An improved and efficient synthesis of panobinostat

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An improved and efficient method for the synthesis of panobinostat was developed. The commercially available starting material 4-(chloromethyl)benzaldehyde was converted to (*E*)-methyl 3-[4-(chloromethyl)phenyl]acrylate *via* the Wittig–Horner reaction and was then directly condensed with 2-(2-methyl-1*H*-indol-3-yl)ethanamine to afford the key intermediate (*E*)-methyl 3-[4-({[2-(2-methyl-1*H*-indol-3-yl)ethyl]amino}methyl)phenyl]acrylate in a one-pot synthesis reactor. Subsequently a nucleophilic substitution reaction was carried out smoothly to generate the desired compound. The key intermediate and target compound were characterised by HRMS, ^{1}H NMR and ^{13}C NMR. This procedure is operationally simple and would be more suitable for industrial production.

Keywords: panobinostat, histone deacetylase inhibitor, synthesis, Wittig–Horner reaction

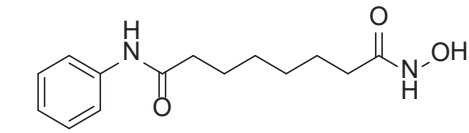
Histone deacetylases (HDACs) are a class of enzymes that catalyse the removal of acetyl groups from the ε-amino groups of lysine residues that are present within the N-terminal extension of the core histones, leading to chromatin condensation and transcriptional repression.[1,2] So far, 18 HDACs have been identified in humans, and they are subdivided into four structurally and functionally different phylogenetic classes. Among them, Class I HDACs (1, 2, 3 and 8) and Class II HDACs (4, 5, 6, 7, 9 and 10) are zinc-dependent proteases, which play important roles in the modulation of chromatin topology and the regulation of gene transcription.[2–5] Consequently, it has been widely recognised that histone deacetylase inhibitors (HDACi) could be a new class of antitumour agents that can inhibit the proliferation of tumour cells in culture and *in vivo* by inducing cell cycle arrest, differentiation and/or apoptosis.[6,7]

Over the past decade there have been extensive efforts to identify and design novel small-molecule HDACi to address unmet medical needs. There are already approved HDACi for the treatment of cancer, such as lymphoma and multiple myeloma (Fig. 1).[8,9] Panobinostat (also known as LBH589, trade name Farydak®) is a novel and potent small molecule nonselective inhibitor of the HDACs, and was approved by the US Food and Drug Administration (FDA) for the treatment of relapsed multiple myeloma in certain patients in February 2015.[10] Panobinostat is in various stages of clinical development worldwide and shows great potential for curing a range of haematological and solid tumours.[11] Therefore, improvement in the preparation of panobinostat is of practical significance.

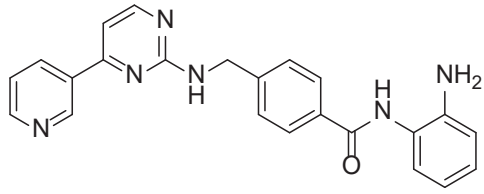
Results and discussion

Considerable synthetic work has recently been devoted to the synthesis of panobinostat.[12–14] Among the available methods, the most common strategies to prepare this compound employ 1-bromo-4-methylbenzene or 4-bromobenzaldehyde as the starting material. For example, as shown in Scheme 1, 1-bromo-4-methylbenzene is transformed to compound **2** by a Suzuki coupling reaction, followed by bromation of the methyl group in the presence of NBS/CCl_4 to form intermediate **3**. Condensation of **3** with 2-(2-methyl-1*H*-indol-3-yl)ethanamine (**1**) affords the intermediate (*E*)-methyl 3-[4-({[2-(2-methyl-1*H*-indol-3-yl) ethyl]amino}methyl)phenyl]acrylate (**4**), which is subsequently attacked by NH_2OH to generate the target compound panobinostat. However, these reported methods often suffer from several drawbacks, such as vigorous conditions, use of expensive or toxic reagents, and the requirement for column chromatography or complicated workups.

