View Article Online View Journal

Organic & Biomolecular Chemistry

Accepted Manuscript

This article can be cited before page numbers have been issued, to do this please use: J. W. Walton, J. M. Cross, T. Riedel and P. Dyson, *Org. Biomol. Chem.*, 2017, DOI: 10.1039/C7OB02339A.



This is an Accepted Manuscript, which has been through the Royal Society of Chemistry peer review process and has been accepted for publication.

Accepted Manuscripts are published online shortly after acceptance, before technical editing, formatting and proof reading. Using this free service, authors can make their results available to the community, in citable form, before we publish the edited article. We will replace this Accepted Manuscript with the edited and formatted Advance Article as soon as it is available.

You can find more information about Accepted Manuscripts in the **author guidelines**.

Please note that technical editing may introduce minor changes to the text and/or graphics, which may alter content. The journal's standard <u>Terms & Conditions</u> and the ethical guidelines, outlined in our <u>author and reviewer resource centre</u>, still apply. In no event shall the Royal Society of Chemistry be held responsible for any errors or omissions in this Accepted Manuscript or any consequences arising from the use of any information it contains.



rsc.li/obc

Journal Name

ARTICLE



Biomolecular Chemistry Accepted Manuscript

2

rdanic

Perfluorinated HDAC inhibitors as Selective Anticancer Agents

James W. Walton,^a Jasmine M. Cross,^a Tina Riedel^b and Paul J. Dyson^b

Received 00th January 20xx, Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

A series of potent histone deacetylase inhibitors is presented that incorporate alkyl or perfluorinated alkyl chains. Several new compounds show greater *in vitro* antiproliferate activity than the clinically approved inhibitor, SAHA. Furthermore, the new compounds show up to 5-fold greater activity against cancer cells than healthy cells. This selectivity is in contrast to SAHA, which is more active against the healthy cell line than the cancer cell line tested. Finally, we report an increase in activity for SAHA under mild hyperthermia, indicating that it could be an interesting candidate to use in combination with thermal therapy.

Introduction

Over the past few decades, cancer chemotherapies have moved away from targeting DNA, which is non-selective and affects any rapidly dividing cell type, towards targeted molecular therapies.¹⁻³ Examples of targeted therapies include activation of tumour suppressor genes,⁴⁻⁶ RNA targeting⁷⁻⁹ and enzyme inhibition.¹⁰⁻¹⁴ Enzymes that control post-translational modification of histone proteins in chromatin are often overexpressed in tumours and have been the focus of much research in this area.¹⁵⁻¹⁸

One such class of enzymes is the histone deacetylases (HDACs).¹⁹⁻²¹ Together with the histone acetylases, they control the extent of acetylation of ε -lysine residues within the histone core.²² Hypoacetylation leads to a charged histone core and a condensed chromatin structure, resulting in suppression of tumour-repressor gene expression.²³ Hyperacetylation has the opposite effect, increasing tumour-repressor gene expression. As a result, the development of HDAC inhibitors as anticancer agents has been actively pursued,²⁴⁻³¹ with four drugs, including vorinostat (suberoyl anilide hydroxamic acid, SAHA,),³² approved for treatment of cutaneous T-cell lymphomas and multiple myeloma.

SAHA (Figure 1) comprises a hydroxamic acid group that chelates Zn²⁺ in a cavity in the enzyme active site, a hydrophobic chain that penetrates the narrow cavity and a phenyl head group that sits at the entrance to the cavity.³³ This head group is amenable to structural variation, leading to changes in binding affinity³⁴ or addition of function to the inhibitor. For example, SAHA-analogues with fluorescent head groups have been developed that have the potential to

monitor HDAC dependent processes in real time through optical microscopy. $^{\rm 35}$

Combining drug activity with responsiveness to external stimuli such as light or heat has the potential to produce highly selective treatments, leading to more efficient cancer treatment. Recently, a photoresponsive HDAC inhibitor has been proposed,³⁶ but no thermoresponsive inhibitors have been reported. Using mild hyperthermia (local heating to 41–42 °C) to increase drug potency is an attractive prospect, as localised heating of a tumour would lead to targeted treatment.^{37,38} One strategy is to encapsulate drugs within nanoparticles, such as liposomes, that release their payload upon heating.³⁹ Additionally, hyperthermia may sensitise some tumour tissues to anticancer drugs,⁴⁰ whilst other drugs are only activated under hyperthermic conditions.⁴¹



Figure 1. Clincally approved inhibitor SAHA and the perfluorinated analogues investigated in this work.

