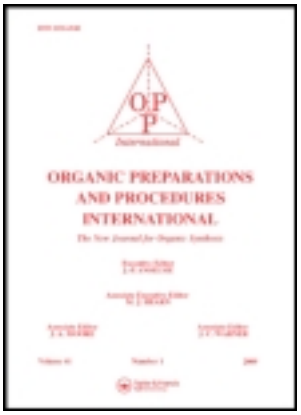

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A Convenient Synthesis of the New Histone Deacetylase Inhibitor Scriptaid

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OPPI BRIEF

A Convenient Synthesis of the New Histone Deacetylase Inhibitor Scriptaid

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Histone deacetylase (HDAC) inhibitors represent a new promising class of anticancer agents, because of their ability to induce cell cycle arrest, differentiation and apoptosis of cancer cells.[1–3] A number of products such as naturally occurring *trichostatin A*, *trapoxins A* and *B*, *romidepsin* as well as the synthetic derivatives suberoylanilide hydroxamic acid (SAHA), *oxamflatin*, *belinostat*, NVP-LAQ-824, *valproic acid* and MS-275 have been identified as HDAC inhibitors and have been shown to possess significant anticancer activity in several preclinical and clinical studies.[4–12] Currently, two HDAC inhibitors – SAHA (Vorinostat or Zolinza®) and *romidepsin* (Istodax®), have been approved by the FDA for the treatment of cutaneous T-cell lymphoma in patients with progressive, persistent or recurrent disease.[10,11] The therapeutic potential of HDAC inhibitors has spurred the synthesis of a large number of hydroxamic acids, cyclic peptides, short-chain fatty acids, benzamides and electrophilic ketones.[3,4,10,12] Amongst them, hydroxamic acid derivatives have received the most attention because of their favorable pharmacokinetic profile and high activity against both hematological and solid tumors at well-tolerated doses.[10,12]

Scriptaid (**3**) was identified by Su *et al.*[13] from a library of 16,320 compounds in a luciferase reporter assay. The compound is a hydroxamic acid and possesses the three pharmacophores common for this class of HDAC inhibitors, a hydroxamic acid zinc-binding group, a hydrophobic spacer, and a recognition cap group. The initial investigations of *scriptaid* showed that it is an effective HDAC inhibitor with low toxicity and high activity similar to those of SAHA.[13] A recent *in vitro* study revealed that *scriptaid* provoked growth inhibition, cell cycle arrest and apoptosis in human endometrial cancer and ovarian cancer cells.[14] An accumulation of acetylated H3 and H4 histone proteins was observed in these cell lines, confirming the effect of *scriptaid* as HDAC inhibitor.

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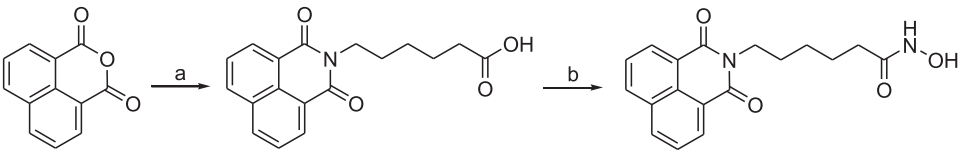

1 2 scriptaid (3)

a) ε–Aminocaproic acid, propionic acid, reflux, 4 h, 79%; b) ClCOOEt, Et_3N, THF, 0 °C, 15 min, followed by NH_2OH, MeOH, rt, 1 h, 71%

Scheme 1

To the best of our knowledge, there are no previous reports on the synthesis of compound **3** in the scientific and patent literature. Here we report a general and efficient two-step procedure (Scheme 1) for the preparation of *scriptaid* under mild reaction conditions and 56% overall yield. The reported method can be easily scaled up or used to quickly synthesize a large number of derivatives for further evaluation.

As shown in *Scheme 1*, the reaction of 1,8-naphthalic anhydride (**1**) and ε-aminocapronic acid was carried out by refluxing in propionic acid for 4 hours and led to the carboxylic acid **2** in 79% yield. Conversion of carboxylic acid **2** to the target hydroxamic acid **3** was achieved via a mixed anhydride formed from **2** and ethyl chloroformate in the presence of triethylamine. The mixed anhydride was reacted *in situ* with freshly prepared hydroxylamine to yield *scriptaid* (**3**) in 71%. The reactions of this two-step procedure for the synthesis of *scriptaid* were repeated three times and the yields were reproducible within 5%.

Experimental Section

Melting points (mp) were determined on a Boetius hot-stage microscope and are uncorrected. Infrared spectra (IR) were recorded on a Specord 71 spectrometer. ^{1}H NMR and ^{13}C NMR spectra were acquired on a Bruker AV600 spectrometer in dimethyl sulfoxide-d6. Chemical shifts were reported in parts per million (ppm, δ) relative to the solvent peak (δ 2.50 ppm for ^{1}H; δ 39.5 ppm for ^{13}C NMR). Coupling constants (J) were measured in hertz (Hz). Reactions were monitored by thin-layer chromatography (TLC) on silica gel plates (Kieselgel 60 F_{254}).