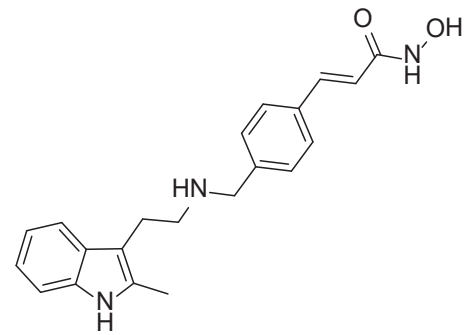
In view of this, we have designed an alternative synthetic route for the synthesis of panobinostat (Scheme 2). Initially this route involved a three-step process. The inexpensive and readily available starting material 4-(chloromethyl) benzaldehyde (**5**) was utilised and it was converted to (*E*)-methyl 3-[4-(chloromethyl)phenyl]acrylate *via* the Wittig–



Vorinostat (SAHA)



Mocetinostat



Panobinostat (Farydak)

Fig. 1 Structures of some selective inhibitors of HDACs.

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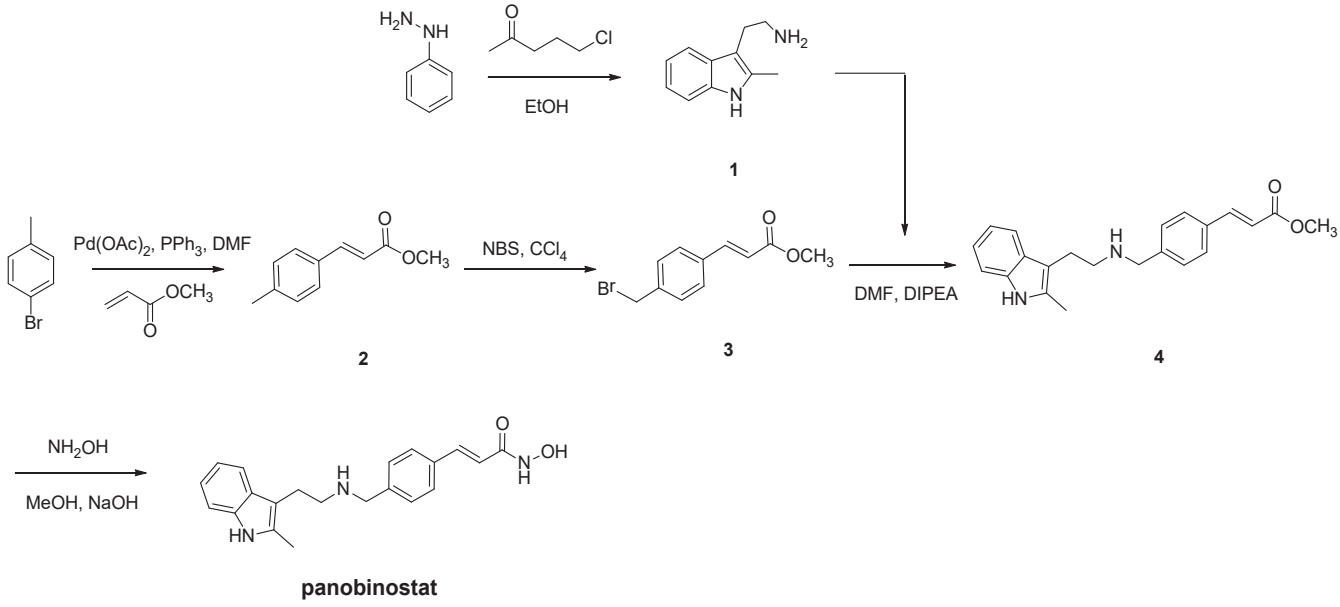
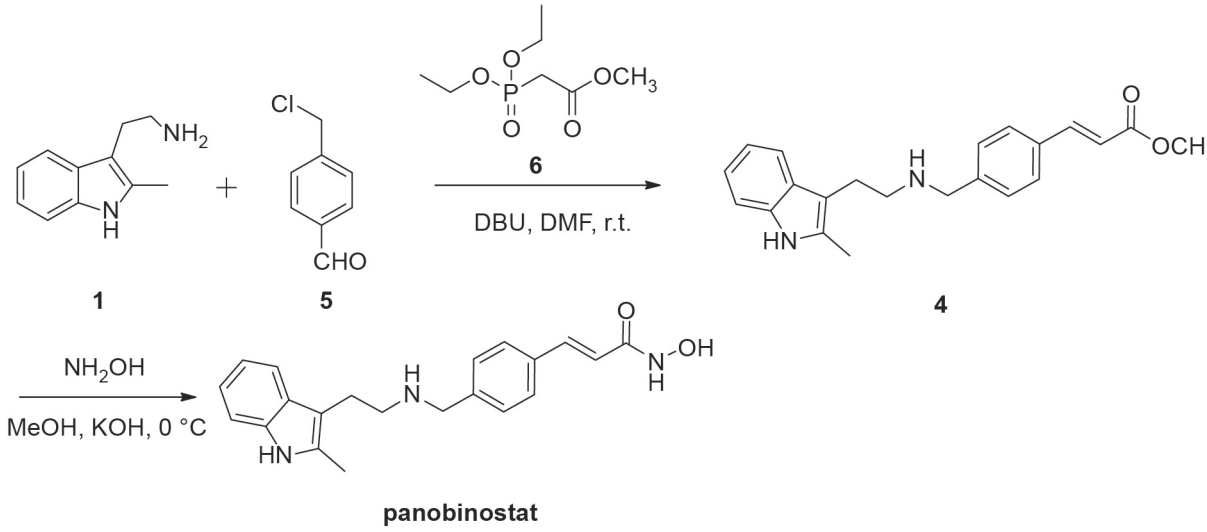


