Bioorganic Chemistry 59 (2015) 145–150

Contents lists available at ScienceDirect

Bioorganic Chemistry

journal homepage: www.elsevier.com/locate/bioorg

An efficient synthesis of SK-658 and its analogs as potent histone deacetylase inhibitors

Md. Shahidul Islam [a,b,*], Md. Nurul Islam [a,b], Md. Ashraful Hoque [a,c], Norikazu Nishino [a], Tamaki Kato [a], Hyun-Jung Kim [d], Akihiro Ito [e], Minoru Yoshida [e]

[a] Graduate School of Life Science and Systems Engineering, Kyushu Institute of Technology, Kitakyushu 808-0196, Japan
[b] Department of Chemistry, Faculty of Science, University of Rajshahi, Rajshahi 6205, Bangladesh
[c] Department of Biochemistry and Molecular Biology, Faculty of Science, University of Rajshahi, Rajshahi 6205, Bangladesh
[d] BioRunxInc., Seoul 110-749, Republic of Korea
[e] Chemical Genetics Laboratory/Chemical Genomics Research Group, RIKEN Advanced Science Institute, Saitama 351-0198, Japan

ARTICLE INFO

Article history:
Received 15 November 2014
Available online 7 March 2015

Keywords:
Histone deacetylase inhibitor
Zinc binding group
SK-658 analogs
SS-hybrid

ABSTRACT

SK-658 is a potent histone deacetylase (HDAC) inhibitor that showed higher activity than SAHA due to the presence of extended hydrophobic group. We designed and synthesized thioester and SS-hybrid bearing SK-658 analogs as HDAC inhibitors. All the compounds were active in nano molar range and showed higher inhibitory activity than SAHA and SK-658. Among these, disulfide compounds showed the highest activity.

1. Introduction

The increased focus on inhibitors of HDAC enzymes as targets for cancer treatment originates from their ability to alter several cellular functions. The search for compounds with anti-tumor activities to develop novel HDAC inhibitors with potency and safety is still going on and with no doubt, very promising area for cancer chemotherapy. Efficacy of HDAC inhibitors is generally considered to be dependent upon the three groups: (1) the terminal zinc binding group which interacts with the active site, (2) a linker group which occupies the tube-like hydrophobic channel and (3) a surface recognition group which interacts with residues on the surface of the active site. The linker group has been optimized as five or six methylene units [1,2]. Targeting surface recognition group modification and zinc binding group optimization, a large number of structurally diverse HDAC inhibitors have been reported in the literatures and patented as the possible candidates for cancer drug. The surface binding groups reported so far are aliphatic [3], aromatic [4], non-peptides [5], mono-peptides [6], cyclic tetrapeptides [7–11], bicyclic tetrapeptides [12,13] etc. and the zinc binding groups are, for instance, hydroxamic acid [14], retro-hydroxamic acid [11], o-aminoanilide, thioether [4], ketone, hydroxymethylketone, carbonyl [15], trifluoromethylketone [10], methoxymethylketone, azide, acrylamide, chloroacetamide, triazolyl [16], borate [17], mercaptan, carboxyl [18], phosphate [19] and so on.

Now the burning question is to find out potent and isoform selective HDAC inhibitors to avoid various side effects. One of the ways is the combination of surface recognition and zinc binding groups. Several reports, for instance, thiol based SAHA analogs [4], chlamydocin analogs [15] etc, on the combination of surface recognition and zinc binding groups have been published.

The release of anticancer drug, ISTODAX® (FK228) (Fig. 1) for the treatment of cutaneous T-cell lymphoma (CTCL) [20] draws special attention for sulfur containing zinc binding groups. Very recently, we reported mono and bicyclic tetrapeptides thioester [21] and CHAP31, trapoxin B and HC-toxin based bicyclic tetrapeptides disulfide [22,23] as potent histone deacetylase inhibitors. In the present study, we report the design and synthesis of SK-658 analog HDAC inhibitors by replacing hydroxamic acid group with different thioesters and SS-hybrids.

