Histone deacetylase 2 (HDAC2) inhibitors containing boron

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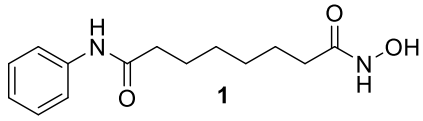
Abstract: Histone deacetylase enzymes (HDACs) are known to be responsible for the global silencing of the tumour suppressor genes. Treatment with histone deacetylase inhibitors (HDACi) can reverse this process and restore normal cell function. Herein we report a small series of boron-based (boronic acid, boronate ester and *closo*-1,2-carborane) HDAC2 inhibitors with IC_{50} values in the nM range. The boronate ester **4b** was the most potent compound assessed in this study (IC_{50} = 40.6 ± 1.5 nM), followed closely by the 1,2-*closo*-carborane derivative (IC_{50} = 42.9 ± 1.5 nM). Compound **4b** exceeded the potency of the gold-standard HDAC pan-inhibitor vorinostat **1** toward this particular HDAC isoform.

Introduction

The rapidly growing field of epigenetics has shown great promise in the development of first-in-class anti-cancer drugs. The ability to regulate genes without altering their chromosomal DNA sequence is an attractive alternative to currently used methods due to its early biomarker detectability.[1] It is known that the human genome experiences constant dynamic modifications that are tightly regulated by two opposing factors, a set of genes contributing to a malignant phenotype and inherent tumour suppressor genes that have the ability to maintain homeostasis.[1-2] Disruption of the genes essential for normal cellular growth can result in dysfunctional cell behavior, including the expression of oncogenes affiliated with cancer.[3]

Global mutations at the genomic level have long been associated as hallmarks of cancer.[1, 4-5] In cancer, the regulatory tumour mechanism that control normal cell growth and homeostasis are turned off leading to tumorigenesis.[6-7] Recent studies have shown the epigenetic state of a cell is malleable and prone to evolve in response to its environment.[1, 3, 8-10] These responses have been correlated to a histone remodeling mechanism, involving the covalent re-organization of histone proteins as a critical component of its biomarker for early detection. The highly dynamic acetylation status of the amino acid residues in histone proteins is controlled by two families of enzymes, histone acetyltransferases (HATs) and histone deacetylase (HDACs), which can be modulated in an opposing manner.[3, 6, 11] Of increasing interest are the histone deacetylase enzymes (HDACs) which are known to be responsible for the global silencing of the tumour suppressor genes.[4, 8, 10-14]The deacetylation of histones triggers characteristic elements of cancer growth and progression: cell proliferation, inflammation, and tumorigenesis. [11, 15-16] The acetylation of lysine residues of histone tails is commonly associated with transcriptionally active chromatin.[16] In the inactive phase, the negatively-charged DNA phosphodiester backbone is bounded tightly to the positively-charged histone proteins. [3, 12] The net positive charge of the histone proteins is extinguished by acetylating the ε-amino group of they lysine residue through the covalent attachment of an acetyl group from acetyl-CoA in the presence of HATs. [7, 17] Consequently, the nucleosome structure is relaxed at the modified site, exposing the DNA to transcriptional proteins. Deacetylation dynamically counters the effect of acetylation, thus restoring the positive charge of the lysine sidechain. [4, 11, 15] When histones are deacetylated, the DNA is packed, and the chromatin architecture cannot be accessed by the cell's transcriptional machinery. The widespread silencing of tumour genes triggered by hyper-deacetylation has been established as a biomarker of cancer.[6, 18-19] With an appropriate small molecule inhibitor, this process can potentially be reversed.