Several known anticancer agents have been modified, with the intention of inducing thermoresponsiveness. For example, a chlorambusil derivative, with a perfluorinated alkyl chain was recently reported,⁴² which showed no significant *in vitro* toxicity at 37 °C, but when dosed cells were heated to 41 °C for

^{a.} Department of Chemistry, Durham University, South Road, Durham, DH1 3LE, United Kingdom.

^{b.} Institut des sciences et ingénierie chimiques, Ecole polytechnique fédérale de Lausanne (EPFL), CH-1015, Lausanne, Switzerland.

⁺ Electronic Supplementary Information (ESI) available: contains experimental methods and HPLC traces See DOI: 10.1039/x0xx00000x

iomolecular Chemistry Accepted Manuscrip

DOI: 10.1039/C7OB02339A Journal Name

ARTICLE

a short time toxicity increased to levels comparable with chlorambusil itself. By selectivity heating the tumour site this activation mechanism could significantly reduce the general toxicity associated with chlorambucil. Anticancer metal complexes have also been designed that show increased anticancer activity under hyperthermia.⁴³ These ruthenium complexes were shown to reduce the growth of adenocarcinomas in athymic mice by 90%, following localised hyperthermia. The fundamental processes behind the thermoresponsiveness is not well understood, but may be due to increased membrane permeability,⁴⁴ selective drug solubility at the elevated temperature or acceleration of chemical processes, such as ester hydrolysis, that activate certain thermoresponsive drugs.⁴⁵

We set out to develop thermoresponsive HDAC inhibitors by modulating the SAHA phenyl head group with perfluorinated alkyl chains of varying lengths (Figure 1). Whilst thermorepsonsiveness was only observed for one compound, we found that several new species are selective towards cancer cells over healthy cells. Furthermore, we report for the first time potential thermorepsonsiveness of SAHA itself.

Results and Discussion

Our target compounds comprise the SAHA pharmacophore, incorporating perfluorinated chains (**5d–f**) linked by ester groups to the *para* position of the phenyl head group. For comparative analysis, the non-fluorinated alkyl chain analogues (**5a–c**) were also synthesised. To aid efficient synthesis, we designed a pathway that included a late stage intermediate, **3a**, common to all compounds (Scheme 1). To prepare this intermediate, 4-aminophenylacetic acid was protected as the methyl ester before ring opening amidation with suberoyl anhydride⁴⁶ afforded intermediate **2**. Standard amide coupling conditions were used to install the benzyl-protected hydroxamic acid, before quantitative deprotection of the methyl ester yielded **3a**. Steglich esterification⁴⁷ reactions with the relevant alcohols gave intermediates **4a–f**, which were deprotected under Pd-catalysed hydrogenation

conditions to give the target compounds **5a–f**. The final compounds were purified by recrystallisation from EtOAc and fully characterised (see ESI⁺). The intermediate **3a** was also deprotected to form **3b**, a potential metabolic by-product of the esters **5a–f**.



Scheme 2.

To ensure dissolution of **4f**, which incorporates the longest fluorinated chain, during hydrogenation step **4** \rightarrow **5**, the reaction was carried out in refluxing methanol for 3 h. Under these conditions, the reaction proceeded to give the amide species **6f** rather than the desired hydroxamic acid **5f** (Scheme 2). This competing reaction could be avoided by carrying out hydrogenation at room temperature with dilute solution. Despite its unplanned synthesis, **6f**, was included in the biological assays, to investigate the role of the hydroxamic acid group upon activity. The purity of all compounds tested in biological assays was assessed by elemental analysis or analytical HPLC.