2. Results and discussion

2.1. Design

SK-658 has the same linker and zinc binding group region as SAHA (suberoylanilide hydroxamic acid) [24]. The IC_{50} values of SK-658 and SAHA have been reported as 2.5 nM and 200 nM

* Corresponding author.
E-mail address: shahidulchem@yahoo.com (Md. Shahidul Islam).

http://dx.doi.org/10.1016/j.bioorg.2015.02.009
0045-2068/

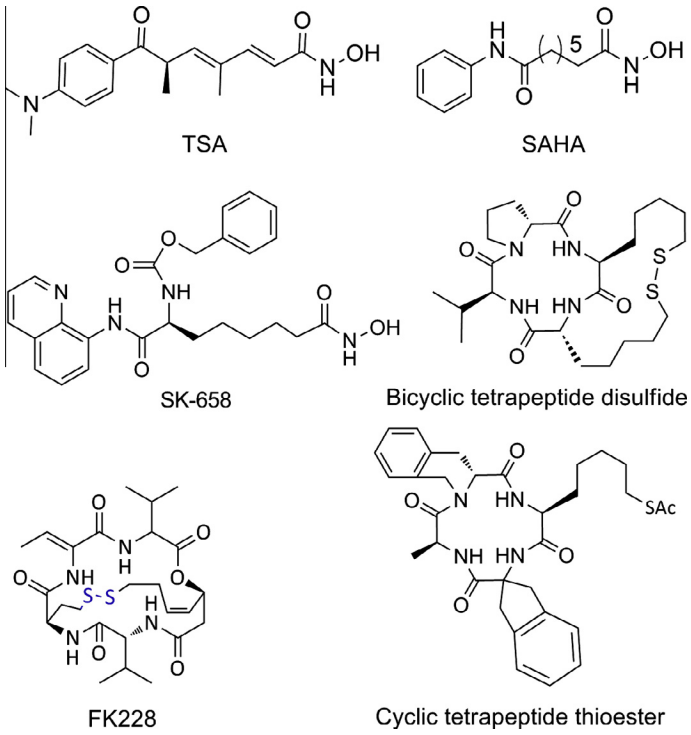


Fig. 1. Some HDAC inhibitors with different structural features.

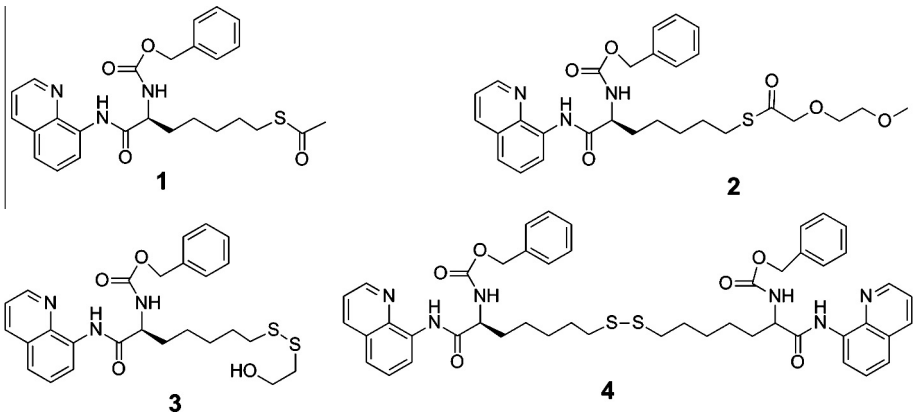


Fig. 2. Structures of designed SK-658 analog HDAC inhibitors.

respectively [6]. Therefore, SK-658 is 80-fold more active than SAHA only due to the presence of extra hydrophobic group in the surface binding part. Considering the potency of the surface binding group of SK-658 and sulfur containing zinc binding group, we designed a series of SK-658 analogs by replacing hydroxamic acid with different thioester and SS-hybrid HDAC inhibitors (Fig. 2).