The first FDA-approved HDAC inhibitor (HDACi), vorinostat (**1**), is currently used for the treatment of cutaneous T-cell lymphoma (CTCL). [20-24] Vorinostat is known as a 'pan-HDAC inhibitor' as it possesses an ability to interact with several isoforms of HDAC metalloenzymes at the Zn^{2+} site by coordination involving its hydroxamic group.[20, 25-26] Though a potent chemotherapeutic agent, vorinostat lacks selectivity for any specific HDAC isoform(s). Class I HDAC inhibitors that have shown potent binding to the Zn^{2+} co-factor in HDACs possess 'hard' Lewis bases, e.g. hydroxyl, carbonyl, sulfonyl and carboxylic acids, that are ideal for 'hard' Lewis acid target engagement of the Zn^{2+} ion.[26-28] In recent years, boron drug discovery is making great inroads in medicinal chemistry with the approval of three boronated drugs (bortezomib, crisaborole, and tavaborole) for clinical use. However, examples of boronated HDACi's are rare. Indeed, such studies have solely focused on the use of boronic acids to coordinate to the Zn^{2+} ion in Class I, II and IV HDACs but with only limited success.[29-31] It has been shown that, to date, hydroxamic acid-based drugs such as **1** are still amongst the most potent inhibitors of Class I HDACs.[20, 26, 32-33]



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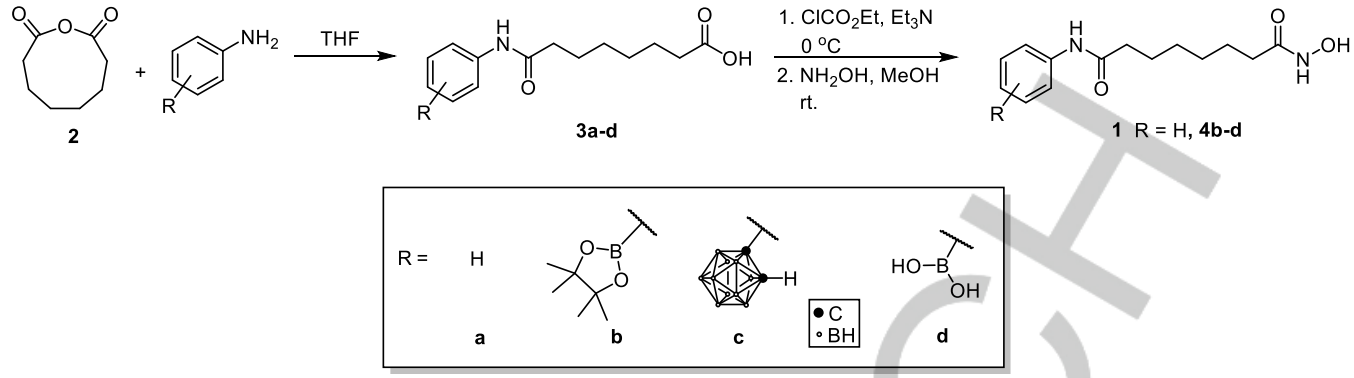

Scheme 1. Synthesis of boronated derivatives of **1**.

To the best of our knowledge, modification of the phenyl capping group in **1** with boron moieties has not been reported previously. There is compelling evidence that modification of the capping group in **1** can potentially direct exquisite HDAC selectivity.[2, 30, 33] To date, the X-ray crystal structures of all human HDAC Class I have been reported.[34-38] With the potential use of isoform-selective HDACi's, Class I HDACs appear to be the most abundant and overexpressed isoforms in various cancers thereby rationalizing the requirement for novel Class I inhibitors that might lead to improved cancer therapeutics. Indeed, the targeting of overexpressed proteins in tumor cells with boron moieties has been the subject of intense interest in recent years.[39-41] Of notable interest is recent discovery of carborane-based epidermal growth factor receptor (EGFR) inhibitors by Couto *et al.*[39, 42] These authors determined that the incorporation of *closo*-1,7-carborane cages into an existing EGFR inhibitor led to a significant (*ca.* 10-fold) increase in inhibition of this receptor when compared to the parent (organic) inhibitor.[40, 42]

X-ray crystallographic analyses of Class I HDACs has shown that the capping group of HDACi is exposed to solvent and interacts with amino acid residues located near the entrance of the active catalytic channel.[33, 36] Given the capping region of the substrate channel is the most variable amongst the HDAC family, potential modifications at this site could generate inhibitors with excellent isoform selectivity. Of direct interest in this work are the boron clusters such as the *closo*-carboranes which have shown high protein receptor affinity and inhibition of enzymes by binding to hydrophobic cavities at or near the receptor site.[27, 33, 43] Herein, we report the synthesis and a preliminary *in vitro* inhibition study of selected group of boronated HDAC2 inhibitors in which the nature of the boron moiety was varied from boronic acid to boronate ester to 1,2-*closo*-carborane. Such modifications will necessarily change the nature of the hydrophobicity/hydrophilicity and steric bulk of the capping group in this class of HDACi's, and these effects upon target engagement will be explored in this study.