Compounds were assessed for their cytotoxicity against ovarian cancer A2780 cells and healthy kidney HEK cells. Following a standard MTT assay protocol,⁴⁸ cells were incubated with compounds for 72 h at 37 °C over the concentration range $0.01 - 50 \mu$ M. IC₅₀ values (concentration of compound required to inhibit cell proliferation by 50%) were calculated from the resulting dose response curves (Table 1, see ESI⁺ for full details).

We found that at 37 °C five of the newly synthesised compounds, **5a–e**, were able to inhibit cell proliferation of the A2780 cancer cell line. These species have comparable *in vitro* toxicity to the clinically approved HDAC inhibitor SAHA, with two compounds, **5a** and **5b**, showing lower inhibitory concentration (IC₅₀:2.6 and 1.3 μ M, respectively) than SAHA (IC₅₀: 3.5 μ M). Several of the new compounds display good



Published on 18 October 2017. Downloaded by University of Newcastle on 18/10/2017 17:21:22

Scheme 1. Synthesis of inhibitors.

selectivity between the two cell lines. For example, the decyl perfluorinated ester compound **5e**, whose activity in the cancer cell line matches that of SAHA, is more than 4 times more active against the A2780 cells than the healthy HEK cell line. The known inhibitor SAHA showed no such selectivity and was, in fact, more active against the healthy cell line. Compound **5b** is both more active against the cancer cell line and much more selective than the known inhibitor SAHA, showing again the potential for these compounds to act as selective anticancer agents.

Table 1. Cytotoxicity of **3b**, **4a**, **5a-f**, **6f** and SAHA against ovarian cancer A2780 cells and healthy kidney HEK cells (MTT assay, 72 h)

Compound	IC₅₀ (A2780) [µM]		IC₅₀ (HEK) [µM]	
	37 °C	41 °C	37 °C	41 °C
3b	> 50	> 50	> 50	> 50
4a	> 50	> 50	> 50	> 50
5a	2.6 ± 0.3	2.5 ± 0.2	4.6 ± 0.5	5.6 ± 0.9
5b	1.33 ± 0.09	1.23 ± 0.08	3.5 ± 0.5	5.3 ± 0.7
5c	3.0 ± 0.3	1.60 ± 0.04	2.8 ± 0.3	1.9 ± 0.3
5d	9.2 ±0.3	8.6 ± 1.5	7.4 ± 0.6	7.3 ± 1.5
5e	3.3 ± 1.0	5.6 ± 0.2	16.0 ± 3.0	9.8 ±3.0
5f	> 50	> 50	> 50	> 50
6f	> 50	> 50	> 50	> 50
SAHA	3.5 ± 0.4	1.0 ± 0.2	2.6 ± 0.4	1.9 ± 0.6

At 37 °C, the dodecyl fluorinated ester compound 5f was found to be inactive against both HEK and A2780 cells lines. These results show that the length of perfluorinated alkyl chain is critical in determining cytotoxicity. It is likely that the longer perfluorinated chain either leads to low solubility in the assay medium or is it possible that interaction between the hydrophobic chain and the cell membrane results in reduced drug uptake. Compound 4a, in which the hydroxamic acid is benzyl protected, shows no cytotoxicity against either tested cell line at 37 °C. This highlights the importance of the hydroxamic acid functionality on the observed toxicity. The analogous deprotected compound 5a has an inhibitory concentration IC₅₀: 2.6 µM against A2780 cells. Interestingly, the carboxylic acid compound 3b, shows no cytotoxicity at 37 °C. This could either be due to an unfavourable interaction between the HDAC enzyme active site and the negatively charged carboxylate or lower cell uptake of 3b, due to repulsion of the carboxylate and the negatively charged phospholipid cell membrane.