Scheme 1 The reported synthesis of panobinostat.



Scheme 2 An improved synthesis of panobinostat.

Horner reaction and was then condensed with **1** to afford the key intermediate **4**. A nucleophilic substitution reaction between **4** and NH_2OH proceeded successfully to form the desired compound in the presence of KOH. However, we accidentally found that (*E*)-methyl 3-[4-(chloromethyl)phenyl]acrylate reacted directly with **1** to afford **4** under the same conditions (DBU/DMF) without purification. Thus, we employed a one-pot synthesis strategy leading to **4**, which had a simplified workup and gave higher yield.

To increase the yield of this route, the reaction conditions were investigated and optimised. First, as the base played an important role in the reaction, a variety of bases such as 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), *N*,*N*-diisopropylethylamine (DIPEA), *t*-BuOK, NaH and K_2CO_3 were examined as the catalyst for the reaction. As shown in Table 1, it was observed that DBU gave the best outcome compared with the other agents (Table 1, entries 1–5). With this preliminary result in hand, the concentration of DBU and methyl diethylphosphonoacetate (**6**) was further studied. As a result, 2.5 equiv. of DBU and **6** was found to be sufficient to obtain a good yield, and no further improvements in the yield of the product were observed with higher mole equivalents, whereas a decrease in mole equivalents ratios resulted in a lower yield (Table 1, entries 6–8). Under the optimised conditions, effort was made to increase the yield of the reaction using different solvents such as DMF, THF, DCM, ACN and 1,4-dioxane. Out of these solvents, DMF gave a maximum yield of the desired product (Table 1, entry 7 *versus* entries 9–12). Hence, DMF was chosen as the solvent for the reaction. Next, the reaction temperature was also investigated, and the results showed that 25 °C is the optimal temperature (Table 1, entry 7 *versus* entries 13 and 14). Finally, panobinostat with the literature properties was obtained efficiently from **5** with an overall yield of 40% based on **1**.

In conclusion, we have developed a straightforward and improved approach for the synthesis of panobinostat. This synthetic route employed 4-(chloromethyl)benzaldehyde as the starting materials to afford panobinostat *via* a two-step reaction. The overall yield of this procedure was 40% based on 2-(2-methyl-1*H*-indol-3-yl)ethanamine. This method shows great potential for practical use in the synthesis of panobinostat owing to its simple operating requirements and low cost.