Results and Discussion

There are several established synthetic routes for the synthesis of the archetypal HDAC inhibitor **1**. The widely used methodology described by Mai *et al.*[23] was employed in order to validate new synthetic routes for the synthesis of **4b**-**d** owing to the high-yield and reproducibility of this particular synthetic method over other known routes.

Commercially-available octanedioic acid was readily converted into the anhydride oxonane-2,9-dione (**2**) in quantitative yield by means of condensation reaction involving acetic anhydride. By using similar conditions to those reported in the preparation of **1**, the commercially-available 4-aminophenylboronic acid pinacol ester and (3-aminophenyl) boronic acid was stirred with **2** in THF solution for 1 h (**Scheme 1**). The success of this reaction was found to be dependent on the ability of the poorly-nucleophilic amine attacking the electrophilic carbonyl atom of the anhydride. Short reaction times coupled with use of dry solvent successfully afforded **3b** (85%) and **3d** (80%), respectively, in excellent yields. 1-(*p*-Nitrophenyl)-*closo*-1,2-carborane was prepared as described previously by Hawthorne *et al.*[44] The reduction of the nitro group was achieved by means of a hydrogenation reaction employing a Pd/C catalyst in MeOH, and the resulting anilino-*closo*-1,2-carborane precursor was purified by means of column chromatography in high yield (85%). The preparation of **3c** was successfully achieved by reacting the anilino-*closo*-1,2-carborane with **2**. Longer reaction times than those used to prepare the other boronated derivatives of **3** allowed for high conversion to **3c** (80%) with no further purification required due to its crystallisation from aqueous solution.

The conversion of the carboxylic acid groups of **3b** and **3d** to the hydroxamic acid derivatives required first, the formation of ethyl carbonic anhydride intermediate by ethyl chloroformate in the presence of triethylamine. Second, the addition of the freshly prepared hydroxylamine resulted in the formation of the desired target compounds **4b** and **4d** in 65% and 70% yields, respectively. Purification of crude **4b** proved to be non-trivial, however, owing to its highly hygroscopic nature.

In the final conversion of **3c** to the desired **4c**, the potential risk of cage deboronation of the *closo*-1,2-carborane in the presence of hydroxylamine was considered. To minimize the attack of the nucleophilic base at the boron cluster, a short reaction time (10 min) was used. $^{11}B\{^{1}H\}$ NMR spectroscopy revealed that a minor amount of deboronation of the carborane cage did indeed occur despite the short reaction time, with the *nido*-carborane peaks observed at the expected upfield shifts (δ = -21.06 to -37.12). Given the hydrophilic nature of the *nido*-7,8-carborane anion by-product over the hydrophobic *closo*-carborane, purification was performed by means of an aqueous workup to yield the desired

closo-1,2-carborane **4c** in good yield (75%). The product was confirmed by means of ESI-MS with a molecular ion peak observed at *m/z* 431.3079 for $[M + Na]^+$ (calculated: *m/z* 431.3079).

Table 1. IC_{50} values for the assessed compounds **1** and **4b-d**.

Compound	IC_{50} ± SEM[a] (nM)
1	44.3 ±1.6
4b	40.6 ±1.5
4c	42.9 ±1.5
4d	61.2 ±1.7

