A Direct Alkylation Route to Branched Derivatives of Suberoylanilide Hydroxamic Acid (SAHA), a Potent Non-Selective Inhibitor of Histone Deacetylases

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Abstract: Alkylation of malonamic esters provides a direct approach to derivatives of suberoylanilide hydroxamic acid (SAHA) that are branched at the amide carbon atom, a location pivotal for enhancing biological and therapeutic activity. Alkylations use NaH in THF followed by addition of the ester of 6-bromohexanoic acid; no protection of the amidic NH group is necessary. By this means, carboxylic acid, ester, amide, hydroxymethyl and 2-benzimidazolyl branching units have been appended to the SAHA backbone. Routes to vary one of the branching units at a time have been developed.

Keywords: malonamic esters, alkylation, trifunctional compounds, suberoylanilide hydroxamic acid, histone deacetylase inhibitors

1. Introduction

Hydroxamic acids[1] play a pivotal role as inhibitors of metal-dependent enzymes including matrix metalloproteinases and histone deacetylases (HDACs).[2-4] The hydrolytic action of histone deacetylases requires coordination of a terminally acetylated lysine residue, usually to zinc(II) in the catalytic site, prior to hydrolysis;[5] this is inhibited by powerful metal chelators, including hydroxamic acid derivatives compatible with the HDAC catalytic site, tunnel and protein periphery. The extent of acetylation levels of terminal lysine residues on histone protein is a major epigenetic regulator of gene expression; up-regulation of HDACs results in aberrant gene repression frequently associated with cancer. HDACs have also recently been shown to affect DNA replication and DNA repair.[3] Several HDAC inhibitors have entered clinical trials for the treatment of cancers. HDAC inhibitors are also used in the treatment Huntington's disease and show potential for the treatment of other neurodegenerative diseases and inflammation.[2-4]

Hydroxamic acids are the largest class of HDAC inhibitors.[2] Of the four HDAC inhibitors approved by the FDA (Fig. 1), three are hydroxamic acids: suberoylanilide hydroxamic acid (SAHA), used in early epigenetic studies, is marketed as Zolinza® for the treatment of

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cutaneous T-cell lymphoma;[6] belinostat is used for the treatment of peripheral T-cell lymphoma,[7] and panobinostat for the treatment of multiple myeloma.[8] Currently, most HDAC inhibitors in clinical trials are relatively nonselective among the nearly 20 known mammalian HDAC isozymes. The provision of more selective HDAC inhibitors with lower toxicity and greater potency are major unmet needs in the area of HDAC therapy.[9,10] The present work describes the synthesis of branched hydroxamic acids, and in particular branched analogues of SAHA, given its pivotal roles as a probe in structural biology,[11] in epigenetic studies,[12] and its continued use as an epigenetic anti-cancer agent.

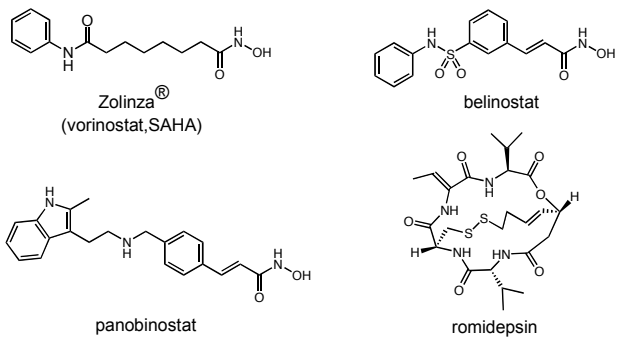
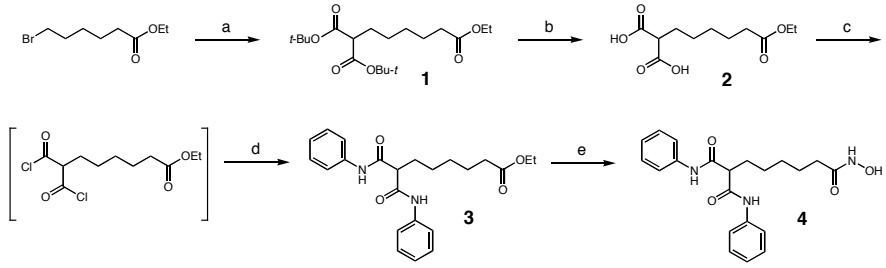


Figure 1. FDA-approved HDAC inhibitors.

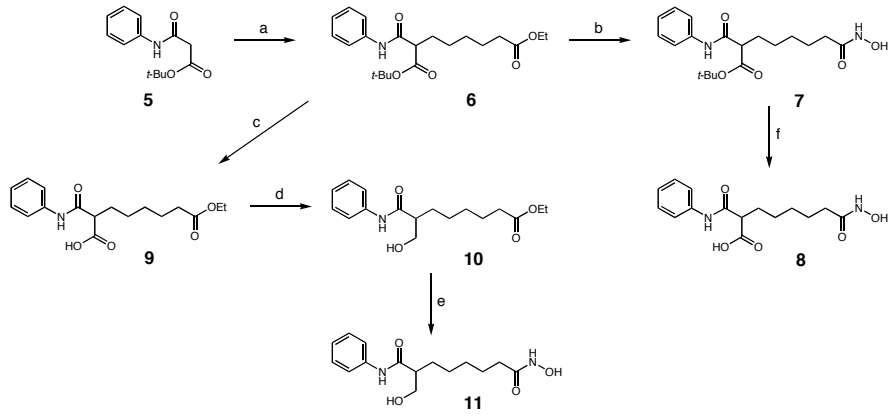
2. Results and Discussion

Branching of HDAC inhibitors in the region that bind to the protein surface can enhance inhibitor potency and has been predicted to improve isozyme selectivity.[13] The branched inhibitor **4** was found to be at least 6-fold more potent[14] than SAHA in an *in vitro* enzyme assay, and to be up to 20-fold more potent in cellular antiproliferation assays against a panel of nine multiple myeloma and non-Hodgkin's lymphoma cell lines.[15] The greatly increased overall inhibition of HDACs (pan-HDAC inhibition) superior pre-clinical data compared to SAHA can be attributed to the contacts made with the enzyme periphery by the additional anilide moiety. Improvements to the first two steps of the route to the branched hydroxamic acid **4** are here described (Scheme 1), enabling a range of symmetrical malonamides to be synthesised in two laboratory steps from the malonic acid **2**.



Scheme 1. Synthesis of a symmetrical bis-malonamide hydroxamic acid.[14] Reagents and conditions:
[a] NaH (1.1 equiv.) first added to di-*tert*-butyl malonate (1 equiv.), THF, 20 °C, 20 min then reflux, 16 h, 74%.
[b] CF_3CO_2H (6 equiv.), CH_2Cl_2, 20 °C, 16 h, 99%.
[c] $SOCl_2$ (6 equiv.), benzene, reflux, 2 h[14] then
[d] $PhNH_2$ (6 equiv.), pyridine (3 equiv.), CH_2Cl_2, 20 °C, 17 h, 76%.[14]
[e] NaOMe, (3 equiv.) and $HONH_2$ (2 equiv.), MeOH, 20 °C, 16 h, 68%.[14]

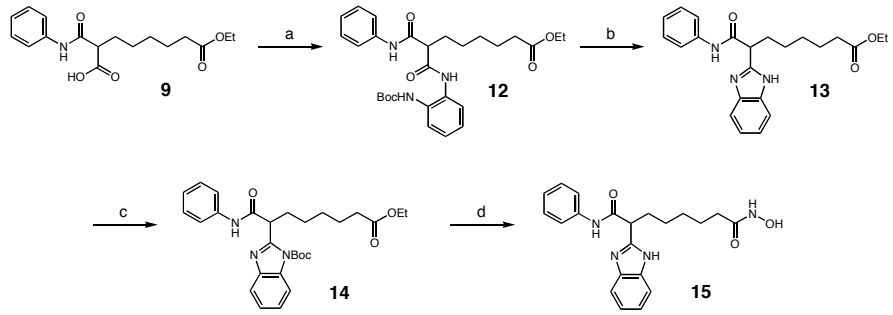
Alkylation of *N*-disubstituted malonamides with linear alkyl halides has been recently described.[16,17] In contrast, few alkylations of NH-malonamides have been described, which to our knowledge have been limited to benzylic halides[18,19] and diiodomethane,[20] being activated halides rather than typical linear alkyl halides. Notwithstanding that, the proposed route to branched derivatives of SAHA was by alkylation of a suitable malonamic ester. The strategy required the compatibility of the trifunctional compounds with reagents and with a transformation of only one group per step, for most sequences. The Boc-protected malonamic ester **5** was selected for the start of the investigation since differential reaction of the ester groups was expected to be reliable. Pleasingly, efficient alkylation of malonamic ester **5** was accomplished by treatment with NaH in THF followed by addition of ethyl 6-bromohexanoate to give the key intermediate **6** in 74% yield (Scheme 2). This compound provided access to a range of new trifunctional compounds, including three hydroxamic acids: direct conversion of **6** into the C-8 hydroxamic acid was achieved using excess aqueous hydroxylamine in the presence of a methanolic solution of 1M KOH and affording **7** in 29% yield. Cleavage of the *tert*-butyl group in 1:1 TFA:dichloromethane afforded the carboxylic acid **8**, unusual in also containing amide and a hydroxamic acid units. Under similar conditions, cleavage of the *tert*-butyl group in ester **6** afforded the desired carboxylic acid **9** which was selectively reduced with $NaBH_4$ in methanol to give the hydroxymethyl ester **10** (77%). This ester underwent conversion into the corresponding hydroxamic acid **11** by treatment with 5 equivalents of hydroxylamine in methanolic KOH; although conversion was efficient, isolation proved difficult, and only 12% was recovered.



Scheme 2. Synthesis of branched derivatives of SAHA. Reagents and conditions:
[a] NaH (1.1 equiv.), ethyl 6-bromohexanoate (1 equiv.), THF, 70 °C, 18 h, 74%.
[b] 50% aqueous $HONH_2$ (10 equiv.), 1 M KOH in MeOH, THF, 20 °C, 1 h, 29%.
[c] 1:1 CF_3CO_2H:CH_2Cl_2, 20 °C, 6 h, 80%.
[d] $ClCO_2Et$ (1.5 equiv.), Et_3N (1.2 equiv), THF, 0 °C, 30 min then $NaBH_4$ (3 equiv.),[21] MeOH, 10 °C, 1.5 h, 77%.
[e] Aqueous 50% $HONH_2$ (5 equiv.), 1M KOH in MeOH, THF, 20 °C, 1.5 h, 12%.
[f] 1:1 CF_3CO_2H:CH_2Cl_2, 20 °C, 30 min, 80%.