To probe whether the compounds are thermoresponsive, separate assays were run in which dosed cells were initially incubated at 41 °C for 2 h, followed by 70 h at 37 °C (Table 1). Whilst no compounds showed high levels of thermoresponsiveness, the dodecyl ester compound **5c** showed around 2-fold increase in activity at the higher temperature in both A2780 and HEK cell lines. This compound has the longest alkyl chain of any tested compound and future studies will focus on extending this alkyl chain length with the intention to induce further thermoresponsiveness. Of all the tested compounds, it is SAHA itself that shows the greatest potential for thermoresponsiveness. A 3.5 fold increase in toxicity is observed under hyperthermia in the A2780 cell line, whilst no such response is observed in the HEK cell line. To our knowledge, this is first time that the potential thermoresponsiveness of SAHA has been reported. We will need to validate this result against more cell lines, but in principle the combination of using hyperthermia in combination with a clinically approved anticancer agent is an exciting prospect, as most of the current drugs evaluated in combination with hyperthermia do not show any synergism in vitro.

Table 2 HDAC activity in presence of potential inhibitors at 0.05 μ M and 1 μ M concentration, measured using commercially available assay kit. Values are reported as percentage activity relative to a positive control (no inhibitor).

Compound	1 µM	0.05 μM
Control	100%	100%
3b	33.5 ± 0.5%	83 ± 3%
4a	97%	96%
5a	47 ± 7%	75 ± 1%
5b	36 ± 3%	69.0 ± 0.5%
5c	67 ± 11%	78 ± 14%
5d	66 ± 9%	81 ± 12%
5e	68 ± 2%	83 ± 1%
5f	59%	75%
6f	96 ± 3%	89 ± 3%
SAHA	10.2 ± 0.1%	53 ± 7%

To elucidate a potential mechanism of action of these novel compounds, HDAC inhibition assays were run, using commercially available assay kit containing HeLa nuclear extract (EnzoLifeSciences). Assays were run at 1 µM and 50 nM drug concentrations and fluorescence measurements used to determine the extent of HDAC activity, with no fluorescence indicating complete HDAC inhibition (see Experimental Methods below for full details). Results are presented as a percentage of HDAC activity, relative to a control with no added inhibitor (Table 2). At 1 µM, compounds 5a-f are able to inhibit the HDAC enzymes. Compound 5b is the most active of the new species in the HDAC assay. This compound was also the most active in the MTT cytotoxicity assay, supporting the hypothesis that HDAC inhibition is a viable mechanism of action of these species. In the HDAC enzyme assay none of the compounds cause inhibition at the same level as SAHA itself. This is in contrast to the MTT cell assay, where activity Published on 18 October 2017. Downloaded by University of Newcastle on 18/10/2017 17:21:22

DOI: 10.1039/C7OB02339A Journal Name

between SAHA and compounds **5a–e** was similar. Together these data suggest that HDAC inhibition is the most likely mechanism of action, but may not be the only pathway by which antiproliferative activity occurs. The ability to inhibit cell proliferation by more than one mechanism of action is considered beneficial, as acquired drug resistance is more likely to occur against drugs that operate via a single mechanism. Such promiscuity may also explain the improvements in cancer cell selectivity over SAHA.

It is of interest to note that, while the dodecyl ester compound **5f** showed no activity in the MTT cell assay, it is able to inhibit HDAC activity to a similar extent to the perfluorinated compounds **5d** and **5e**. This suggests other factors, such as low cell uptake or low solubility, lead to the lack of observed toxicity *in vitro* of **5f**. In a similar way, the carboxylate compound **3b** was inactive in the MTT assay, but is the most active new compound in the HDAC enzyme assay. This supports a low level of cell uptake of **3b** leading to the observed low cell toxicity, rather than a lack of enzyme inhibitory potency, although other explanations for the lack of activity in cytotoxicity assays are possible.

When the concentration of potential inhibitors **5a–f** is lowered to 50 nM HDAC activity increases slightly, but remains less than in the absence of inhibitor. Two compounds are unable to inhibit HDAC activity. They are: (i) the benzylprotected hydroxamic acid compound **4a** and (ii) the amide compound **6f**. This indicates the requirement for a hydroxamic chelating group and provides further evidence for a mechanism of action for compounds **5a–e** involving HDAC inhibition.