[a]*SEM = standard error of the mean (n = 3).*

The ability of compounds **1** and **4b**-**d** to inhibit HDAC2 activity was assessed by means of an *in vitro* HDAC2 assay. Notably, all compounds assessed in this work were found to exhibit potent HDAC2 inhibition at the nM level (**Table 1**). Compound **4b** (pinacol ester) was found to be the most potent inhibitor of HDAC2 followed by **4c** (*closo*-1,2-carborane), **1** and **4d** (boronic acid). It is clear that the electrophilic boronate ester group enhanced HDAC2 inhibition compared to **1** but, notably, the bulkier and more hydrophobic *closo*-1,2- carboranyl group also led to a potent derivative **4c** even though it does not possess any electrophilic boron atoms. These results indicate that hydrophobicity of the capping group might be an important parameter governing the nature of the capping group. Indeed, the hydrophilic boronic acid **4d** was the least potent inhibitor prepared in this study. The Hill coefficient was determined for **4b**-**d** and, in each case, it was equal to 1, consistent with independent (non-cooperative) binding of the boronated inhibitors to HDAC2. Motifs such as cyclic peptides and macrocyclic capping groups that can potentiate greater interactions with amino-acid residues at the rim of the channel than the traditional phenyl cap in **1** have been explored for their ability to confer HDAC selectivity.[45-49] The boronated compounds prepared in this work add to this group of motifs and demonstrate that the nature of the capping group motif does not significantly alter the nature of target engagement but instead increased hydrophobicity and/or steric bulk appears to confer selectivity for Class I HDACs, in this case HDAC2.

Current HDACis are mostly pan-inhibitors with a number of side-effects including fatigue, dehydration and thrombocytopenia. Even though the therapeutic advantages of isoform-selective HDACis are yet to be proven clinically proven, it is possible that higher selectivity for one particular HDAC isoform may result in a better therapeutic index with fewer adverse side-effects. By studying the currently-available X-ray crystal structures of Class I HDAC enzymes, an elucidation of both mechanism and relative orientation of the inhibitor at the active site can be determined. X-ray diffraction data have shown that HDAC1 and HDAC2 possess a single residue difference at S262 and A264, respectively.[50-51] The ability to design a small molecule inhibitor that can successfully distinguish between these two isoforms would allow one to determine whether exploiting the small difference between the HDAC1 and HDAC2 isoforms can lead to a higher isoform selectivity and potency. HDAC3 and HDAC8 have a more pronounced difference in their protein structure, with HDAC3 having a single insertion of F199 residue altering the orientation of Y198 and HDAC8 with a noticeable loop L1, formed by the insertion of seven amino acid residues (located at positions 30-36).[51] The presence of these secondary features allows for a more facile exploitation and selective binding of an inhibitor due to their absence from other Class I HDACs. Unsurprisingly, HDACi research over the past decade has focused on the design of HDAC3 and HDAC8 inhibitors due to their significant structural differences.[31, 52-55]

To date, integration of boron moieties into HDAC inhibitors such as **1** has only had limited success, with their *in vitro* potency being surpassed by more traditional organic fragments. Previous work in this field has focussed on the re-design the skeletal structure of **1** by altering either (a) its linker or (b) Zn^{2+}-binding domain to improve the drug's metal-complexing capability. For instance, Suzuki and co-workers prepared a library of boronic acid structures by altering the linker component of the skeletal structure.[30] Here, the researchers replaced the hydroxamic acid moiety with boronic acid group. Their design logic was consistent with the mechanism of action of inhibitors such as **1** where the hydroxamic acid moiety interacted with the Zn^{2+} ion which is located near the 'foot' pocket of the enzyme active site. It was thought that the increased electrophilicity of the carbonyl oxygen in the substrate would result from coordination to the Lewis acidic Zn^{2+} ion. The coordination of the metal ion made the carbonyl group prone to a nucleophilic attack by a water molecule activated by the nearby His140 and His141 residues. This particular interaction results in a tetrahedral transition state which is stabilised by the Zn-O interaction and additional hydrogen bonding interactions with Tyr303 and His140. The proton transfer from His141 to the N-atom of the intermediate triggers scission of the C-N bond to afford the acetate and lysine products. By replacement of the hydroxamic acid by boronic acids, Suzuki *et al.* proposed the vacant *p*-orbital of the boron atom would interact with the water molecule at the active site to afford a stable tetrahedral boronate complex. This complex would then bind the Zn^{2+} ion and form two hydrogen bonds to Tyr303 and His140 (HDAC1 numbering), thus leading to HDAC inhibition. Despite their efforts, the authors failed to obtain a boronic acid inhibitor which was at least comparable to **1** in terms of potency.