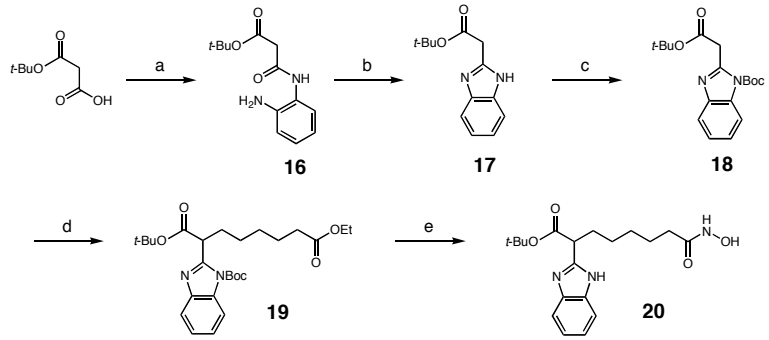
The benzimidazole ring system as a capping group for HDAC inhibitors has shown potential in models of pancreatic cancer,[22] and so was used in the present study as a representative heterocycle. Having trifunctional acid **9** available in quantity, the introduction of a range of amides at the branching position was feasible, and hence a series of the corresponding hydroxamic acids should be accessible. In a relatively challenging test of the protocol, the carboxylic acid **9** was reacted with *tert*-butyl *N*-(2-aminophenyl)carbamate using *N*-(3-dimethylaminopropyl)-*N*'-ethylcarbodiimide hydrochloride (EDC.HCl) and 1-hydroxybenzotriazole monohydrate (HOBt), giving the malonamide **12** in 66% yield. Ring closure was effected by heating in acetic acid at reflux, affording the benzimidazole **13** (77%). However, direct conversion of ester **13** into the desired hydroxamic acid **15** upon treatment with hydroxylamine and KOH in aqueous methanol resulted in difficulties in purification of the hydroxamic acid which was too polar for column chromatography and could not be satisfactorily purified by recrystallisation. This was circumvented by Boc-protection of **13** to give **14** and treatment with the standard solution containing hydroxylamine. Concomitant conversion into the hydroxamate and cleavage of the Boc group occurred, affording in one laboratory step the desired deprotected hydroxamic acid **15** in 50% yield. Scheme 3 established that differential amidation of **9** could be achieved, and given that ester to hydroxamic acid conversion is tolerated by a range of functional groups, is a likely general route to unsymmetrical malonamides and their corresponding hydroxamic acids. Additionally,

heterocyclisation involving the amide group should permit a variety of heterocycles to be installed using well-established ring-closures.



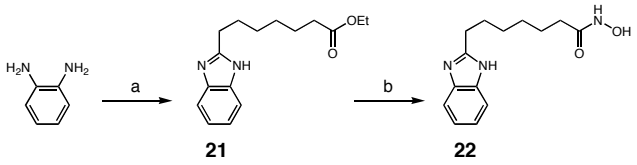
Scheme 3. Synthesis of a branched 2-benzimidazolinyl derivative of SAHA. Reagents and conditions:
[a] *tert*-Butyl *N*-(2-aminophenyl)carbamate (1 equiv.), EDC.HCl (1.1 equiv.), HOBt (1.1 equiv.), Et_3N (2.2 equiv), DMF, 20 °C, 18 h, 66%.
[b] TFA, reflux, 2 h, 75%.
[c] Di-*tert*-butyl dicarbonate (1.5 equiv.), THF, 20 °C, 7 d, 64% conversion.
[d] Aqueous 50% $HONH_2$ (10 equiv.), 1 M KOH in MeOH, THF, 20 °C, 6 h, 50%.

A more convergent approach to SAHA analogs containing heterocyclic rings at the branch point than that of Scheme 3 could be achieved if the order of reactions could be reversed, so that the heterocycle is installed earlier on, as an acetate ester such as **17** (Scheme 4). This sequence would also be desirable when other functionality present (or stereocentres) is incompatible with the conditions for the formation of heteroaromatic rings, usually quite harsh. The malonamic ester **16**, formed by acylation of 1,2-phenylenediamine with 3-*tert*-butoxy-3-oxopropanoic acid using *N*,*N*'-dicyclohexylcarbodiimide (DCC), underwent heterocylisation in acetic acid at 90 °C (96%) to give the benzimidazole **17**. Boc-protection gave the derivative **18** (97%) which was deprotonated using NaH in THF, and underwent alkylation using ethyl 6-bromohexanoate, albeit in low yield (33%); the *N*-Boc protected ester **19** underwent efficient conversion into the hydroxamic acid, again accompanied by selective *N*-Boc-deprotection, to give the branched hydroxamic acid **20** in 67% yield. These two strategies are complementary; different heterocycles may be attached to the same amide using Scheme 3, but different amides may also be attached to the same heterocycle using Scheme 4.



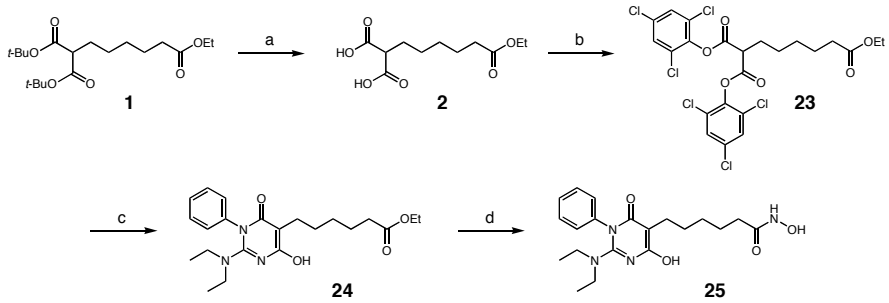
Scheme 4. Synthesis of a branched hydroxamic acid with a 2-benzimidazolyl capping group. Reagents and conditions:
[a] 1,2-Phenylenediamine (1 equiv.), *N,N'*-dicyclohexylcarbodiimide (1.1 equiv.), MeCN, 20 °C, 20 min, 50%.
[b] AcOH, 90 °C, 1 h, 96%.
[c] Di-*tert*-butyl dicarbonate (1.2 equiv.), THF, 20 °C, 3 d, 97%.
[d] NaH (1.1 equiv.), THF, 60 °C, 18 h, 33%**.**
[e] 50% aqueous $HONH_2$ (10 equiv.), 1 M KOH in MeOH, THF, 20 °C, 30 min, 67%.

For future comparison of biological activities of branched *versus* non-branched hydroxamic acids, two linear hydroxamic acids were prepared, the first being the parent compound **22** of the above branched benzimidazole derivatives, synthesised succinctly according to Scheme 5. For comparison with a heterocyclic analog of SAHA constrained by annulation and lacking an NH group, which in the case of SAHA is required for hydrogen-bonding with an aspartate residue (Asp99 in HDAC1), pyrimidinone **25** was selected, since it also contains a cyclic symmetrical malonamide motif.



Scheme 5. Succinct synthesis of a linear hydroxamic acid with a 2-benzimidazolyl capping group. Reagents and conditions:
[a] Suberic anhydride (1 equiv.), THF, 20 °C, 20 min; then 4% conc. H_2SO_4 in EtOH, 29%.
[b] Aqueous 50% $HONH_2$, 1 M KOH in MeOH, THF, 20 °C, 6 h, 61%.

Attempts to form the pyrimidinone **24** via the diacid dichloride of **2**, or by activation of the carboxylic acid groups of **2** with ethyl chloroformate were unsuccessful. The synthesis of pyrimidinone **24** was eventually accomplished by reaction of diacid **2** with 2,4,6-trichlorophenol in the presence of $POCl_3$[23] to give the ester **23** which with *N,N*-diethyl-*N'*-phenylguanidine at 150 °C underwent rapid conversion into the desired pyrimidinone **25**.



Scheme 6. Synthesis of a SAHA analog constrained by annulation. Reagents and conditions:
[a] CF_3CO_2H (6 equiv.), CH_2Cl_2, 20 °C, 24 h, 99%.
[b] 2,4,6-Trichlorophenol (2 equiv.), $POCl_3$ (2.6 equiv.), 100 °C, 5 h, 49%.
[c] *N,N*-Diethyl-*N'*-phenylguanidine (1 equiv.), 5 min, 150 °C, 68%.

[d] Aqueous 50% $HONH_2$ (10 equiv.), 1M KOH in MeOH, THF, 20 °C, 2 h, 51%.

3. Conclusion

Alkylation of malonamic esters has been shown to provide a direct approach to derivatives of suberoylanilide hydroxamic acid (SAHA) that are branched *alpha* to the amide carbon atom, a location pivotal for enhancing biological and therapeutic activity. Deprotonation of malonamic esters was conveniently achieved using NaH in THF followed by treatment with an ester of 6-bromohexanoic acid; no protection of the amidic NH group was necessary. By this means, carboxylic acid, ester, amide, hydroxymethyl and 2-benzimidazolyl branching units have been appended to the SAHA backbone. A 2-benzimidazolyl unit can be added by cyclisation, or alternatively by alkylation of a 2-benzimidazolyl acetate. These complementary routes enable variation of either branching unit at a time: the heterocyclic branching unit or alternatively the carboxy chain. Improvements to synthesis of branched hydroxamic acids from malonyl derivatives have also been achieved, and in addition the synthesis of a new SAHA derivative constrained by heterocyclic annulation.