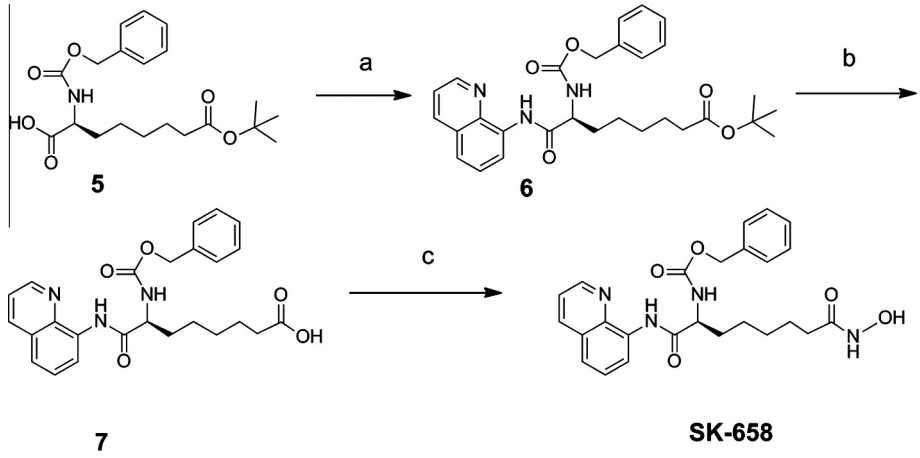
2.2. Synthesis

SK-658 was synthesized starting from protected L-amino suberic acid Z-L-Asu(O^{t}Bu)-OH (**5**). Compound **5** was coupled with 8-amino quinoline (AQ) in anhydrous dichloromethane (DCM) in the presence of coupling agent DCC at room temperature to yield Z-L-Asu(O^{t}Bu)-QA (**6**). After deprotection of tertiary butoxy group by TFA, hydroxamic acid was incorporated by reacting with hydroxyl amine hydrochloride ($HCl{\cdot}H_2NOH$) in presence of coupling agent BOP to yield SK-658 (see Scheme 1).

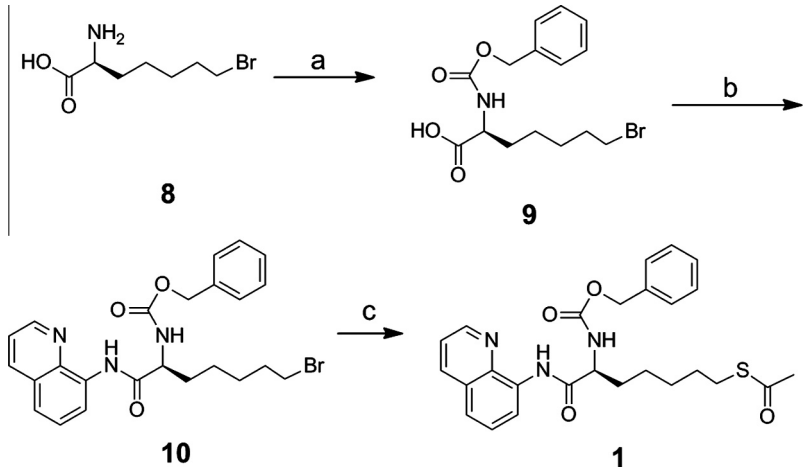
SK-658 analogs were successfully synthesized starting from 2-amino-7-bromoheptanoic acid (H-L-Ab-7-OH) (**8**). The condensation between H-L-Ab-7-OH and benzyloxycarbonyl chloride (Z–Cl) was carried out in NaOH and ether at 0 °C. The oily product, Z-L-Ab7-OH (**9**) was then coupled with AQ in DCM in the presence of DCC to get the crystalline solid compound Z-L-Ab7-QA (**10**). The desired thioester compound Z-L-Am7(Ac)-QA (**1**) was obtained by treating compound **10** with potassium thioacetate (AcSK) in DMF at room temperature (Scheme 2).