Computational modelling studies were undertaken in order to validate the hypothesis that HDAC inhibition is the predominant cause of cell antiproliferate activity. Docking studies were run using the X-ray structure of HDAC8 (PDB ID: 1t69).⁴⁹ Pleasingly, the docking study with SAHA closely



Fig 2. X-ray structure of HDAC8 (PDB ID: 1t69) with bound SAHA (magenta).⁴⁹ (A) and (B): predicted binding poses of SAHA (yellow) and (C) and (D): predicted binding poses of **3b** (green). Key interactions with amino acid residues: *a* H-bond between Asp101 and SAHA amide carbonyl; *b* H-bond between Tyr100 and **3b** carboxylate.

matched the binding site observed in the crystal structure (Figure 2A and 2B), with a key H-bond interaction between the SAHA amide carbonyl and protonated Asp101. When the carboxylic acid derivative **3b** was docked, a similar binding mode was observed (Figure 2C and 2D). In addition to the carboxamide H-bond, **3b** also shows a second H-bond interaction between the carboxylate end group and Tyr100. This additional interaction may explain the increased potency of **3b** over the ester derivatives **5a–f**. When docking was attempted with compounds **5a–5f**, hydroxamate chelation with Zn was predicted, but the alkyl and perfluoroalkyl chains found several potential docking conformations with no strong interaction with the cavity entrance. Future studies will use computational modelling to maximise the enzyme-inhibitor interactions, leading to more potent drug candidates.

Conclusions

We have synthesised a series of new perfluorinated and alkyl derivatives of SAHA and investigated their potential as anticancer agents. Five of the new compounds showed high levels of in vitro toxicity towards A2780 ovarian cancer cells, with compounds 5a and 5b, which incorporates octyl and decyl esters, respectively, showing higher cytotoxicity than the clinically approved SAHA compound. Compared to SAHA, much higher levels of selectivity (up to 5-fold for 5e) towards cancer cells over healthy cells were observed for several of the new compounds. Compound 5b shows excellent promise as a lead compound for further investigation, as it was both more active than the clinically-approved drug and showed good selectivity towards the cancer cells over healthy cells. Fluorescence assays support HDAC inhibition as a plausible mechanism of action, while potential binding in the HDAC active site was validated computational docking studies. in Thermoresponsiveness was investigated and 5c was found to have 2 fold greater antiproliferate activity under hyperthermic conditions. Furthermore, SAHA was found to have thermoresponsiveness, with a 3.5-fold increase in toxicity under hyperthermia. Future studies will be dedicated to investigating this potentially exciting new finding and to use computational docking to design more potent HDAC inhibitors.

Conflicts of Interest

There are no conflicts of interest to declare.

Acknowledgements

We thank Dr Ehmke Pohl for advice on computational docking studies. JWW and JMC thank Durham University for financial support. JWW partially funded through RSC JWT Jones Travelling Fellowship.