4. Experimental Section

4.1 General. All moisture-sensitive reactions were performed under an atmosphere of nitrogen and the glassware was pre-dried in an oven (130 °C). Evaporation refers to the removal of solvent under reduced pressure. Melting points were measured by a microscope hot-stage Electrothermal 9100 apparatus. Infra-red (IR) spectra were recorded on a Perkin-Elmer PE-983 spectrophotometer. ^{1}H NMR spectra were recorded on a Bruker AC300 (300 MHz) spectrometer or a Bruker AMX 500 (125 MHz) spectrometer; data are reported in parts per million (δ). Coupling constants (*J*) are given in Hertz (Hz). The following abbreviations were used in signal assignments: singlet (s), broad singlet (br s), doublet (d), triplet (t), quartet (q), and multiplet (m). ^{13}C NMR spectra were recorded on Bruker AMX300 (75 MHz), Bruker AMX400 (100 MHz) or Bruker AMX 500 (125 MHz) spectrometers; data are reported in parts per million (δ), with $CHCl_3$ as an internal standard. Mass spectra were recorded on a VG7070H mass spectrometer with Finigan Incos II data system at University College London. Optical rotations were measured using a Perkin-Elmer 343 digital polarimeter. Thin-layer chromatography was performed on Merck 0.2 mm aluminium-backed silica gel 60 F_{254} plates and visualised by UV (254 nm) or by staining with alkaline potassium permanganate spray and subsequent heating. Flash column chromatography was performed using Merck 0.040-0.063 mm, 230-400 mesh silica gel.

The following compounds were prepared according to the literature: *tert*-butyl 3-oxo-3-(phenylamino)propanoate (**5**);[14] *tert*-butyl *N*-(2-aminophenyl)carbamate;[24] *tert*-butyl 3-

oxopropanoate;[25] oxonane-2,9-dione;[26] bis(2,4,6-trichlorophenyl) malonate;[23] *N,N*-diethyl-*N'*-phenylguanidine.[27]

4.2 Synthesis

6-Ethyl 1,1-bis(*tert*-butyl)hexane-1,1,6-tricarboxylate (1). To a solution of di-*tert*-butyl malonate (5.0 g, 23.1 mmol) in dry tetrahydrofuran (230 mL) was added sodium hydride (1.02 g of a 60% dispersion in mineral oil, 25.4 mmol). After stirring at 20 °C for 20 min, ethyl-6-bromohexanoate (5.16 g, 23.1 mmol) was added and the mixture was heated at reflux for 16 h. After allowing to cool, the solvent was then evaporated and water (50 mL) added to the residue. The mixture was extracted with diethyl ether (2 x 30 mL) and the combined organic layers dried ($MgSO_4$), filtered and evaporated. Column chromatography (1:9 ethyl acetate:40-60 °C petroleum ether) of the oily residue gave ester **1** (6.11 g, 74%) as a colourless oil; IR ν_{max} 2935, 1732, 1369 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 4.04 (2H, q, *J*=7.1 Hz, CH_2O), 3.02 (2H, t, *J*=7.6 Hz, CH_2COOEt), 2.20 (2H, t, *J*=7.5 Hz, $CHCH_2$), 1.79-1.70 (2H, m, CH_2CH_2COOEt, 1.63-1.52 (2H, m, $CHCH_2CH_2CH_2$), 1.38 (18H, s, $C(CH_3)_3$), 1.34-1.25 (2H, m, $CHCH_2CH_2$), 1.17 (3H, t, *J*=7.1 Hz, CH_2CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 173.5 (*C*OOEt), 168.8 (*C*OOC$(CH_3)_3$), 81.1 (*C*$(CH_3)_3$), 60.1 (*C*H_2CH_3), 53.8 (CH), 34.1 (*C*H_2COOEt), 28.7 (CH*C*H_2), 28.3 (*C*$H_2CH_2CH_2$COOEt), 27.8 (C(*C*$H_3)_3$), 26.8 ($CHCH_2CH_2$), 24.6 (*C*H_2CH_2COOEt), 14.2 (*C*H_3CH_2); *m*/*z* (CI, %) 381 (M+H, 100), 269 (25), 247 (75), 201 (13); HRMS (M+Na) calcd for $C_{19}H_{34}O_6$ 381.2253. Found: 381.2260.

2-Carboxyoctanedioic acid 8-ethyl ester (2). To a stirred solution of 6-ethyl 1,1-bis(*tert*-butyl) hexane-1,1,6-tricarboxylate (**1**) (6.09 g, 17.0 mmol) in dichloromethane (170 mL) was added trifluoroacetic acid (11.6 g, 102 mmol) and the solution stirred for 24 h. The volatile material was then evaporated to give the acid **2** (4.14 g, 99%) as a white crystalline solid, mp 71-73 ˚C; IR ν_{max} 2939, 2613, 1705 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 4.12 (2H, q, *J*=7.1 Hz, CH_2CH_3), 3.42 (1H, t, *J*=7.4 Hz, CH), 2.30 (2H, t, *J*=7.4 Hz, CH_2COOEt), 1.98-1.85 (2H, m, CH_2CH_2COOEt), 1.65-1.52 (2H, m, $CHCH_2$), 1.43-1.25 (4H, m, $CHCH_2CH_2$, $CHCH_2CH_2CH_2$), 1.18 (3H, t, *J*=7.1 Hz, CH_2CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 174.6 (COOH), 174.5 (COOEt), 60.7 (*C*H_2CH_3), 51.5 (CH), 34.2 (*C*H_2COOEt), 28.6 ($CHCH_2CH_2CH_2$), 28.5 ($CHCH_2$), 26.8 ($CHCH_2CH_2$), 24.5 (*C*H_2CH_2COOEt), 14.2 (CH_2CH_3); *m*/*z* (CI, %) 247 (M+H, 31), 201 (21), 185 (100), 157 (27). Anal. Calcd for $C_{11}H_{18}O_6$ C, 53.65; H, 7.37. Found: C, 53.48; H, 7.41.

***tert*-Butyl 3-oxo-3-(phenylamino)propanoate (5)**. Oxalyl chloride (11.7 g, 92.3 mmol) was added slowly to a stirred solution of 3-*tert*-butoxy-3-oxopropanoic acid (4.93 g, 30.8 mmol) in dichloromethane (300 mL) followed by DMF (10 drops). The mixture was warmed to 40 ˚C for 2 h then evaporated. The resulting red oil was dissolved in dichloromethane (300 mL),

and aniline (3.09 g, 33.9 mmol) added, giving a precipitate. DMAP (4.14 g, 33.9 mmol) was added and the mixture was then stirred at 20 °C for 2 h. The solvent was evaporated and the residue dissolved in ethyl acetate (50 mL). The organic layer was washed with 2 M hydrochloric acid (2 x 30 mL) followed by saturated aqueous sodium hydrogen carbonate (30 mL), then dried ($MgSO_4$) and filtered. The solvent was evaporated to leave a red oil which was purified by column chromatography (3:7 ethyl acetate:40-60 petroleum ether) to give ester **5** (6.92 g, 89%) as a white crystalline solid, mp 72-74 ˚C; IR ν_{max} 3308, 3267, 1721, 1556 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 9.35 (1H, s, NH), 7.55 (2H, dd, *J*=0.9, 8.5 Hz, 2,6-aryl), 7.29 (2H, t, *J*=7.9 Hz, 3,5-aryl), 7.08 (1H, t, *J*=7.4 Hz, 4-aryl), 3.36 (2H, s, CH_2), 1.48 (9H, s, $C(CH_3)_3$); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 168.9 (*C*OOBu^t), 163.8 (CONH), 137.7 (1-aryl), 128.9 (3,5-aryl), 124.4 (4-aryl), 120.1 (2,6-aryl), 82.9 ($C(CH_3)_3$), 42.9 (CH_2), 28.0 ($(CH_3)_3$); *m*/*z* (CI, %) 235 (M+, 41), 179 (81), 162 (17), 119 (19), 93 (100). Anal. Calcd for $C_{13}H_{17}NO_3$ C, 66.36; H, 7.28; N, 5.95. Found C, 66.35; H, 7.34; N, 5.98.

1-*tert*-Butyl 8-ethyl-2-(phenylcarbamoyl)octanedioate (6). Sodium hydride (773 mg of a 60 % dispersion in oil, 19.3 mmol) was added slowly to a stirred solution of *tert*-butyl 3-oxo-3-(phenylamino)propanoate (**5**) (4.45 g, 17.57 mmol) in dry tetrahydrofuran (175 mL) at 0 °C. After stirring at 20 °C for 20 min, ethyl 6-bromohexanoate (3.92 g, 17.6 mmol) was added and the mixture heated at 70 ˚C for 18 h. After allowing to cool the solvent was evaporated. The residue was taken up in ethyl acetate (50 mL) and washed with 2 M hydrochloric acid (2 x 20 mL) then with brine (20 mL), dried ($MgSO_4$) and filtered. The residue was purified by column chromatography (1:9 ethyl acetate:40-60 °C petroleum ether) to give the ester **6** (4.94 g, 74%) as pale yellow crystals, mp 65-66 ˚C; IR ν_{max} 3307, 2944, 1726, 1656, 1554 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.75 (1H, s, NH), 7.54 (2H, d, *J*=8.3 Hz, 2,6-aryl), 7.32 (2H, t, *J*=7.9 Hz, 3,5-aryl), 7.10 (1H, t, *J*=7.4 Hz, 4-aryl), 4.11 (2H, q, *J*=7.1 Hz, C*H*$_2$CH$_3$), 3.24 (1H, t, *J*=7.3 Hz, CH), 2.28 (2H, t, *J*=7.4 Hz, CH_2COO), 2.00-1.90 (2H, m, CHC*H*$_2$), 1.68-1.57 (2H, m, C*H*$_2$CH$_2$COO), 1.49 (9H, s, $(CH_3)_3$), 1.44-1.32 (4H, m, C*H*$_2$CH$_2$CH$_2$COO, CHCH$_2$C*H*$_2$), 1.24 (3H, t, *J*=7.1 Hz, CH$_2$C*H*$_3$); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 173.6 (COOEt), 172.0 (CONH), 167.0 (COOBu*t*), 137.8 (1-aryl), 129.0 (3,5-aryl), 124.3 (4-aryl), 119.9 (2,6-aryl), 82.7 ($C(CH_3)_3$), 60.2 (*C*H$_2$CH$_3$), 54.4 (CH), 34.2 (*C*H$_2$COO), 31.5 (CH*C*H$_2$), 28.6 (*C*H$_2$CH$_2$CH$_2$CHOO), 28.0 ($(CH_3)_3$), 26.9 (CHCH$_2$*C*H$_2$), 24.6 (*C*H$_2$CH$_2$COO), 14.2 (CH$_2$*C*H$_3$); *m*/*z* (EI, %) 377 (M+, 13), 322 (12), 258 (11), 179 (53), 161 (37), 93 (100). Anal. Calcd for $C_{21}H_{31}NO_5$ C, 66.82; H, 8.28; N, 3.71. Found C, 66.72; H, 8.32; N, 3.69.

