807–1812.
- 30 P.-D. St-Coeur, S. Kinley, C. M. Vogels, A. Decken, P. Morin Jr. and S. A. Westcott, *Can. J. Chem.*, 2016, **95**, 207–213.
- 31 D. Zhu, C. D. Hunter, S. R. Baird, B. R. Davis, A. Bos, S. J. Geier, C. M. Vogels, A. Decken, C. A. Gray and S. A. Westcott, *Heteroat. Chem.*, 2017, **28**, e21405.
- 32 R. S. Scott, A. J. Veinot, D. L. Stack, P. T. Gormley, B. Ninh Khuong, C. M. Vogels, J. D. Masuda, F. J. Baerlocher, T. J. MacCormack and S. A. Westcott, *Can. J. Chem.*, 2018, **96**, 906–911.
- 33 P. T. Gormley, S. J. Geier, C. M. Vogels, B. Ninh Khuong, T. J. MacCormack, J. Masuda and S. A. Westcott, *J. Braz. Chem. Soc.*, 2020, **31**, 1541–1550.
- 34 A. M. Irving, C. M. Vogels, L. G. Nikolcheva, J. P. Edwards, X.-F. He, M. G. Hamilton, M. O. Baerlocher,



- F. J. Baerlocher, A. Decken and S. A. Westcott, *New J. Chem.*, 2003, **27**, 1419–1424.
- 35 A. E. Patterson, A. J. Flewelling, T. N. Clark, S. J. Geier, C. M. Vogels, J. D. Masuda, C. A. Gray and S. A. Westcott, *Can. J. Chem.*, 2015, **93**, 1305–1311.
- 36 S. Ramsaywack, A. Bos, C. M. Vogels, C. A. Gray and S. A. Westcott, *Can. J. Chem.*, 2018, **96**, 1065–1070.
- 37 D. J. Bennett and G. W. Kirby, *J. Chem. Soc. C*, 1968, **4**, 442–446.
- 38 L. Adaszek, D. Gadomska, L. Mazurek, P. Lyp, J. Madany and S. Winiarczyk, *Res. Vet. Sci.*, 2019, **123**, 14–19 and references therein.
- 39 G. Aquilina, G. Bories, A. Chesson, P. S. Cocconcelli, J. de Knecht, N. A. Dierick, M. A. Gralak, J. Gropp, I. Halle, C. Hogstrand, R. Kroker, L. Leng, S. López Puente, A.-K. Lundebye Haldorsen, A. Mantovani, G. Martelli, M. Mézes, D. Renshaw, M. Saarela, K. Sejrnsen and J. Westendorf, *EFSA J.*, 2012, **10**, 2785.
- 40 G. Cocco, C. Strozzi and D. Chu, *Clin. Cardiol.*, 1979, **2**, 212–216.
- 41 H. Ramuz, *Arzneim.-Forsch.*, 1978, **28**, 2048–2051.
- 42 N. S. Khurmi, C. W. Robinson, M. J. O'Hara and E. B. Raftery, *Eur. J. Clin. Pharmacol.*, 1986, **30**, 387–392.
- 43 S. D. Rubbo and J. Cymerman-Craig, *Nature*, 1955, **176**, 887.
- 44 P. P. T. Sah and S. A. Peoples, *J. Am. Pharm. Assoc.*, 1954, **43**, 513–524.
- 45 C. Tejel, R. Bravi, M. A. Ciriano, L. A. Oro, M. Bordonaba, C. Graiff, A. Tiripicchio and A. Burini, *Organometallics*, 2000, **19**, 3115–3119.
- 46 E. Fernández and A. M. Segarra, in *Iridium Complexes in Organic Synthesis*, ed. L. A. Oro and C. Claver, John Wiley & Sons, Inc., 2008. ch. 7, pp. 173–194.
- 47 L. Wang, C. Cao and C. Cao, *J. Phys. Org. Chem.*, 2019, **32**, e3969.
- 48 D. G. Ghiano, P. B. Carvalho, B. L. Tekwani, M. A. Avery and G. Labadie, *ARKIVOC*, 2011, **2011**, 297–311.
- 49 D. P. Overy, F. Berrue, H. Correa, N. Hanif, K. Hay, M. Lanteigne, K. McQuillan, S. Duffy, P. Boland, R. Jagannathan, G. S. Carr, M. Vansteeland and R. G. Kerr, *Mycology*, 2015, **5**, 130–144.