Notes and references

- 1 I. Collins and P. Workman, *Nat. Chem. Biol.*, 2006, **2**, 689–700.
- 2 D. R. Newell, Eur. J. Cancer, 2005, 41, 676–682.
- 3 M. Góngora-Benítez, J. Tulla-Puche and F. Albericio, *Chem. Rev.*, 2014, 114, 901–926.
- I. Gomez-Monterrey, A. Bertamino, A. Porta, A. Carotenuto, S. Musella, C. Aquino, I. Granata, M. Sala, D. Brancaccio, D. Picone, C. Ercole, P. Stiuso, P. Campiglia, P. Grieco, P. Ianelli, B. Maresca and E. Novellino, *J. Med. Chem.*, 2010, **53**, 8319–8329.
- 5 D. Lai, S. Visser-Grieve and X. Yang, *Biosci. Rep.*, 2012, **32**, 361–374.
- 6 E. Pazos, C. Portela, C. Penas, M. E. Vazquez and J. L. Mascarenas, Org. Biomol. Chem., 2015, 13, 5385–5390.
- 7 M. D. Disney, I. Yildirim and J. L. Childs-Disney, Org. Biomol. Chem., 2014, 12, 1029–1039.
- H. Ling, M. Fabbri and G. A. Calin, *Nat. Rev. Drug Discov.*, 2013, 12, 847–865.
- 9 R. Garzon, G. Marcucci and C. M. Croce, Nat. Rev. Drug Discov., 2010, 9, 775–789.
- 10 R. Manetsch, A. Krasiński, Z. Radić, J. Raushel, P. Taylor, K. B. Sharpless and H. C. Kolb, *J. Am. Chem. Soc.*, 2004, **126**, 12809– 12818.
- 11 J. Wang, S. Tian, R. A. Petros, M. E. Napier and J. M. Desimone, J. Am. Chem. Soc., 2010, **132**, 11306–11313.
- 12 J. Zhang, P. Yang and N. Gray, *Nat. Rev. Cancer*, 2009, **9**, 28–39.
- 13 K. J. Kilpin and P. J. Dyson, *Chem. Sci.*, 2013, **4**, 1410.
- 14 A. Casini and J. Reedijk, *Chem. Sci.*, 2012, **3**, 3135–3144.
- 15 M. M. Müller and T. W. Muir, Chem. Rev., 2015, 115, 2296– 2349.
- 16 D. C. Juvale, V. V Kulkarni, H. S. Deokar, N. K. Wagh, S. B. Padhye and V. M. Kulkarni, *Org. Biomol. Chem.*, 2006, 4, 2858–2868.
- 17 T. Maes, E. Carceller, J. Salas, A. Ortega and C. Buesa, *Curr. Opin. Pharmacol.*, 2015, 23, 52–60.
- 18 Y. Itoh, K. Aihara, P. Mellini, T. Tojo, Y. Ota, H. Tsumoto, V. R. Solomon, P. Zhan, M. Suzuki, D. Ogasawara, A. Shigenaga, T. Inokuma, H. Nakagawa, N. Miyata, T. Mizukami, A. Otaka and T. Suzuki, *J. Med. Chem.*, 2016, **59**, 1531–1544.
- 19 M. Paris, M. Porcelloni, M. Binaschi and D. Fattori, J. Med. Chem., 2008, **51**, 3330.
- 20 R. Wu, Z. Lu, Z. Cao and Y. Zhang, J. Am. Chem. Soc., 2011, 133, 6110–6113.
- 21 K. V. Butler, J. Kalin, C. Brochier, G. Vistoli, B. Langley and A. P. Kozikowski, *J. Am. Chem. Soc.*, 2010, **132**, 10842–10846.
- 22 P. A. Marks and W.-S. Xu, J. Cell. Biochem., 2009, 107, 600-8.
- 23 M. D. Shahbazian and M. Grunstein, *Annu. Rev. Biochem.*, 2007, **76**, 75–100.
- 24 J. M. Cross, T. R. Blower, N. Gallagher, J. H. Gill, K. L. Rockley and J. W. Walton, *Chempluschem*, 2016, **81**, 1276–1280.
- 25 D. Wutz, D. Gluhacevic, A. Chakrabarti, K. Schmidtkunz, D. Robaa, F. Erdmann, C. Romier, W. Sippl, M. Jung and B. Konig, Org. Biomol. Chem., 2017, 15, 4882–4896.
- 26 K. Ververis, A. Hiong, T. C. Karagiannis and P. V. Licciardi, *Biol. Targets Ther.*, 2013, 7, 47–60.
- 27 T. Qiu, L. Zhou, W. Zhu, T. Wang, J. Wang, Y. Shu and P. Liu, *Future Oncol.*, 2013, 9, 255–69.
- 28 D. Griffith, M. P. Morgan and C. J. Marmion, *Chem. Commun.*, 2009, 6735.
- 29 D. Can, H. W. Peindy N'Dongo, B. Spingler, P. Schmutz, P. Raposinho, I. Santos and R. Alberto, *Chem. Biodivers.*, 2012, 9, 1849–1866.