The thioester, Z-L-Am7(Ac)-QA (**1**) was treated with $MeNH_2$/MeOH in DMF to obtain the corresponding thiol (mercaptan). The thiol was treated separately with 2-(2-methoxyethoxy)acetyl chloride, 2-marcaptoethanol and iodine to obtain Z-L-Am7(AcEtMe)-QA (**2**), Z-L-Am7(betaMe)-QA (**3**) and (Z-L-Am7(S-)-QA)$_2$ (**4**) respectively (Scheme 3).

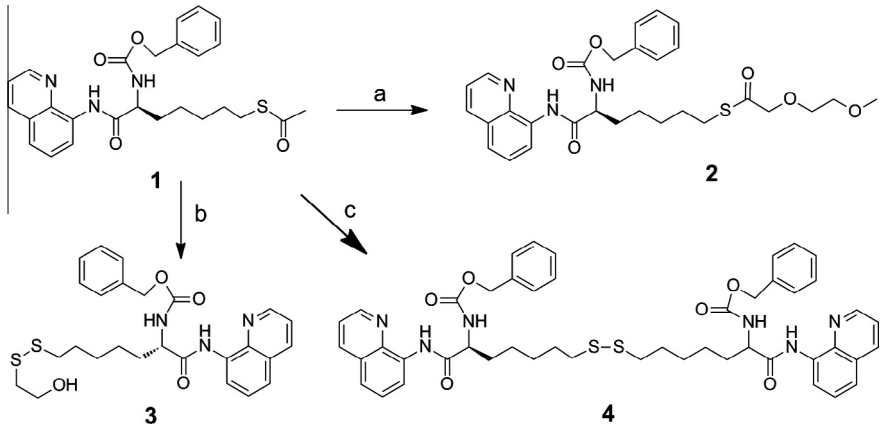
All the synthesized compounds were characterized by high resolution FAB-MS and high performance liquid chromatography (HPLC). The purity of the compounds was determined by HPLC analysis and the synthesized compounds showed purity 97–100%.



Scheme 1. Synthesis of SK-658. Reagents and conditions: (a) DCC, 8-aminoquinoline, 16 h, 25 °C, 75%; (b) TFA, 3 h, 25 °C, 86%; (c) DMF, HCl·H_2NOH, benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate (BOP), DIEA, 30 min, 25 °C, 63%.



Scheme 2. Synthesis of designed compound **1**. Reagents and conditions: (a) Z–Cl, NaOH (aq), ether, 0 °C, 3 h, 81%; (b) 8-aminoquinoline, DCC, DCM, 86%; (c) AcSK, DMF, 12 h, 68%.



Scheme 3. Synthesis of designed compounds **2**–**4**. Reagents and conditions: (a) 2-(2-methoxyethoxy)acetyl chloride, $MeNH_2$/MeOH, DMF, 16 h, 25 °C, 27%; (b) 2-marcaptoethanol, $MeNH_2$/MeOH, DMF, I_2/EtOH, 5 h, 25 °C, 60%; (c) $MeNH_2$/MeOH, DMF, I_2/EtOH, 5 h, 25 °C, 86%.

2.3. Enzyme inhibition and biological activity

The synthesized compounds were assayed for HDAC inhibitory activity using HDAC1, HDAC4 and HDAC6 enzymes prepared by 293T cells [25] with the aid of 0.1 mM of dithiothreitol (DTT) which is known to reduce S–S bond to sulfhydryl group. In addition, to know the inhibitory activity of these compounds in cell based condition, we carried out p21 promoter assay according to the

Table 1
HDAC inhibitory activity and p21 promoter assay data of synthesized and reported compounds.