***tert*-Butyl 8-(hydroxyamino)-8-oxo-2-(phenylcarbamoyl)octanoate (7)**. To a solution of 1-*tert*-butyl 8-ethyl 2-(phenylcarbamoyl)octanedioate (**6**) (300 mg, 0.79 mmol) in tetrahydrofuran (8 mL) was added 50% aqueous hydroxylamine (0.53 mL, 7.95 mmol) and 1 M potassium hydroxide in methanol (2.37 mL, 2.37 mmol) dropwise. The mixture was stirred

at 20 °C for 1 h then acidified with 2 M hydrochloric acid. The solvent was evaporated to a volume of 5 mL then water (20 mL) added. The aqueous mixture was extracted with ethyl acetate (4 x 15 mL) and the combined yellow extracts dried over Na_2SO_4. Evaporation of the solvent gave a yellow oil which was purified by column chromatography (ethyl acetate) to give the hydroxamic acid **7** (84 mg, 29%) as a yellow oil; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.02 (1H, s, NH), 7.52 (2H, d, *J*=7.7 Hz, 2,6-aryl), 7.26 (2H, t, *J*=7.7 Hz, 3,5-aryl), 7.06 (1H, t, *J*=7.3 Hz, 4-aryl), 3.27 (1H, t, *J*=7.0 Hz, CH), 2.13-2.03 (2H, m, C*H*$_2$CONHOH), 1.95-1.83 (2H, m, CHC*H*$_2$), 1.64-1.50 (2H, m, C*H*$_2$CH$_3$CONHOH), 1.44 (9H, s, C(CH$_3$)$_3$), 1.40-1.25 (4H, m, CHCH$_2$C*H*$_2$, CHCH$_2$CH$_2$C*H*$_2$); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.7 (*C*OOC(CH$_3$)$_3$), 171.3 (*C*ONHOH), 167.8 (CONHPh), 137.7 (1-aryl), 128.9 (3,5-aryl), 124.6 (4-aryl), 120.3 (2,6-aryl), 82.7 (*C*(CH$_3$)$_3$), 54.2 (CH), 32.5 (*C*H$_2$CONHOH), 30.5 (CH*C*H$_2$), 28.3 (CHCH$_2$CH$_2$*C*H$_2$), 28.0 (C(*C*H$_3$)$_3$), 26.6 (*C*H$_2$CH$_2$CONHOH), 25.0 (CHCH$_2$*C*H$_2$); *m*/*z* (CI, %) 387 (M+Na, 100), 365 (M+H, 45), 328 (22), 309 (35). HRMS calcd for $C_{19}H_{28}N_2O_5$ (M+H) 365.2071. Found: 365.2079.

8-(Hydroxyamino)-8-oxo-2-(phenylcarbamoyl)octanoic acid (8). To a solution of *tert*-butyl 8-(hydroxyamino)-8-oxo-2-(phenylcarbamoyl)octanoate (**7**) (170 mg, 0.47 mmol) in dichloromethane (2 mL) was added trifluoroacetic acid (2 mL) and the mixture stirred for 30 min. Evaporation of the solvent gave a pale yellow solid which was washed with cold diethyl ether then with dichloromethane to give the hydroxamic acid **8** (116 mg, 80%) as a white solid, mp 150-152 °C; IR ν_{max} 2931, 2856, 1733, 1597, 1547 cm^{-1}; ^{1}H NMR (CD_3OD, 300 MHz) δ 7.55 (2H, d, *J*=7.6 Hz, 2,6-aryl), 7.30 (2H, t, *J*=7.3 Hz, 3,5-aryl), 7.09 (1H, t, *J*=7.1 Hz, 4-aryl), 3.44 (1H, t, *J*=7.1 Hz, CH), 2.07 (2H, t, *J*=6.8 Hz, C*H*$_2$CONH), 2.02-1.86 (2H, m, CHC*H*$_2$), 1.76-1.58 (2H, m, C*H*$_2$CH$_2$CONH), 1.53-1.30 (4H, m, CHCH$_2$C*H*$_2$, CHCH$_2$CH$_2$C*H*$_2$); ^{13}C NMR (CD_3OD, 75 MHz) δ 173.4 (COOH), 173.0 (CONHPh), 170.4 (CONHOH), 139.6 (1-aryl), 129.9 (3,5-aryl), 125.5 (4-aryl), 121.4 (2,6-aryl), 54.4 (CH), 33.7 (*C*H$_2$CONH), 30.2 (CH*C*H$_2$), 29.9 (CHCH$_2$CH$_2$*C*H$_2$), 28.1 (*C*H$_2$CH$_2$CONH), 26.3 (CHCH$_2$*C*H$_2$); *m*/*z* (CI, %) 331 (M+Na, 100), 309 (M+H, 83). Anal. Calcd for $C_{15}H_{20}N_2O_5$ C, 58.43; H, 6.54; N, 9.09. Found C, 58.16; H, 6.51; N, 8.75.

8-Ethoxy-8-oxo-2-(phenylcarbamoyl)octanoic acid (9). Trifluoroacetic acid (9 mL) was added to a solution of 1-*tert*-butyl-8-ethyl-2-(phenylcarbamoyl)octanedioate (**6**) (1.33 g, 3.52 mmol) in dichloromethane (9 mL) and the solution stirred for 6 h. The solvent was evaporated and the residue washed with a 1:1 diethyl ether:40-60 °C petroleum ether to give the acid **9** (0.91 g, 80%) as a white powder, mp 108-110 °C; IR ν_{max} 3426, 3340, 2933, 1730, 1600 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 10.17 (1H, br s, OH), 9.05 (1H, s, NH), 7.50 (2H, d, *J*=7.8 Hz, 2,6-aryl), 7.30 (2H, t, *J*=7.7 Hz, 3,5-aryl), 7.14 (1H, t, *J*=7.3 Hz, 4-aryl), 4.12 (2H, q, *J*=7.1 Hz, C*H*$_2$CH$_3$), 3.47 (1H, t, *J*=6.2 Hz, CH), 2.29 (2H, t, *J*=7.3 Hz, CH$_2$COO), 2.06-1.95 (2H,

m, CHCH_2), 1.68-1.53 (2H, m, CH_2CH$_2$COO), 1.48-1.30 (4H, m, CH_2CH$_2$CH$_2$COO, CHCH$_2$CH_2), 1.24 (3H, t, *J*=7.1 Hz, CH$_3$); ^{13}C NMR (CDCl$_3$, 75 MHz) δ 175.1 (COOH), 174.6 (COOEt), 169.1 (CONH), 136.7 (1-aryl), 129.1 (3,5-aryl), 125.5 (4-aryl), 120.8 (2,6-aryl), 60.9 (*C*H$_2$CH$_3$), 52.2 (CH), 34.1 (*C*H$_2$COO), 31.1 (CH*C*H$_2$), 28.3 (*C*H$_2$CH$_2$CH$_2$COO), 26.5 (CHCH$_2$*C*H$_2$), 24.4 (*C*H$_2$CH$_2$COO), 14.1 (CH$_3$); *m*/*z* (EI, %) 321 (M+, 8), 277 (43), 232 (54), 179 (36), 135 (97), 93 (100). Anal. Calcd for $C_{17}H_{23}NO_5$ C, 63.53; H, 7.21; N, 4.36. Found C, 63.08; H, 7.18; N, 3.92.

Ethyl 7-(hydroxymethyl)-8-oxo-8-(phenylamino)octanoate (10). To a stirred solution of 8-ethoxy-8-oxo-2-(phenylcarbamoyl)octanoic acid (**9**) (300 mg, 0.94 mmol) in dry tetrahydrofuran (3.0 mL) at 0 ˚C was added triethylamine (114 mg, 1.13 mmol) and ethyl chloroformate (152 mg, 1.40 mmol). The mixture was stirred at 0 ˚C for 30 min then filtered. The solid was washed with tetrahydrofuran (2 x 3 mL) and the combined filtrate was cooled to 10 ˚C. Sodium borohydride (107 mg, 2.82 mmol) was added in one portion, followed by dropwise addition of methanol (0.6 mL) over a period of 1 h. After stirring for a further 30 min the reaction was quenched by dropwise addition of 2 M hydrochloric acid, then extracted with dichloromethane (2 x 10 mL). The combined organic layers were dried (MgSO$_4$), filtered and evaporated. The residue was purified by column chromatography (3:2 ethyl acetate:40-60 °C petroleum ether) to give ester **10** (222 mg, 77%) as a crystalline white solid, mp 132-134 ˚C; IR ν_{max} 2935, 2669, 1684, 1408 cm^{-1}; ^{1}H NMR (CDCl$_3$, 300 MHz) δ 8.73 (1H, s, NH), 7.53 (2H, d, *J*=7.7 Hz, 2,6-aryl), 7.23 (2H, t, *J*=7.9 Hz, 3,5-aryl), 7.04 (1H, t, *J*= 7.4 Hz, 4-aryl), 4.08 (2H, q, *J*=7.1 Hz, C*H*$_2$CH$_3$), 3.95 (1H, br s, OH), 3.73 (1H, t, *J*=9.0 Hz, C*H*$_2$OH), 3.73-3.53 (1H, m, C*H*$_2$OH), **2.45 (1H, m, CH),** 2.22 (2H, t, *J*=7.4 Hz, CH$_2$COO), 1.56 (3H, CHCH*H*, C*H*$_2$CH$_2$COO), 1.40-1.18 (8H, m, CHCH*H*, C*H*$_2$CH$_2$CH$_2$COO, CHCH$_2$C*H*$_2$, C*H*$_3$); ^{13}C NMR (CDCl$_3$, 75 MHz) δ 174.1 (COOEt), 174.1 (CONH), 138.1 (1-aryl), 128.8 (3,5-aryl), 124.2 (4-aryl), 120.2 (2,6-aryl), 63.5 (CH$_2$OH), 60.4 (*C*H$_2$CH$_3$), 49.7 (CH), 34.2 (*C*H$_2$COO), 29.0 (*C*H$_2$CH$_2$CH$_2$COO), 28.7 (CH*C*H$_2$), 26.9 (CHCH$_2$*C*H$_2$), 24.6 (*C*H$_2$CH$_2$COO), 14.2 (CH$_3$); *m*/*z* (CI, %) 308 (M+H, 100), 262 (53), 197 (63), 169 (51). Anal. Calcd for $C_{17}H_{25}NO_4$ C, 66.43; H, 8.20; N, 4.56. Found C, 66.49; H, 8.34; N, 4.65.