Another past study of relevance to this work was a computational study undertaken by Bakri *et al.* where they developed an *in-silico* query using various integrated software packages.[31] In this study, multiple sequence alignment was performed against HDAC class II human enzymes, resulting in an idealised molecular docking simulation. In conjunction with Lipinski's 'rule of five', and Egan's and Veber's rules, the paper reported four new boronated ligands that met these parameters with good predicted oral bioavailability. Further analysis of the ligand's health impact including ADME (absorption, distribution, metabolism, excretion) and toxicology were estimated using the Benigni-Bossa rules. These four ligands also were found to have more negative $\Delta G_{binding}$ values than that of **1**. It was concluded by these authors that the use of boron derivatives of **1** have promising potential as HDAC II enzyme candidates but no such candidates have been prepared to date.

Conclusion

We have successfully prepared a small library of boronated compounds that possess the ability to alter the Zn^{2+}-binding domain of **1**. Our lead inhibitor **4b** shows a higher HDAC2 potency over the gold standard HDAC drug **1**. One unique feature of Class I HDAC enzymes such as HDAC2 over the other enzyme classes is the presence of a 14 Å internal cavity, located at the internal bottom channel adjacent to the Zn^{2+} binding site.[33, 35, 56] It is clear that HDACis incorporating hydroxamates are the most potent enzyme inhibitors to date, however, X-ray diffraction studies show only a minimal set of non-covalent interactions between the hydroxamic acid and adjacent cavity [57]. The exploitation of this cavity is one intriguing way of enhancing enhance isoform selectivity. Research in the field suggests that 2-aminoanilide is an excellent fragment with a higher selectivity for HDACs 1-3 when compared to related hydroxamates [52, 58-59]. An X-ray crystallographic study of HDAC2 with an 2-aminoanilide inhibitor has confirmed an anilide interaction with the 'foot' pocket adjacent to the catalytic region. By expanding on the substituted 5-position of the ring, compounds containing the anilide moiety have shown up to a 31-fold higher selectivity for HDAC1 over HDAC2, with potencies in the nM range [60]. Of greater interest is the inclusion of bulky, branched capping groups allowing for an additional 10-fold increase in potency[61]. The inclusion of 2-aminoanilide into our boronated structures has the potential to give low nM HDAC2 inhibitory activity, and we are currently studying the effects of enhancing the bulk of the boronic ester at the capping position in conjunction with the incorporation of a substituted 2-aminoanilide ring. The results of this work will be reported in due course.

Experimental Section

Material and methods: NMR spectra were recorded on a Bruker Avance III 300 or 400 spectrometers in DMSO-d_6 unless otherwise noted (^{1}H at 400.13 MHz and ^{11}B at 128.37 MHz). All chemical shifts (δ) are given in ppm relative to TMS = 0, using trace isotopic protons in deuterated solvents as the internal reference, relative integral, multiplicity (s= singlet, br = broad singlet, d = doublet, dd= doublet of doublets, dt = double of triplets, t = triplet, m = multiplet), and coupling constants (*J*, Hz). Low resolution mass spectrometry was performed using ThermoQuest Finnigan LCQ-Deca ion trap mass spectrometer with electrospray ionization in positive (+ESI) or negative (-ESI) mode. Column chromatography was carried out over Scharlau 60 40-60 µm silica. Thin layer chromatography (TLC) was carried out on Merck Kiesel gel 60 F_{254} aluminum back plates. Visualization of carborane-containing compounds on TLC plates was achieved using an acidified $PdCl_2$ (1%) stain and heat. 1,2-*closo*-carborane was purchased from Katchem (Czech Republic).

The fluorogenic assays was performed using the HDAC2 assay kit (Green) purchased from BPS Bioscience (San Diego, CA). A 50 µL buffer mixture containing the human recombinant HDAC2 enzyme isoform, test compound (dissolved in <1% DMSO), and the corresponding HDAC2 substrate was added into a 96-well assay plate. The plate was incubated at 37 ºC for 30 min, followed by the addition of 50 µL of HDAC developer reagent and incubated at room temperature for an additional 20 min. Fluorescence intensity of the assay plates was measured on a BMG Labtech 96-microplate reader using an excitation wavelength of 355 nm and detection wavelength of 460 nm for all compounds. The fluorescence intensity data was analyzed using Prism (GraphPad Software, San Diego, CA). The DMSO controls (F_t) and enzyme-free controls (F_b) were defined as 100% and 0% HDAC2 activity, respectively. The percent (%) activity of each compound was calculated as $(F-F_b)/(F_t-F_b)$, where F represents the fluorescence intensity value at the specified compound concentration. A positive control (Trichostatin A) was used.