Compounds	HPLC retention time (min)	IC_{50} (nM)			p21 promoter assay EC_{1000} (nM)
		HDAC1	HDAC4	HDAC6	
SAHA	–	290	340	270	1200
SK-658	6.36	10	11	45	12
1	7.68	47	18	34	49
2	8.19	19	18	29	61
3	7.88	4.9	2.0	3.2	82
4	10.76	8.2	3.4	7.5	7800

The IC_{50} and EC_{1000} values were the means of at least three independent experiments.

literature [15]. Detailed experimental procedure for the preparation and assay performed are being explained in Section 4. The results of HDAC inhibitory activity and the p21 promoter assay of the compounds are shown in Table 1.

The synthesized compounds were active in nano molar range against HDAC1, 4 and 6 in both cell free and cell based conditions and were more active than the approved anticancer drug, SAHA.

The higher inhibitory activity of SS-hybrid compounds **3** and **4** than their mother compound, SK-658 implies that the sulphydryl group has strong affinity to the active site compared to hydroxamic acid group. This observation was supported by our previous work [16].

In cell-free conditions, SS-hybrid compounds **3** and **4** were more active than thioester compounds **1** and **2**. The similar observation was also reported by Nishino and co-workers [26]. Although both thioester and SS-hybrid groups reduced to sulfhydryl group by DTT, the difference in activity may be due to the difference in reduction mechanism. Hogue et al. reported that the inhibitory activity of disulfide and thioester were increased in different extent in presence of DTT. They assumed that the disulfide group reduced completely while the thioester reduced partially in presence of DTT [22].

However, in cell based condition the reverse trend was observed. This may be due to the different reduction mechanism inside the cell [25]. The least *in vivo* activity of compound **4** can be explained by transport mechanism of drug molecules through the cell membrane. Generally lipid soluble molecule easily diffuses across the cell membrane. Small drug molecule diffuse more rapidly than large drug molecule [27]. As a large molecule compared to other compounds (**1**–**3**), it is not favorable for this compound **4** to diffuse across the cell membrane easily and ultimate results is its less activity.

3. Conclusion

In this paper, we describe the designed and easy synthesis of SK-658 and its analogs having thioesters and SS-hybrid groups as HDAC inhibitor. All the compounds were active in nano molar range. Among these, disulfide compounds **3** and **4** showed the highest activity. Due to easy synthesis, excellent activity and stability, these compounds demanding more advanced research to be potential drug candidates.

4. Experimental

4.1. General

Unless otherwise noted, all solvents and reagents were reagent grade and used without purification. Flash chromatography was performed using silica gel 60 (230–400) eluting with solvents as indicated. All compounds were routinely checked by thin layer chromatography (TLC) or high performance liquid chromatography (HPLC). TLC was performed on aluminum-backed silica gel plates (Merck DC-Alufolien Kieselgel 60 F_{254}) with spots visualized by UV light. Analytical HPLC were performed on a Hitachi instrument equipped with a chromolith performance RP-18e column. The mobile phases used were A: H_2O with 0.1% TFA, B: CH_3CN with 0.1% TFA using a solvent gradient of A–B over 15 min with detection at 220 nm with a flow rate of 2 mL/min. FAB-mass spectra and high resolution mass spectra (HRMS) were measured on a JEOL JMS-SX 102A instrument.

4.2. Synthesis of Z-L-Asu(NHOH)-QA (SK-658)

4.2.1. Synthesis of Z-L-Asu(O^tBu)-QA (**6**)

To a chilled solution of Z-L-Asu(O^tBu)-OH (**5**) (0.759 g, 2 mmol) in anhydrous DCM (4 mL), DCC (0.206 g, 1 mmol) was added and stirred for 1 h. 8-Aminoquinoline (0.346 g, 2.4 mmol) was added and stirred at room temperature for 3 h. The reaction mixture was cooled again and DCC (0.289 g, 1.4 mmol) was added and stirred for 12 h at room temperature. After completion of the reaction, DCM was evaporated and the residue was dissolved in EtOAc and successfully washed with 10% citric acid, 4% $NaHCO_3$ and brine respectively. The ethyl acetate solution was dried over anhydrous $MgSO_4$ and concentrated to remain an oily substance which was purified by silica gel chromatography using a mixture of chloroform and methanol (99:1) to yield Z-L-Asu(O^tBu)-QA (**6**) (0.76 g, 1.50 mmol, 75%).