Table 1 Optimisation of reaction conditions

Entry	Catalyst (equiv.)	**6** (equiv.)	Temperature (°C)	Time (h)	Solvent	Yield (%)[a]
1	K_2CO_3 (3.0)	3.0	25	6	DMF	–[b]
2	DBU (3.0)	3.0	25	6	DMF	52
3	DIPEA (3.0)	3.0	25	6	DMF	–[b]
4	NaH (3.0)	3.0	25	6	THF	Trace
5	*t*-BuOK (3.0)	3.0	25	6	THF	–[b]
6	DBU (1.0)	3.0	25	6	DMF	18
7	DBU (2.5)	2.5	25	6	DMF	55
8	DBU (1.5)	1.5	25	6	DMF	32
9	DBU (2.5)	2.5	25	6	THF	20
10	DBU (2.5)	2.5	25	6	DCM	22
11	DBU (2.5)	2.5	25	6	ACN	23
12	DBU (2.5)	2.5	25	6	1,4-Dixone	30
13	DBU (2.5)	2.5	0	6	DMF	31
14	DBU (2.5)	2.5	50	3	DMF	45
15	DBU (2.5)	2.5	25	3	DMF	35

[a]Isolated yield.

[b]No reaction.

Experimental

4-(Chloromethyl)benzaldehyde was obtained from ZhengZhou Alfa Chemical Industrial Corporation. Other reagents were obtained from Adamas and Tansoole and used without further purification unless otherwise noted. Melting points were determined on X-4 microscopic melting point apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were obtained from solution in DMSO-d_6 and $CDCl_3$ with TMS as internal standard using a Bruker-600 MHz spectrometer. MS spectra were obtained with an Aglient 6470 Triple Quad LC-MS instrument. HRMS spectra were acquired with an Agilent 6210 ESI/TOF mass spectrometer.

*Synthesis of 2-(2-methyl-1*H*-indol-3-yl)ethanamine* (**1**)

Compound **1** was prepared following the literature method.[15] A mixture of phenylhydrazine (19.8 mL, 200 mmol) and 5-chloro-2-pentanone (25 mL, 210 mmol) in EtOH (300 mL) was heated to reflux for 4 h. After cooling, the solvent was removed under reduced pressure. Water (100 mL) was added and the pH was adjusted to 2–3 with 2 M HCl. The aqueous layer was washed with ethyl acetate (2 × 50 mL), then separated. The pH of the aqueous layer was readjusted to 11–12 with 20% NaOH aqueous solution, and the resulting solution was extracted with ethyl acetate twice, and the organic layer was combined, successively washed with brine and dried over anhydrous Na_2SO_4. It was filtered and concentrated under reduced pressure to afford compound **1** as: Red oil; yield 23.9 g (69%); ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.72 (brs, 2H), 2.32 (s, 3H), 2.84 (t, *J* = 6.6 Hz, 2H), 2.94 (t, *J* = 6.6 Hz, 2H), 7.09 (m, 2H), 7.11 (d, *J* = 7.2 Hz, 1H), 7.23 (d, *J* = 7.2 Hz, 1H), 8.14 (brs, 1H); HRMS *m/z* calcd for $C_{11}H_{14}N_2$ $[M + H]^+$: 175.1230; found: 175.1231.

Synthesis of (E)*-methyl 3-[4-({[2-(2-methyl-1*H*-indol-3-yl)ethyl]amino}methyl)phenyl]acrylate hydrochloride* (**4**)