- 30 M. Librizzi, A. Longo, R. Chiarelli, J. Amin, J. Spencer and C. Luparello, Chem. Res. Toxicol., 2012, 25, 2608–2616.
- C. A. Ocasio, S. Sansook, R. Jones, J. M. Roberts, T. G. Scott, N. Tsoureas, P. Coxhead, M. Guille, G. J. Tizzard, S. J. Coles, H. Hochegger, J. E. Bradner and J. Spencer, *Organometallics*, 2017, 36, 3276–3283.
- 32 J. L. Spratlin, T. M. Pitts, G. N. Kulikowski, M. P. Morelli, J. J. Tentler, N. J. Serkova and S. G. Eckhardt, *Anticancer Res.*, 2011, 31, 1093–103.
- 33 P. A. Marks and R. Breslow, *Nat. Biotechnol.*, 2007, **25**, 84–90.
- 34 C. Salmi-Smail, A. Fabre, F. Dequiedt, A. Restouin, R. Castellano, S. Garbit, P. Roche, X. Morelli, J. M. Brunel and Y. Collette, J. Med. Chem., 2010, 53, 3038–3047.
- 35 R. K. Singh, T. Mandal, N. Balasubramanian, G. Cook and D. K. Srivastava, Anal. Biochem., 2011, 408, 309–315.
- 36 A. Leonidova, C. Mari, C. Aebersold and G. Gasser, Organometallics, 2016, 35, 851–854.
- 37 R. D. Issels, Curr. Opin. Oncol., 2008, 20, 438-43.
- 38 K. Pietzner, R. B. Schmuck, C. Fotopoulou, J. Gellermann, F. Ismaeel, C. H. Cho, M. Kalden and J. Sehouli, *Anticancer Res.*, 2011, **31**, 2675–2677.
- 39 H. Maeda, Bioconjug. Chem., 2010, 21, 797-802.
- 40 W. Rao, Z.-S. Deng and J. Liu, *Crit. Rev. Biomed. Eng.*, 2010, **38**, 101–116.
- 41 R. D. Issels, Eur. J. Cancer, 2008, 44, 2546-2554.
- 42 C. M. Clavel, O. Zava, F. Schmitt, B. Halamoda Kenzaoui, A. A. Nazarov, L. Juillerat-Jeanneret and P. J. Dyson, *Angew. Chemie Int. Ed.*, 2011, **50**, 7124–7127.
- 43 C. M. Clavel, P. Nowak-Sliwinska, E. Păunescu, A. W. Griffioen and P. J. Dyson, *Chem. Sci.*, 2015, **6**, 2795.
- 44 C. M. Clavel, E. Păunescu, P. Nowak-Sliwinska and P. J. Dyson, *Chem. Sci.*, 2014, 5, 1097.
- 45 C. M. Clavel, P. Nowak-Sliwinska, E. Păunescu and P. J. Dyson, Med. Chem. Commun., 2015, 6, 2054–2062.
- 46 L. K. Gediya, P. Chopra, P. Purushottamachar, N. Maheshwari and V. C. O. Njar, *J. Med. Chem.*, 2005, **48**, 5047–5051.
- 47 B. Neises and W. Steglich, Angew. Chemie Int. Ed. English, 1978, 17, 522–524.
- 48 T. Mosmann, J. Immunol. Methods, 1983, 65, 55-63.
- J. R. Somoza, R. J. Skene, B. A. Katz, C. Mol, J. D. Ho, A. J. Jennings, C. Luong, A. Arvai, J. J. Buggy, E. Chi, J. Tang, B. C. Sang, E. Verner, R. Wynands, E. M. Leahy, D. R. Dougan, G. Snell, M. Navre, M. W. Knuth, R. V. Swanson, D. E. McRee and L. W. Tari, *Structure*, 2004, **12**, 1325–1334.

Organic & Biomolecular Chemistry Accepted Manuscript

Perfluorinated histone deacetylase inhibitors show more potent cytotoxicity and greater selectivity towards ^{View Article Online} DOI: 10.1039/C7OB02339A ovarian carcinoma cells over human embryonic kidney cells, compared to the clinically-approved inhibitor, SAHA.