4.2.2. Preparation of Z-L-Asu-QA (**7**)

Z-L-Asu(O^tBu)-QA (**6**) (0.430 g, 0.85 mmol) was dissolved in TFA (3 mL) completely and kept at room temperature for 3 h with occasional sacking. After completion of the tertiary butoxide group de-protection, TFA was evaporated and the residue was crystallized with ether/pet ether to yield Z-Asu-QA (**7**) (0.33 g, 0.73 mmol, 86%).

4.2.3. Synthesis of SK-658

To a solution of Z-L-Asu-QA (**7**) (0.160 g, 0.35 mmol) in DMF (4 mL), $HCl{\cdot}H_2NOH$ (49 mg, 0.7 mmol), BOP reagent (0.232 g, 0.525 mmol), DIEA (274 μL, 1.58 mmol) were added and stirred for 30 min at room temperature. After completion of the reaction, DMF was evaporated and the residue was washed with water and crystallized with ether to yield Z-L-Asu (NHOH)-QA (0.103 g, 0.22 mmol, 63%). Analytical RP HPLC, retention time 6.36 min, purity 97%. HRMS (FAB, *m*/*z*): $(M + H)^+$ found: 465.2141 (calcd for $C_{25}H_{29}N_4O_5$: 465.2138).

4.3. Synthesis of Z-L-Am7(Ac)-QA (**1**)

4.3.1. Synthesis of Z-L-Ab7-OH (**9**)

To a cooled solution of H-L-Ab7-OH (2-amino-7-bromoheptanoic acid) **(8)** (2.23 g, 10 mmol) in 1 M aqueous sodium hydroxide (12 mL) containing ether (3 mL), Z–Cl (0.42 mL, 3 mmol) was added and stirred for 15 min. To this solution, 1 M aqueous sodium hydroxide (10 mL) and Z–Cl (1.7 mL, 12 mmol) were added in separate four portions in every 15 min with stirring. After completion of the reaction, the aqueous phase was washed with ether while pH of the aqueous layer was maintained in the basic region. The acid was extracted into ethyl acetate at pH 3–4 by using solid citric acid. The organic phase was dried with anhydrous magnesium sulfate, filtered and evaporated to get the oily Z-L-Ab7-OH (**9**) (3.57 g, 10 mmol, 100%). Analytical RP HPLC, retention time 7.19 min, 81%.

*4.3.2. Synthesis of Z-L-Ab7-QA (**10**)*

To a cooled solution of Z-L-Ab7-OH (**9**) (3.45 g, 9.7 mmol) in anhydrous DCM (20 mL), DCC (0.6 equiv, 1.20 g, 5.8 mmol) was added and stirred for 1 h. 8-aminoquinoline (1.39 g, 9.7 mmol) was added and stirred for 3 h. The reaction mixture was cooled again and DCC (0.6 equiv, 1.20 g, 5.8 mmol) was added and stirred for 12 h at room temperature. After completion of the reaction, DCM was evaporated and the residue was dissolved in ethyl acetate and successively washed with 10% citric acid, 4% sodium bicarbonate and brine respectively. The ethyl acetate solution was dried over anhydrous $MgSO_4$ and concentrated to remain an oily substance which was purified by silica gel chromatography using a mixture of chloroform and methanol (99:1) and crystallized with a mixture of ether and petroleum ether (1:6, v/v) to yield Z-L-Ab7-QA (**10**) (4.03 g, 8.34 mmol, 86%). Analytical RP HPLC, retention time 8.07 min, 100%.