***N*^{8}-hydroxy-2-(hydroxymethyl)-*N*^{1}-phenyloctanediamide (11).** To a stirred solution of ethyl 7-(hydroxymethyl)-8-oxo-8-(phenylamino)octanoate (**10**) (600 mg, 1.95 mmol) in tetrahydrofuran (20 mL) was added 50% aqueous hydroxylamine (0.64 mL, 9.76 mmol) and 1 M potassium hydroxide in methanol (3.9 mL, 3.9 mmol) and the resultant solution stirred for 1.5 h. Methanol was evaporated from the yellow solution then 0.5M hydrochloric acid (10 mL) added. The hydroxamic acid **11** (70 mg, 12%) crystallised from the aqueous solution as cream solid, mp 150-151 ˚C; IR ν_{max} 3398, 3291, 3185, 2920, 1626 cm^{-1}; ^{1}H NMR ((CD$_3$)$_2$SO, 300 MHz) δ 10.30 (1H, s, NH), 9.83 (1H, s, NHO*H*), 8.62 (1H, s, NH), 7.62 (2H, d, *J*=7.8

Hz, 2,6-aryl), 7.27 (2H, t, *J*=7.9 Hz, 3,5-aryl), 7.00 (1H, t, *J*=7.4 Hz, 4-aryl), 4.71 (1H, t, *J*=5.0 Hz, OH), 3.64-3.55 (1H, m, C*H*HOH), 3.45 (1H, td, *J*=5.1, 10.2 Hz, CH*H*OH), 2.57-2.45 (1H, m, CH), 1.90 (2H, t, *J*=7.3 Hz, CH_2CONH), 1.54-1.35 (4H, m, CH_2CH$_2$CONH, CHCH_2), 1.30-1.17 (4H, m, CHCH$_2$CH$_2$CH_2, CHCH$_2$CH_2); ^{13}C NMR ((CD$_3$)$_2$SO, 75 MHz) δ 173.0 (PhNHCO), 169.0 (CONHOH), 139.3 (1-aryl), 128.5 (3,5-aryl), 122.9 (4-aryl), 119.1 (2,6-aryl), 62.9 (CH$_2$OH), 49.8 (CH), 32.2 (*C*H$_2$CONH), 28.7 (CHCH$_2$CH$_2$*C*H$_2$), 28.6 (CH*C*H$_2$), 26.6 (CHCH$_2$*C*H$_2$), 25.0 (*C*H$_2$CH$_2$CONH); *m*/*z* (CI, %) (M+Na, 100), 285 (17), 276 (15), 242 (13), 217 (13). Anal. Calcd for $C_{15}H_{22}N_2O_4$ C, 61.21; H, 7.53; N, 9.52. Found: C, 60.71; H, 7.49; N, 9.39.

Ethyl 8-(2-(*tert*-butoxycarbonylamino)phenylamino)-8-oxo-7-(phenylcarbamoyl)-octanoate (12). To a stirred solution of 8-ethoxy-8-oxo-2-(phenylcarbamoyl)octanoic acid (**9**) (1.0 g, 3.11 mmol) in DMF (30 mL) was added *tert*-butyl 2-aminophenylcarbamate (648 mg, 3.11 mmol), triethylamine (692 mg, 6.84 mmol), EDC.HCl (657 mg, 3.42 mmol) and HOBt (462 mg, 3.42 mmol). The mixture was stirred for 18 h then evaporated and water (50 mL) added to the residue. The mixture was extracted with ethyl acetate (2 x 25 mL) and the combined organic layers were washed with water (15 mL), saturated aqueous ammonium chloride (15 mL) and lastly with saturated aqueous sodium hydrogen carbonate (15 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to give a yellow oil which was purified by column chromatography (1:2 40-60 °C petroleum ether: ethyl acetate) to give amide **12** (1.05 g, 66%) as a white solid, used without further purification.

Ethyl 7-(1*H*-benzo[*d*]imidazol-2-yl)-8-oxo-8-(phenylamino)octanoate (13). To a solution of ethyl 8-(2-(*tert*-butoxycarbonylamino)phenylamino)-8-oxo-7-(phenylcarbamoyl)octanoate (**12**) (0.88 g, 1.72 mmol) in dichloromethane (9 mL) was added trifluoroacetic acid (9 mL). The solution was heated at reflux for 2 h. The solvent was evaporated and the residue recrystallised from a mixture of ethyl acetate and 40-60 °C petroleum ether to give ester **13** (505 mg, 75%) as a white crystalline solid, mp 211-212 ˚C; IR ν_{max} 3284, 2926, 1734, 1666 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 11.95 (1H, s, NH), 11.47 (1H, s, NH), 7.66 (3H, m, 2,6-aryl, 7-benzimidazolyl), 7.48 (1H, m, 4-benzimidazolyl), 7.25 (4H, m**,** 3,5-aryl, 5,6-benzimidazolyl), 7.10 (1H, t, *J*=7.4 Hz, 4-aryl), 4.65 (1H, t, *J*=7.7 Hz, CH), 4.02 (2H, q, *J*=7.1 Hz, CH_2CH$_3$), 2.32 (1H, m, CHC*H*H), 2.15 (1H, m, CHCH*H*), 1.99 (2H, t, *J*=7.5 Hz, CH$_2$COO), 1.36 (4H, m, CHCH$_2$CH_2, CH_2CH$_2$COO), 1.19 (5H, m, CH_2CH$_2$CH$_2$COO, CH$_2$CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 173.5 (COO), 170.8 (NHCO), 153.3 (2-benzimidazolyl), 142.1 (7a-benzimidazolyl), 138.2 (1-aryl), 134.2 (3a-benzimidazolyl), 129.0 (3,5-aryl), 124.7 (4-aryl), 123.2 (7-benzimidazolyl), 122.4 (4-benzimidazolyl), 120.4 (2,6-aryl), 118.3 (6-benzimidazolyl), 111.7 (5-benzimidazolyl), 60.1 (*C*H$_2$CH$_3$), 48.3 (CH), 34.0 (*C*H$_2$COO), 33.6 (CH*C*H$_2$), 28.5 (*C*H$_2$CH$_2$CH$_2$COO), 27.2 (CHCH$_2$*C*H$_2$), 24.5

(CH_2CH_2COO), 14.2 (CH_2CH_3); *m*/*z* (CI, %) 394 (M+H, 100), 293 (58), 274 (23). Anal. Calcd for $C_{23}H_{27}N_3O_3$ C, 70.21; H, 6.92; N, 10.68. Found C, 70.17; H, 7.01; N, 10.79.

***tert*-Butyl 2-(8-ethoxy-1,8-dioxo-1-(phenylamino)octan-2-yl)-1*H*-benzo[*d*]imidazole-1-carboxylate (14)**. Di-*tert*-butyl dicarbonate (403 mg, 1.85 mmol) was added to a stirred solution of ethyl 7-(1*H*-benzo[*d*]imidazol-2-yl)-8-oxo-8-(phenylamino)octanoate (**13**) (484 mg, 1.23 mmol) in tetrahydrofuran (12 mL). The solution was stirred at 20 °C for 7 d. Evaporation gave a residue was purified by column chromatography (1:4 ethyl acetate:40-60 °C petroleum ether) to give recovered **13** (220 mg, 45%) and ester **14** (210 mg, 35%) as a colourless oil; IR ν_{max} 3319, 2936, 1732, 1600 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 9.46 (1H, s, NH), 7.94-7.89 (1H, m, 7-benzimidazolyl), 7.82-7.77 (1H, m, 4-benzimidazolyl), 7.57 (2H, d, *J*=8.5 Hz, 2,6-aryl), 7.39-7.35 (2H, m, 5,6-benzimidazolyl), 7.28 (2H, t, *J*=7.5 Hz, 3,5-aryl), 7.04 (1H, t, *J*=7.5 Hz, 4-aryl), 4.82 (1H, t, *J*=7.2 Hz, CH), 4.07 (2H, q, *J*=7.1 Hz, CH_2CH_3), 2.38-2.25 (4H, m, $CHCH_2$, CH_2COO), 1.72 (9H, s, $C(CH_3)_3$), 1.69-1.57 (2H, m, CH_2CH_2COO), 1.55-1.35 (4H, m, $CHCH_2CH_2$, $CHCH_2CH_2CH_3$), 1.21 (3H, t, *J*=7.1 Hz, CH_2CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 173.7 (COOEt), 168.1 (CONH), 154.1 ($COOBu^t$), 149.2 (2-benzimidazolyl), 141.7 (7a-benzimidazolyl), 138.2 (1-aryl), 132.6 (3a-benzimidazolyl), 128.9 (3,5-aryl), 125.0 (6-benzimidazolyl), 124.5 (5-benzimidazolyl), 124.1 (4-aryl), 119.9 (7-benzimidazolyl), 119.7 (2,6-aryl), 115.2 (4-benzimidazolyl), 86.7 ($C(CH_3)_3$), 60.2 (CH_2CH_3), 48.1 (CH), 34.2 (CH_2COO), 33.5 ($CHCH_2$), 28.9 ($CHCH_2CH_2CH_2$), 28.1 ($C(CH_3)_3$), 27.0 ($CHCH_2CH_2$), 24.7 (CH_2CH_2COO), 14.3 (CH_2CH_3); *m*/*z* (CI, %) 516 (M+Na, 49), 494 (M+H, 92), 394 (28), 335 (100), 276 (19). HRMS (M+H) calcd for $C_{28}H_{35}N_3O_5$ 494.2655. Found: 494.2650.