Compounds **1, 2** and **3a** were prepared by the methods of Mai *et al.*[23] and were isolated without further purification. Compound **3a** was isolated as two polymorphic white solids (2.41 g, 63%) and (0.50 g, 13%), respectively.

***8-Oxo-8-((4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)amino)octanoic acid* (3b):** Compound **3b** was prepared by adapting a procedure described by Mai *et al.* Compound **2** (1.41 g, 9.1 mmol) and 4-aminophenylboronic acid pinacol ester were stirred in THF for 1 h at RT. The resulting mixture was filtered off to give **3b** as an off-white powder (2.5 g, 85% yield). ^{1}H NMR (300 MHz d_6-DMSO, δ): 1.28 (s, 12H), 1.34 (m, 4H), 1.56 (m, 4H), 2.18 (m, 2H), 2.30 (m, 2H), 6.52 (d, 2H, $^3J_{HH}$ = 8.46 Hz, Ph), 7.31 (d, 2H, $^3J_{HH}$ = 8.40 Hz, Ph), 9.84 (s, 1H, NH) and 11.95 (s, 1H, COOH). ESI-MS (*m/z*): 398 (100%, [M + Na]$^+$).

8-(1-(p-aminophenyl)-*closo*-1,2-carborane)-8-oxooctanoic acid (3c): Compound **3c** was prepared by adapting a procedure described by Mai *et al.* Compound **1** (0.9 g, 1.2 mmol) 1-(*p*-aminophenyl)-*closo*-1,2-carborane were stirred THF for 1.5 h at RT. The resulting mixture was filtered off to give **3c** as a yellow powder (2.5 g, 85%). ATR-FTIR (cm^{-1}): 3292 (br, OH), 2935 (CH), 1656 (C=O), 1599 (C=O). ^{1}H NMR (400 MHz, d_6-DMSO, δ): 1.22-3.40 (br, BH), 1.36 (br, 4H), 1.61 (br, 4H), 2.22 (t, 2H), 2.29 (t, 2H), 3.91 (s, 2H). 4.41 (br, CH), 4.9 (br, NH), 7.58 (d, 2H, $^3J_{HH}$ = 7.77 Hz, Ph), 7.71 (d, 2H, $^3J_{HH}$ = 7.71 Hz, Ph), 8.57 (br, COOH). ^{11}B{^{1}H} (128 MHz, DMSO-d_6, δ): -12.4, -11.0, -8.7, -4.5, -2.4. ESI-MS (*m/z*): 414.20 (61%, [M+Na]$^+$), 415.21 (100%, [M+Na]$^+$), 416.20 (80%, [M+Na]$^+$), 417.21 (43%, [M+Na]$^+$).

8-((3-Boronophenyl)amino)-8-oxooctanoic acid (3d): Compound **3d** was prepared by adapting a procedure described by Mai *et al.* Compound **1** (1.51 g, 9.1 mmol) and (3-aminophenyl)boronic acid (2.0 g, 9.1 mmol) were stirred in THF for 1.5 h at RT. The resulting mixture was filtered off to give **3d** as an off-white powder (2.5 g, 85%). ATR-FTIR (cm^{-1}): 3292 (br, OH), 2935 (CH), 1656 (C=O), 1599 (C=O). ^{1}H NMR (300 MHz, d_6-DMSO, δ): 1.33 (m, 4H), 1.49 (m, 4H), 1.60 (m, 4H), 2.18 (m, 2H), 2.29 (m, 2H), 7.45 (d, 2H, $^3J_{HH}$ = 7.46 Hz, Ph), 7.71 (d, 2H, $^3J_{HH}$ = 7.71 Hz, Ph), 9.76 (s, 1H, NH) and 11.94 (s, 1H, COOH). ESI-MS (*m/z*): 316 (100%, [M + Na]$^+$).

Compounds **4b - 4d** were prepared by adapting a procedure described Mai *et al*.[23] At 0 ºC, solutions of **3b - d** were treated with excess amounts of triethylamine and ethyl chloroformate, followed by the addition of freshly-prepared hydroxylamine (4.3 mmol).