*6-[1,3-Dioxo-1*H*-benzo[de]isoquinolin-2(3*H*)-yl]hexanoic acid (2)*

A suspension of 1,8-naphthalic anhydride (**1**, 1.98 g, 10 mmol) and ε-aminocapronic acid (1.98 g, 15 mmol) in propionic acid (50 mL) was refluxed for 4 h, until the anhydride **1** was no longer detectable by TLC (toluene:chloroform:ethyl acetate/3:1:1). The obtained solution was poured into ice-water (200 mL) with vigorous stirring. The product was precipitated, filtered and washed with water (50 mL). Recrystallization from ethanol afforded **2** (2.46 g, 79%) as a white powder, mp 135–136°C (*lit.*[15] mp 136°C). IR (nujol): 2900–3100, 1690, 1660, 1590, 1430,1340, 1220, 790 cm^{-1}. ^{1}H NMR (DMSO-d_6, 600 MHz): δ 1.31–1.36 (m, 2H, CH_2), 1.51–1.56 (m, 2H, CH_2), 1.59–1.64 (m, 2H, CH_2), 2.21 (t, 2H, CH_2CO,

J = 7.4), 4.01 (t, 2H, NCH_2, J = 7.4), 7.84 (t, 2H, ArH, J = 7.6), 8.42 (d, 2H, ArH, J = 8.2), 8.46 (d, 2H, ArH, J = 7.1), 12.00 (s, 1H, COOH). ^{13}C NMR (DMSO-d_6, 151 MHz): δ 24.7, 26.5, 27.7, 33.9, 39.9, 122.5, 127.7, 127.8, 131.2, 131.7, 134.7, 163.8, 174.9.

6-[1,3-Dioxo-1H***-benzo[de]isoquinolin-2(3***H***)-yl]-***N***-hydroxyhexaneamide (***Scriptaid***, 3)***

To a cooled solution of carboxylic acid **2** (1.40 g, 4.5 mmol) in tetrahydrofuran (10 mL), triethylamine (0.9 mL, 6.3 mmol) was added, followed by ethyl chloroformate (0.6 mL, 6.0 mmol). A precipitate of triethylamine hydrochloride appeared. The mixture was stirred at 0 °C for 15 min and then filtered off. The filtrate was added to a suspension of hydroxylamine, prepared by mixing of solutions of hydroxylamine hydrochloride (0.54 g, 7.8 mmol) in methanol (10 mL) and potassium hydroxide (0.44 g, 6.2 mmol) in methanol (5 mL). The resulting mixture was stirred 1 h at room temperature (TLC - chloroform:methanol / 9:1). The solvents were evaporated under reduced pressure and water (50 mL) was added to the residue. The obtained precipitate was filtered off, washed with water and dried in air. Recrystallization from acetonitrile gave **3** (0.95 g, 71%) as white crystals, mp. 152–153°C. IR (nujol): 3150–3100, 3050, 1640, 1610, 1590, 1450, 1350, 790 cm^{-1}. ^{1}H NMR (DMSO-d_6, 600 MHz): δ 1.28–1.33 (m, 2H, CH_2), 1.51–1.56 (m, 2H, CH_2), 1.59–1.64 (m, 2H, CH_2), 1.95 (t, 2H, CH_2CO, J = 7.4), 3.99–4.00 (m, 2H, NCH_2), 7.83–7.86 (m, 2H, ArH), 8.42–8.47 (m, 4H, ArH), 8.68 (s, 1H, OH), 10.34 (s, 1H, NH). ^{13}C NMR (DMSO-d_6, 151 MHz): δ 25.4, 26.6, 27.8, 32.6, 40.0, 122.5, 127.7, 127.8, 131.2, 131.7, 134.8, 163.8, 169.5.

Anal. Calcd for $C_{18}H_{18}N_2O_4$: C, 66.25; H, 5.56; N, 8.58. Found: C, 66.12; H, 5.77; N, 8.36.

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References

1. P. A. Marks, T. Millery and V. M. Richon, *Curr. Opin. Pharmacol*., **3**, 344 (2003).
2. P. A. Marks and M. Dokmanovic, *Expert Opin. Investig. Drugs*, **14**, 1497 (2005).
3. W. K. Rasheed, R. W. Johnstone and H. M. Prince, *Expert Opin. Investig. Drugs*, **16**, 659 (2007).
4. W. K. Kelly, O. A. O'Connor and P. A. Marks, *Expert Opin. Investig. Drugs*, **11**, 1695 (2002).
5. T. A. Miller, *Expert Opin. Ther. Patents*, **14**, 791 (2004).
6. C. Monneret, *Eur. J. Med. Chem*., **40**, 1 (2005).
7. M. Paris, M. Porcelloni, M. Binaschi and D. Fattori, *J. Med. Chem*., **51**, 1505 (2008).
8. P. Bertrand, *Eur. J. Med. Chem*., **45**, 2095 (2010).
9. P. A. Marks, *Expert Opin. Investig. Drugs*, **19**, 1049 (2010).
10. J. M. Wagner, B. Hackanson, M. Lübbert and M. Jung, *Clin. Epigenet*., **1**, 117 (2010).

11. F. Thaler and S. Minucci, *Expert Opin. Drug Discov.*, **6**, 393 (2011).

12. T. A. Miller, D. J. Witter and S. Belvedere, *J. Med. Chem.*, **46**, 5097 (2003).

13. G. H. Su, T. A. Sohn, B. Ryu and S. E. Kern, *Cancer Res.*, **60**, 3137 (2000).

14. N. Takai, T. Ueda, M. Nishida, K. Nasu and H. Narahara, *Int. J. Mol. Med.*, **17**, 323 (2006).

15. F. Nolde, J. Qu, C. Kohl, N. G. Pschirer, E. Reuther and K. Müllen, *Chem. Eur. J.*, **11**, 3959 (2005).