A mixture of 2-(2-methyl-1*H*-indol-3-yl)ethanamine (**1**, 1.5 g, 9 mmol), DMF (10 mL), DBU (3.8 g, 25 mmol), LiCl (0.04g, 1 mmol) and methyl diethylphosphonoacetate (**6**, 5.2 g, 25 mmol) was stirred at 0 °C under a nitrogen atmosphere for 10 min, and then this mixture was slowly treated with a solution of 4-(chloromethyl)benzaldehyde (**5**, 1.5 g, 10 mmol) in DMF (5 mL). The reaction was then warmed to room temperature and stirred at this temperature for 6 h to give a red solution. Water (50 mL) was added to quench the reaction and it was extracted with ethyl acetate (2 × 50 mL). The combined organic layer was washed with brine and dried over anhydrous Na_2SO_4 and filtered. Then saturated HCl/1,4-dioxane solution was added to this filtrate until pH = 2–3, and concentrated to dryness. The residue was stirred in hot ethyl acetate/EtOH for 10 min, and the resulting precipitate was filtered and dried to give the pure compound **4** as: Brown solid; yield 1.8 g (55%); m.p. 239–243 °C (lit. [12] 245–247 °C); ^{1}H NMR (600 MHz, DMSO-d_6): δ: 2.34 (s, 3H), 2.92 (m, 2H), 3.17 (m, 2H), 3.74 (s, 3H), 4.21 (t, *J* = 5.8 Hz, 2H), 6.72 (d, *J* = 16.1 Hz, 1H), 7.01 (m, 2H), 7.25 (d, *J* = 8.0 Hz, 1H), 7.46 (d, *J* = 7.8 Hz, 1H), 7.65 (d, *J* = 8.2 Hz, 2H), 7.69 (d, *J* = 16.1 Hz, 1H), 7.80 (d, *J* = 8.2 Hz, 2H), 9.59 (brs, 2H), 10.90 (s, 1H); ^{13}C NMR (150 MHz, DMSO-d_6): δ 11.6, 21.0, 47.4, 49.8, 52.0, 66.8, 105.6, 111.0, 117.6, 118.7, 119.0, 120.6, 128.2, 128.9, 130.9, 133.1, 134.9, 135.6, 144.2, 167.0; MS (ESI) *m/z* $[M + H]^+$: 349.0; HRMS *m/z* calcd for $C_{22}H_{24}O_2N_2$ $[M + H]^+$: 349.1911; found: 349.1914.

Synthesis of (E)-N*-hydroxy-3-[4-({[2-(2-methyl-1*H*-indol-3-yl)ethyl]amino}methyl)phenyl]acrylamide* (**panobinostat**)

A solution of potassium hydroxide (1.17 g, 21 mmol) in methanol (5 mL) was added to a stirred solution of hydroxylamine hydrochloride (0.97 g, 14 mmol) in methanol (10 mL) at 0 °C. The mixture was stirred at 0 °C for 15 min. The precipitate was removed by filtration and the filtrate was collected to provide fresh hydroxylamine solution. The ester (0.48 g, 1.4 mmol) was added to the above freshly prepared hydroxylamine solution at 0 °C. The reaction mixture was then stirred at this temperature under a nitrogen atmosphere for 4 h. After the reaction was completed, the mixture was diluted with water and neutralised with NH_4Cl aqueous solution to pH = 7–8. The precipitate that formed was collected by filtration, washed with water and recrystallised from MeOH/H_2O to give the title compound as: Off-white solid; yield 0.35 g (73%); m.p. 89–91 °C (lit. [12] 86–88 °C); ^{1}H NMR (600 MHz, DMSO-d_6): δ 2.31 (s, 3H), 2.69 (t, *J* = 7.5 Hz, 2H), 2.81 (t, *J* = 7.5 Hz, 2H), 3.77 (s, 2H), 6.45 (d, *J* = 15.8 Hz, 1H), 6.90 (m, 1H), 6.95 (m, 1H), 7.22 (d, *J* = 8.0 Hz, 1H), 7.38 (m, 3H), 7.44 (d, *J* = 15.8 Hz, 1H), 7.49 (d, *J* = 8.0 Hz, 2H), 10.70 (brs, 1H); ^{13}C NMR (150 MHz, DMSO-d_6): δ 11.7, 24.7, 50.0, 52.8, 108.5, 110.8, 117.8, 118.4, 118.8, 120.3, 127.7, 128.8, 128.9, 132.2, 133.6, 135.6, 138.6, 142.7, 163.2; MS (ESI) *m/z* $[M + H]^+$: 350.0; HRMS *m/z* calcd for $C_{21}H_{23}O_2N_3$ $[M + H]^+$: 350.1863; found: 350.1864.

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Electronic Supplementary Information

The ESI associated with this paper can be found at:
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