2-(1*H*-Benzo[*d*]imidazol-2-yl)-N^8-hydroxy-N^1-phenyloctanediamide (15). To a stirred solution of *tert*-butyl 2-(8-ethoxy-1,8-dioxo-1-(phenylamino)octan-2-yl)-1*H*-benzo[*d*]imidazole-1-carboxylate (**14**) (210 mg, 0.43 mmol) in tetrahydrofuran (4 mL) was added 50% aqueous hydroxylamine (0.28 mL, 4.25 mmol) followed by dropwise addition of 1 M potassium hydroxide in methanol (1.29 mL). The pale yellow solution was stirred for 6 h then evaporated. Water (10 mL) was added to the residue followed by saturated aqueous ammonium chloride (10 mL) and the precipitate collected by filtration. The solid was recrystallised from ethanol to give the hydroxamic acid **15** (81 mg, 50%) as a white crystalline solid, mp 184-185 °C; IR ν_{max} 3261, 3093, 2924, 1637 cm^{-1}; ^1H NMR (CD_3OD, 300 MHz) δ 7.75-7.45 (4H, m, 2,6-aryl, 4,7-benzimidazolyl), 7.27 (2H, t, *J*=7.5 Hz, 3,5-aryl), 7.24-7.18 (2H, m, 5,6-benzimidazolyl), 7.06 (1H, t, *J*=7.5 Hz, 4-aryl), 4.20-4.00 (1H, m, CH), 2.28-1.97 (4H, m, $CHCH_2$, CH_2CONH), 1.68-1.50 (2H, m, CH_2CH_2CONH), 1.48-1.30 (4H, m, $CHCH_2CH_2$, $CHCH_2CH_2CH_2$); ^{13}C NMR ($(CD_3)_2SO$, 125 MHz) δ 169.3 (PhNHCO), 169.3 (CONHOH), 152.7 (2-benzimidazolyl), 142.7 (benzimidazolyl), 138.9 (1-aryl), 134.6

(benzimidazolyl), 128.7 (3,5-aryl), 123.5 (4-aryl), 121.8 (benzimidazolyl), 121.0 (benzimidazolyl), 119.3 (benzimidazolyl), 118.3 (benzimidazolyl), 111.3 (benzimidazolyl), 47.8 (CH), 32.2 (CH_2CONHOH), 31.1 (CHCH_2), 28.4 (CHCH$_2$CH$_2$$CH_2$), 26.8 (CHCH$_2$$CH_2$), 25.0 ($CH_2CH_2$CONHOH). Anal. Calcd for $C_{21}H_{24}N_4O_3$.0.5H_2O C, 64.75; H, 6.47; N, 14.39. Found C, 65.18; H, 6.36; N, 14.13.

***tert*-Butyl 3-(2-aminophenylamino)-3-oxopropanoate (16)**. To a solution of 3-*tert*-butoxy-3-oxopropanoic acid (200 mg, 1.25 mmol) and 1,2-phenylenediamine (135 mg, 1.25 mmol) in acetonitrile (5 mL) was added a solution of DCC (283 mg, 1.37 mmol) in acetonitrile (2 mL) and the reaction stirred for 20 min. The white suspension was filtered and the filtrate evaporated to leave a dark yellow oil which was purified by column chromatography (1:1 ethyl acetate:40-60 °C petroleum ether) followed by recrystallisation from a mixture of ethyl acetate and 40-60 °C petroleum ether to give amide **16** (155 mg, 50%) as a white crystalline solid, mp 122-123 °C; IR ν_{max} 3428, 3318, 1718, 1655 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.89 (1H, s, NH), 7.29-7.25 (1H, m, 3-aryl), 7.09-7.02 (1H, m, 5-aryl), 6.84-6.77 (2H, m, 4,6-aryl), 3.59 (2H, br s, NH_2), 3.40 (2H, s, CH_2), 1.50 (9H, s, $(CH_3)_3$); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.1 (COOBu^t), 164.2 (CONH), 140.6 (2-aryl), 127.2 (4-aryl), 125.3 (6-aryl), 123.8 (1-aryl), 119.3 (5-aryl), 117.7 (3-aryl), 83.1 ($C(CH_3)_3$), 42.0 (CH_2), 28.0 ($(CH_3)_3$). Anal. Calcd for $C_{13}H_{18}N_2O_3$ C, 62.38; H, 7.25; N, 11.19. Found C, 62.29; H, 7.28; N, 11.13.

***tert*-Butyl 2-(1*H*-benzo[*d*]imidazol-2-yl)acetate (17)**. *tert*-Butyl 3-(2-aminophenylamino)-3-oxopropanoate (**16**) (70 mg, 0.28 mmol) was dissolved in acetic acid (0.15 mL) and the solution heated to 90 °C for 1 h. After allowing to cool the solvent was evaporated and the residue recrystallised from a mixture of ethyl acetate and 40-60 °C petroleum ether to give ester **17** (62 mg, 96%) as a white crystalline solid, mp 158-161 °C; IR ν_{max} 2984, 1722, 1435 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 10.0 (1H, br s, NH), 7.56 (2H, dd, *J*=3.2, 6.0 Hz, 4,7-benzimidazolyl), 7.22 (2H, dd, *J*=3.2, 6.0 Hz, 5,6-benzimidazolyl), 3.99 (2H, s, CH_2), 1.46 (9H, s, $(CH_3)_3$); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.0 (COOBu^t), 147.8 (2-benzimidazolyl), 138.3 (3a,7a-benzimidazolyl), 122.5 (4,7-benzimidazolyl), 115.0 (5,6-benzimidazolyl), 82.7 ($C(CH_3)_3$), 35.7 (CH_2), 28.0 ($(CH_3)_3$). Anal. Calcd for $C_{13}H_{16}N_2O_2$ C, 67.22; H, 6.49; N, 12.06. Found C, 67.10; H, 6.97; N, 11.97.

***tert*-Butyl 2-(2-*tert*-butoxy-2-oxoethyl)-1*H*-benzo[*d*]imidazole-1-carboxylate (18)**. To a stirred solution of *tert*-butyl 2-(1*H*-benzo[*d*]imidazol-2-yl)acetate (**17**) (3.37 g, 14.5 mmol) in tetrahydrofuran (33 mL) was added di-*tert*-butyl dicarbonate (3.80 g, 17.4 mmol) and the solution stirred at 20 °C for 3 d. Evaporation gave a residue that was subjected to column chromatography (1:4 ethyl acetate:40-60 °C petroleum ether) to give ester **18** (4.68 g, 97%) as a colourless viscous oil which solidified on standing to a white solid, mp 82-83 °C; IR ν_{max} 2979, 1750, 1729 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.93-7.87 (1H, m, 7-benzimidazolyl),

7.74-7.67 (1H, m, 4-benzimidazolyl), 7.38-7.28 (2H, m, 5,6-benzimidazolyl), 4.19 (2H, s, CH_2), 1.68 (9H, s, $(CH_3)_3$), 1.43 (9H, s, $(CH_3)_3$); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 167.9 (NCOO), 149.7 (CH_2COO), 148.9 (2-benzimidazolyl), 142.1 (3a-benzimidazolyl), 132.9 (7a-benzimidazolyl), 124.6 (7-benzimidazolyl), 124.1 (4-benzimidazolyl), 119.8 (5-benzimidazolyl), 114.9 (6-benzimidazolyl), 85.7 ($C(CH_3)_3$), 81.7 ($C(CH_3)_3$), 39.1 (CH_2), 28.0 (($CH_3)_3$), 28.0 (($CH_3)_3$). Anal. Calcd for $C_{18}H_{24}N_2O_3$ C, 65.04; H, 7.28; N, 8.43. Found C, 65.02; H, 7.26; N, 8.30.

1-*tert*-Butyl, 8-ethyl 2-(1-(*tert*-butoxycarbonyl)-1*H*-benzo[*d*]imidazol-2-yl)octanedioate (19). Sodium hydride (337 mg of a 60% dispersion in mineral oil, 14.0 mmol) was added to a stirred solution of *tert*-butyl 2-(2-*tert*-butoxy-2-oxoethyl)-1*H*-benzo[*d*]imidazole-1-carboxylate (**18**) (4.24 g, 12.8 mmol) in dry tetrahydrofuran (130 mL). The suspension was stirred for a further 30 min, then ethyl 6-bromohexanoate (3.13 g, 14.0 mmol) added and the mixture stirred at 60 ˚C for 18 h. A further portion of sodium hydride (337 mg, 14.0 mmol) was then added (with effervescence) and stirring continued at 60 ˚C for 4 h. After allowing to cool the solvent was evaporated and ethyl acetate (80 mL) added. The suspension was washed with saturated aqueous ammonium chloride (40 mL), dried ($MgSO_4$), filtered and evaporated to give a brown oil which was purified by column chromatography (15:85 ethyl acetate:40-60 °C petroleum ether) to give ester **19** (2.01 g, 33%) as a yellow oil; IR ν_{max} 2978, 1731, 1453 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.88-7.83 (1H, m, 7-benzimidazolyl), 7.73-7.68 (1H, m, 4-benzimidazolyl), 7.28-7.23 (2H, m, 5,6-benzimidazolyl), 4.39 (1H, dd, *J*=6.1, 8.3 Hz, CH), 4.05 (2H, q, *J*=7.1 Hz, CH_2CH$_3$), 2.36-2.09 (4H, m, CHCH_2, CH_2COO), 1.66 (9H, m, $(CH_3)_3$), 1.65-1.57 (2H, m, CH_2CH$_2$COO), 1.55-1.43 (4H, m, CHCH$_2$CH_2, CHCH$_3$CH$_3$CH_2), 1.40 (9H, m, $(CH_3)_3$), 1.18 (3H, t, *J*=7.1 Hz, CH$_2$CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 173.6 (COOEt), 170.5 (CHCOOBu^t), 153.5 (NCOO), 149.1 (2-benzimidazolyl), 142.1 (7a-benzimidazolyl), 132.8 (3a-benzimidazolyl), 124.4 (7-benzimidazolyl), 124.0 (4a-benzimidazolyl), 120.0 (5-benzimidazolyl), 115.0 (6-benzimidazolyl), 85.5 ($C(CH_3)_3$), 81.2 ($C(CH_3)_3$), 60.0 (CH_2CH_3), 48.2 (CH), 34.2, (CH_2COO), 29.8 (CHCH_2), 28.9 (CHCH$_2$CH$_2$CH_2), 28.1 (($CH_3)_3$), 27.8 (($CH_3)_3$), 27.5 (CHCH$_2$CH_2), 24.7 (CH_2CH$_2$COO), 14.2 (CH$_2$CH_3); *m*/*z* (EI, %) 497 (M+H, 34), 441 (33), 397 (57), 297 (100), 251 (86). HRMS (M+H) calcd for $C_{26}H_{38}N_2O_6$ 497.2628. Found: 497.2620.