***N*^{1}-Hydroxy-*N*^{8}-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)octanediamide (4b)**: Brown oil (312 mg, 71%). ^{1}H NMR (400 MHz, d_6-DMSO, δ): 1.28 (s, 12H), 1.34 (m, 4H), 1.56 (m, 4H), 2.18 (m, 2H, $H_{21,22}$), 2.30 (m, 2H), 6.52 (d, 2H, $^3J_{HH}$ = 8.46 Hz, Ph), 7.31 (d, 2H, $^3J_{HH}$ = 8.40 Hz, Ph), 9.84 (s, 1H, NH) and 10.95 (br, 1H, OH). ^{11}B{^{1}H} (128 MHz, DMSO-d_6, δ): 30.9. HRMS (+ESI): Calc. for $C_{20}H_{31}BN_2O_5$: 413.22182, found 413.22183 ([M+Na]$^+$).

***N*^{1}(1-(*p*-aminophenyl)-*closo*-1,2-carboranyl)-*N*^{8}-hydroxyoctanediamide** (**4c**): Yellow powder (391 mg, 75%). ^{1}H NMR (400 MHz, DMSO-d_6, δ): 1.22-3.40 (br, BH), 1.36 (br, 4H), 1.61 (br, 4H), 2.22 (t, 2H), 2.29 (t, 2H), 3.91 (s, 2H). 4.41 (br, CH), 4.9 (br, NH), 8.57 (br, OH). ^{11}B{^{1}H} (128 MHz, d_6-DMSO, δ): -12.8, -10.8, -8.9, -4.3, -2.0. HRMS (+ESI): 427.30229 (8%, $C_{10}H_{30}{}^{10}B_7{}^{11}B_3N_2NaO_3$ [M+Na]$^+$, gives 427.30778), 428.29866 (38%, $C_{10}H_{30}{}^{10}B_6{}^{11}B_4N_2NaO_3$ [M+Na]$^+$, gives 428.29883), 429.29503 (74%, $C_{10}H_{30}{}^{10}B_5{}^{11}B_5N_2NaO_3$ [M+Na]$^+$, gives 429.29851), 430.30140 (100%, $C_{10}H_{30}{}^{10}B_4{}^{11}B_6N_2NaO_3$ [M+Na]$^+$, gives 430.30756), 431.30790 (89%, $C_{10}H^{10}B_3{}^{11}B_7N_2NaO_3$ [M+Na]$^+$, gives 431.30791), 432.30414 (41%, $C_{10}H^{10}B_2{}^{11}B_8N_2NaO_3$ [M+Na]$^+$, gives 432.30485), 433.31096 (10%, $C_{10}H^{10}B_1{}^{11}B_9N_2NaO_3$ [M+Na]$^+$, gives 433.31021).

(3-(8-(Hydroxyamino)-8-oxooctanamido)phenyl)boronic acid (4d): White powder (416 mg, 81%). ^{1}H NMR (400 MHz, d_6-DMSO, δ): 1.33 (m, 4H), 1.49 (m, 4H), 1.60 (m, 4H), 2.18 (m, 2H), 2.29 (m, 2H), 7.43 (m, 1H, Ph), 7.50 (m, 3H, Ph), 8.98 (s, 1H, NH) and 10.94 (br, 1H, COOH). ^{11}B{^{1}H} (128 MHz, DMSO-d_6, δ): 29.0. HRMS (+ESI): Calc. for $C_{14}H_{21}BN_2O_5$: 309.1532, found 331.14357 ([M+Na]$^+$).

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Keywords: epigenetics • cancer • boron • HDAC inhibitor • Vorinostat

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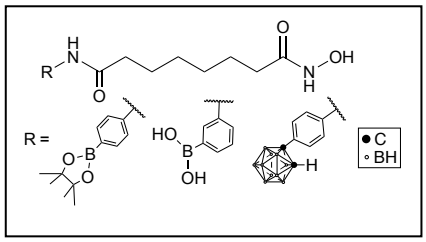

Insert text for Table of Contents here. We report the first boron-based histone deacetylase inhibitors of HDAC2, showcasing boron's untapped potential in the design of new classes of epigenetic enzyme inhibitors.

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