***tert*-Butyl 2-(1*H*-benzo[*d*]imidazol-2-yl)-8-(hydroxyamino)-8-oxooctanoate (20)**. To a stirred solution of 1-*tert*-butyl 8-ethyl 2-(1-(*tert*-butoxycarbonyl)-1*H*-benzo[*d*]imidazol-2-yl)octanedioate (**19**) (1.0 g, 2.11 mmol) in tetrahydrofuran (20 mL) was added 50% aqueous hydroxylamine (1.39 mL, 21.1 mmol) followed by dropwise addition of 1 M potassium hydroxide in methanol (6.33 mL). The mixture was stirred for 30 min then the solvent was evaporated. Water (15 mL) was added to the oily residue and the mixture neutralised with 1M

hydrochloric acid. On cooling, the precipitate was collected by filtration, air-dried and recrystallised from aqueous ethanol to give the hydroxamic acid **20** (508 mg, 67%) as a white crystalline solid, mp 110-115 °C; IR ν_{max} 3341, 2934, 1704, 1650 cm^{-1}; ^1H NMR ($(CD_3)_2SO$, 300 MHz) δ 12.31 (1H, br s, OH), 10.32 (1H, br s, NH), 8.65 (1H, br s, NH), 7.54 (1H, d, J=7.6 Hz, 7-benzimidazolyl), 7.44 (1H, d, J=7.0 Hz, 4-benzimidazolyl), 7.19-7.08 (2H, m, 5,6-benzimidazolyl), 3.80 (1H, t, *J*=7.7 Hz, CH), 2.06-1.97 (2H, m, $CHCH_2$), 1.90 (2H, t, *J*=7.3 Hz, CH_2CONH), 1.52-1.43 (2H, m, CH_2CH_2CONH), 1.37 (9H, s, $C(CH_3)_3$), 1.33-1.24 (4H, m, $CHCH_2CH_2$, $CHCH_2CH_2CH_2$); ^{13}C NMR ($(CD_3)_2SO$, 75 MHz) δ 170.2 (COO), 169.0 (CONH), 151.7 (2-benzimidazolyl), 142.8 (7a-benzimidazolyl), 134.4 (3a-benzimidazolyl), 121.8 (7-benzimidazolyl), 120.9 (4-benzimidazolyl), 118.4 (5-benzimidazolyl), 111.1 (6-benzimidazolyl), 80.8 ($C(CH_3)_3$), 46.8 (CH), 32.1 (CH_2CONH), 30.5 ($CHCH_2$), 28.2 ($CHCH_2CH_2CH_2$), 27.6 ($C(CH_3)_3$), 26.5 (CH_2CH_2CONH), 24.9 ($CHCH_2CH_2$); *m/z* (EI, %) 384 (M+Na, 100), 362 (54), 329 (79), 306 (36), 176 (99), 154 (99). HRMS (M+Na) calcd for $C_{19}H_{27}N_3O_4$ 384.1899. Found: 384.1906.

Ethyl 7-(1*H*-benzo[*d*]imidazol-2-yl)heptanoate (21). A solution of oxononane-2,9-dione (3.0 g, 19.2 mmol) in tetrahydrofuran (15 mL) was added dropwise to a stirred solution of 1,2-phenylenediamine (2.08 g, 19.2 mmol) in tetrahydrofuran (30 mL) and the brown solution stirred for 45 min. Evaporation gave a residue which was dissolved in a solution of 4% by volume of concentrated sulfuric acid in ethanol (190 mL), previously prepared by slow addition of sulfuric acid to cold ethanol (CAUTION!). The orange solution was heated at 90 °C for 16 h then allowed to cool and quenched with saturated aqueous sodium hydrogen carbonate. The mixture was evaporated and water (20 mL) was added. This mixture was extracted with ethyl acetate (3 x 20 mL) and the combined organic layers were dried ($MgSO_4$), filtered and evaporated to give a brown oil which was purified by column chromatography (1:4 ethyl acetate:40-60 °C petroleum ether) to give an cream solid. Recrystallisation from diethyl ether afforded the ester **21** (1.52 g, 29%) as white needles, mp 95-97 °C; IR ν_{max} 2934, 1720, 1175, 1026 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 10.78 (1H, br s, NH), 7.54 (2H, dd, *J*=3.2, 6.0 Hz**,** 4,7-benzimidazolyl), 7.20 (2H, dd, *J*=3.2, 6.0 Hz, 5,6-benzimidazolyl), 4.10 (2H, q, *J*=7.1 Hz, CH_2CH_3), 2.93 (2H, t, *J*=7.6 Hz, $NCCH_2$), 2.21 (2H, t, *J*=7.4 Hz, CH_2COO), 1.89-1.77 (2H, m, CH_2CH_2COO), 1.58-1.47 (2H, m, $NCCH_2CH_2$), 1.39-1.19 (7H, m, $NCCH_2CH_2CH_2$, $CH_2CH_2CH_2COO$, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 174.0 (COO), 155.5 (2-benzimidazolyl), 138.6 (3a,7a-benzimidazolyl), 122.0 (4,7-benzimidazolyl), 114.6 (5,6-benzimidazolyl), 60.3 (CH_2CH_3), 34.2 (CH_2COO), 29.2 ($NCCH_2$), 28.8 ($NCCH_2CH_2$), 28.6 ($CH_2CH_2CH_2COO$), 28.1 ($NCCH_2CH_2CH_2$), 24.7 (CH_2CH_2COO), 14.2 (CH_3); *m/z* (CI, %) 275 (M+H, 100), 229 (6), 187 (4). Anal. Calcd for $C_{16}H_{22}N_2O_2$ C, 70.04; H, 8.08; N, 10.21. Found C, 69.87; H, 8.07; N, 10.12.

7-(1*H*-Benzo[*d*]imidazol-2-yl)-*N*-hydroxyheptanamide (22). To a stirred solution of ethyl 7-(1*H*-benzo[*d*]imidazol-2-yl)heptanoate (**21**) (1.20 g, 4.37 mmol) in tetrahydrofuran (40 mL) was added 50% aqueous hydroxylamine (2.89 mL, 43.7 mmol) followed by slow addition of 1 M potassium hydroxide in methanol (6.56 mL). The mixture was stirred at 20 °C for 2 h then evaporated. To the yellow residue was added water (60 mL) then the solution was acidified with 2M hydrochloric acid to give a white precipitate. After filtering, the product was washed with water, methanol and lastly with diethyl ether to give the hydroxamic acid **22** (696 mg, 61%) as a white solid, mp 226-227 ˚C; IR ν_{max} 3284, 2930, 2324, 1642 cm^{-1}; ^1H NMR ($(CD_3)_2SO$, 300 MHz) δ 10.33 (1H, s, NH), 8.67 (1H, s, NH), 7.51-7.30 (2H, m, 4,7-benzimidazolyl), 7.13-7.05 (2H, m, 5,6-benzimidazolyl), 2.77 (2H, t, *J*=7.5 Hz, $NNCCH_2$), 1.92 (2H, t, *J*=7.3 Hz, CH_2CO), 1.78-1.68 (2H, m, $NNCCH_2CH_2$), 1.54-1.42 (2H, m, CH_2CH_2CO), 1.38-1.23 (4H, m, $CH_2CH_2CH_2CH_2CO$, $CH_2CH_2CH_2CO$); ^{13}C NMR ($(CD_3)_2SO$, 75 MHz) δ 174.2 (CO), 160.2 (2-benzimidazolyl), 148.4 (7a-benzimidazolyl), 139.4 (3a-benzimidazolyl), 126.4 (7-benzimidazolyl), 125.9 (4-benzimidazolyl), 123.1 (6-benzimidazolyl), 115.8 (5-benzimidazolyl), 37.3 ($NNCCH_2$), 33.6 (CH_2CO), 33.5 ($NNCCH_2CH_2$), 33.4 ($CH_2CH_2CH_2CO$), 32.5 ($CH_2CH_2CH_2CH_2CO$), 30.1 (CH_2CH_2CO); *m/z* (CI, %) 262 (M+H, 100), 242 (57), 201 (9). Anal. Calcd for $C_{14}H_{19}N_3O_2$ C, 64.35; H, 7.33; N, 16.08. Found C, 64.36; H, 7.51; N, 15.89.

6-Ethyl 1,1-bis(2,4,6-trichlorophenyl)hexane-1,1,6-tricarboxylate (23). A mixture of 2-carboxyoctanedioic acid 8-ethyl ester (**2**) (1.34 g, 5.44 mmol) and 2,4,6-trichlorophenol (2.15 g, 10.9 mmol) in phosphorus oxychloride (2.17 g, 14.4 mmol) was heated to 100 ˚C for 5 h. After allowing to cool, water (10 mL) was added. The mixture was extracted with ethyl acetate (2 x 10 mL) and the combined organic layers were washed with saturated aqueous sodium hydrogen carbonate (10 mL) and then with brine (10 mL). The organic layer was dried ($MgSO_4$), filtered and the solvent evaporated to give a brown oil which was purified by column chromatography (5:95 ethyl acetate:40-60 °C petroleum ether) to give ester **23** as a colourless oil (1.61 g, 49%); IR ν_{max} 2937, 1769, 1731, 1566 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.44-7.37 (4H, m, 3,5-aryl), 4.13 (2H, q, *J*=7.1 Hz, CH_2CH_3), 4.05 (1H, t, *J*=7.4 Hz, COCHCO), 2.38-2.24 (4H, m, $CHCH_2$, CH_2CO_2Et), 1.77-1.58 (4H, m, $CH_2CH_2CO_2Et$, $CHCH_2CH_2$), 1.57-1.40 (2H, m, $CHCH_2CH_2CH_2$), 1.25 (3H, t, *J*=7.1 Hz, CH_2CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 173.5 (COOEt), 164.6 (COOAr), 142.4 (1-Ar), 132.6 (4-Ar), 129.5 (Ar) 128.8 (Ar), 60.3 (CH_2CH_3), 50.7 (CH), 34.1 (CH_2COOEt), 29.2 ($CHCH_2$), 28.6 ($CH_2CH_2CH_2COOEt$), 27.0 ($CHCH_2CH_2$), 24.6 (CH_2CH_2COOEt), 14.1 (CH_3CH_2); *m/z* (CI, %) 626 (18), 211 (26), 176 (100). HRMS calcd for $C_{23}H_{20}Cl_6O_6$ (M+Na) 624.9289, found 624.9275.

Ethyl 6-(2-(diethylamino)-4-hydroxy-6-oxo-1-phenyl-1,6-dihydropyrimidin-5-yl)-

hexanoate (24). A stirred mixture of 6-ethyl 1,1-bis(2,4,6-trichlorophenyl)hexane-1,1,6-tricarboxylate (**23**) (1.40 g, 2.31 mmol) and *N*,*N*-diethyl-*N'*-phenylguanidine (443 mg, 2.31 mmol) was heated to 150 ˚C for 5 min. After allowing to cool to room temperature the viscous brown oil was purified by column chromatography (1:1 ethyl acetate:hexane) to give the ester **24** (635 mg, 68%) as a pale yellow oil; IR ν_{max} 2935, 1730, 1595, 1524 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.36 (2H, t, *J*=7.4 Hz, 3,5-aryl), 7.28 (1H, t, *J*=7.3 Hz, 4-aryl), 7.19 (2H, d, *J*=7.1 Hz, 2,6-aryl), 4.02 (2H, q, *J*=7.1 Hz, CH_2CH_3), 2.97 (4H, q, *J*=6.9 Hz, $N(CH_2CH_3)_2$), 2.33 (2H, t, *J*=7.5 Hz, CCH_2), 2.20 (2H, t, *J*=7.5 Hz, CH_2COOEt), 1.63-1.53 (2H, m, CH_2CH_2COOEt), 1.50-1.40 (2H, m, CCH_2CH_2), 1.36-1.25 (2H, m, $CCH_2CH_2CH_2$), 1.15 (3H, t, *J*=7.1 Hz, CH_2CH_3), 0.75 (6H, t, *J*=7.0 Hz, $N(CH_2CH_3)_2$); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 174.1 (COOEt), 165.1 (4-pyrimidyl), 163.7 (6-pyrimidyl), 155.5 (2-pyrimidyl), 138.1 (1-aryl), 128.9 (3,5-aryl), 128.8 (2,6-aryl), 128.0 (4-aryl), 95.1 (5-pyrimidyl), 60.1 (CH_2CH_3), 44.6 ($N(CH_2CH_3)_2$), 34.4 (CH_2COOEt), 29.1 ($CCH_2CH_2CH_2$), 27.9 ($CHCH_2CH_2$), 24.9 (CH_2CH_2COOEt), 23.1 (CCH_2), 14.2 (CH_2CH_3), 12.4 ($N(CH_2CH_3)_2$); *m*/*z* (EI, %) 401 (M^+, 2), 291 (27), 171 (59), 125 (100); HRMS calcd for $C_{22}H_{31}N_3O_4$ 401.2314. Found: 401.2311.

6-(2-(Diethylamino)-4-hydroxy-6-oxo-1-phenyl-1,6-dihydropyrimidin-5-yl)-*N*-hydroxy-hexanamide (25). To a stirred solution of ethyl 6-(2-(diethylamino)-4-hydroxy-6-oxo-1-phenyl-1,6-dihydropyrimidin-5-yl)hexanoate (**24**) (250 mg, 0.62 mmol) in tetrahydrofuran (6 mL) was added 50% aqueous hydroxylamine (0.41 mL, 6.23 mmol) followed by dropwise addition of 1 M potassium hydroxide in methanol (1.87 mL). The mixture was stirred for 5 min then evaporated and water (20 mL) added to the residue. The mixture was neutralised with 1 M hydrochloric acid then extracted with ethyl acetate (4 x 20 mL). The combined organic layers were dried (Na_2SO_4), filtered and evaporated to give an orange oil which was purified by column chromatography (ethyl acetate) to give the hydroxamic acid **25** (124 mg, 51%) as an orange oil; IR ν_{max} 3192, 2932, 1616, 1522 cm^{-1}; ^1H NMR (CD_3OD, 300 MHz) δ 7.62-7.38 (3H, m, 3,4,5-aryl), 7.27 (2H, d, *J*=7.0 Hz, 2,6-aryl), 3.08 (4H, q, *J*=7.0 Hz, $N(CH_2CH_3)_2$), 2.36 (2H, t, *J*=7.5 Hz, CH_2CO), 2.07 (2H, t, *J*=7.5 Hz, CCH_2), 1.62 (2H, dt, *J*=15.0, 7.5 Hz, CH_2CH_2CO), 1.57-1.25 (4H, m, $CH_2CH_2CH_2CH_2CO$, $CH_2CH_2CH_2CO$), 0.80 (6H, *t*, *J*=7.0 Hz, $N(CH_2CH_3)_2$); ^{13}C NMR (CD_3OD, 75 MHz) δ 173.2 (4-pyrimidyl), 167.7 (CONHOH), 167.2 (6-pyrimidyl), 160.0 (2-pyrimidyl), 139.9 (1-aryl), 130.3 (3,5-aryl), 130.2 (2,6-aryl), 129.3 (4-aryl), 95.8 (5-pyrimidyl), 46.0 ($N(CH_2CH_3)_2$), 33.7 (CH_2CO), 30.0 ($CH_2CH_2CH_2CO$), 29.0 ($CH_2CH_2CH_2CH_2CO$), 26.7 (CH_2CH_2CO), 23.9 (CCH_2), 12.9 ($N(CH_2CH_3)_2$); *m*/*z* (CI, %) 411 (M+Na, 100), 389 (M+H, 65), 321 (17), 192 (70). HRMS calcd for $C_{20}H_{28}N_4O_4$ (M+H) 389.2183, found 389.2198.

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Legends

Figure 1. FDA-approved HDAC inhibitors.

Scheme 1. Synthesis of a symmetrical bis-malonamide hydroxamic acid.[14] Reagents and conditions:
[a] NaH (1.1 equiv.) first added to di-*tert*-butyl malonate (1 equiv.), THF, 20 °C, 20 min then reflux, 16 h, 74%.
[b] CF_3CO_2H (6 equiv.), CH_2Cl_2, 20 °C, 16 h, 99%.
[c] $SOCl_2$ (6 equiv.), benzene, reflux, 2 h[14] then
[d] $PhNH_2$ (6 equiv.), pyridine (3 equiv.), CH_2Cl_2, 20 °C, 17 h, 76%.[14]
[e] NaOMe, (3 equiv.) and $HONH_2$ (2 equiv.), MeOH, 20 °C, 16 h, 68%.[14]

Scheme 2. Synthesis of branched derivatives of SAHA. Reagents and conditions:
[a] NaH (1.1 equiv.), ethyl 6-bromohexanoate (1 equiv.), THF, 70 °C, 18 h, 74%.

[b] 50% aqueous $HONH_2$ (10 equiv.), 1 M KOH in MeOH, THF, 20 °C, 1 h, 29%.
[c] 1:1 CF_3CO_2H:CH_2Cl_2, 20 °C, 6 h, 80%.
[d] $ClCO_2Et$ (1.5 equiv.), Et_3N (1.2 equiv), THF, 0 °C, 30 min then $NaBH_4$ (3 equiv.),[21] MeOH, 10 °C, 1.5 h, 77%.
[e] Aqueous 50% $HONH_2$ (5 equiv.), 1M KOH in MeOH, THF, 20 °C, 1.5 h, 12%.
[f] 1:1 CF_3CO_2H:CH_2Cl_2, 20 °C, 30 min, 80%.

Scheme 3. Synthesis of a branched 2-benzimidazolinyl derivative of SAHA. Reagents and conditions:
[a] *tert*-Butyl *N*-(2-aminophenyl)carbamate (1 equiv.), EDC.HCl (1.1 equiv.), HOBt (1.1 equiv.), Et_3N (2.2 equiv), DMF, 20 °C, 18 h, 66%.
[b] AcOH, reflux, 100 °C, 1 h, 77%.
[c] Di-*tert*-butyl dicarbonate (1.5 equiv.), THF, 20 °C, 7 d, 64% conversion.
[d] 50% aqueous $HONH_2$ (10 equiv.), 1 M KOH in MeOH, THF, 20 °C, 6 h, 50%.

Scheme 4. Synthesis of a branched hydroxamic acid with a 2-benzimidazolyl capping group. Reagents and conditions:
[a] 1,2-Phenylenediamine (1 equiv.), *N,N'*-dicyclohexylcarbodiimide (1.1 equiv.), MeCN, 20 °C, 20 min, 50%.
[b] AcOH, 90 °C, 1 h, 96%.
[c] Di-*tert*-butyl dicarbonate (1.2 equiv.), THF, 20 °C, 3 d, 97%.
[d] NaH (1.1 equiv.), THF, 60 °C, 18 h, 33%**.**
[e] 50% aqueous $HONH_2$ (10 equiv.), 1 M KOH in MeOH, THF, 20 °C, 30 min, 67%.

Scheme 5. Succinct synthesis of a linear hydroxamic acid with a 2-benzimidazolyl capping group. Reagents and conditions:
[a] Suberic anhydride (1 equiv.), THF, 20 °C, 20 min; then 4% conc. H_2SO_4 in EtOH, 29%.
[b] Aqueous 50% $HONH_2$, 1 M KOH in MeOH, THF, 20 °C, 6 h, 61%.

Scheme 6. Synthesis of a SAHA analog constrained by annulation. Reagents and conditions:
[a] CF_3CO_2H (6 equiv.), CH_2Cl_2, 20 °C, 24 h, 99%.
[b] 2,4,6-Trichlorophenol (2 equiv.), $POCl_3$ (2.6 equiv.), 100 °C, 5 h, 49%.
[c] *N,N*-Diethyl-*N'*-phenylguanidine (1 equiv.), 5 min, 150 °C, 68%.
[d] Aqueous 50% $HONH_2$ (10 equiv.), 1M KOH in MeOH, THF, 20 °C, 2 h, 51%.