*4.3.3. Synthesis of Z-L-Am7(Ac)-QA (**1**)*

To a solution of Z-L-Ab7-QA (**10**) (3.81 g, 7.9 mmol) in DMF (63 mL), potassium thioacetate (1.5 equiv, 1.35 g, 11.8 mmol) was added and stirred for 12 h at room temperature. After completion of the reaction, DMF was evaporated and the residue was dissolved in ethyl acetate and successively washed with 10% citric acid and brine. The ethyl acetate solution was dried over anhydrous $MgSO_4$ and concentrated to remain an oily substance which was purified by silica gel chromatography using a mixture of chloroform and methanol (99:1) and crystallized with a mixture of ether and petroleum ether (1:6, v/v) to yield Z-L-Am7(Ac)-QA (**1**) (2.57 g, 5.36 mmol, 68%). Analytical RP HPLC, retention time 7.68 min, purity 100%. HRMS (FAB, *m*/*z*): $(M + H)^+$ found: 480.1937 (calcd for $C_{26}H_{29}N_3O_4S$: 480.1957).

*4.4. Synthesis of Z-L-Am7(AcEtMe)-QA (**2**)*

To a cooled solution of Z-L-Am7(Ac)-QA (**1**) (1.17 g, 2.45 mmol) in DMF (25 mL), 40% solution of $MeNH_2$/MeOH (3 mL, 27 mmol) was added and stirred at room temperature for 5 h under argon. DMF was evaporated and the residue was dissolved in pyridine (5 mL) to which 2-(2-methoxyethoxy)acetyl chloride (1 equiv, 2.45 mmol, 0.373 g) was added and stirred overnight at room temperature. After completion of the reaction, pyridine was evaporated and the residue was dissolved in ethyl acetate and washed with brine. The ethyl acetate solution was dried over anhydrous $MgSO_4$ and concentrated to an oily substance which was subjected to gel filtration to get the oily Z-L-Am7(AcEtMe)-QA (**2**) (0.37 g, 0.67 mmol, 27%). Analytical RP HPLC, retention time 8.19 min, purity 100%. HRMS (FAB, *m*/*z*): $(M + H)^+$ found: 554.2350 (calcd for $C_{29}H_{35}N_3O_6S$: 554.2325).

*4.5. Synthesis of Z-L-Am7(betaMe)-QA (**3**)*

To a cooled solution of Z-L-Am7(Ac)-QA (**1**) (0.80 g, 1.67 mmol) in DMF (17 mL), 40% solution of $MeNH_2$/MeOH (2 mL, 18 mmol) was added and stirred at room temperature for 5 h under argon. DMF was evaporated and the residue was dissolved in DMF (50 mL) to which 2-marcaptoethanol (10 equiv, 16.7 mmol, 1.17 mL) was added and stirred. To this reaction mixture, iodine (5.5 equiv, 2.33 g, 9.19 mmol) solution in ethanol was added drop wise. After completion of the reaction, DMF was evaporated and the residue was dissolved in ethyl acetate and washed with brine. The ethyl acetate solution was dried over anhydrous $MgSO_4$ and concentrated to an oily substance which was subjected to gel filtration to get the oily Z-L-Am7(betaMe)-QA (**3**) (0.52 g, 1.01 mmol, 60%). Analytical RP HPLC, retention time 7.88 min, purity 100%. HRMS (FAB, *m*/*z*): $(M + H)^+$ found: 514.1833 (calcd for $C_{26}H_{31}N_3O_4S_2$: 514.1834).

*4.6. Synthesis of (Z-L-Am7(S-)-QA)$_2$ (**4**)*

To a cooled solution of Z-L-Am7(Ac)-QA (**1**) (0.48 g, 1 mmol) in DMF (10 mL), 40% solution of $MeNH_2$/methanol (1 mL, 9 mmol) was added and stirred at room temperature for 5 h under argon. DMF was evaporated and the residue was dissolved in DMF (25 mL) to which iodine (1 equiv, 0.253 g, 1 mmol) solution in ethanol was added drop wise. After completion of the reaction, DMF was evaporated and the residue was dissolved in ethyl acetate and washed with brine. The ethyl acetate solution was dried over anhydrous $MgSO_4$ and concentrated to an oily substance which was subjected to gel filtration to get the crystalline solid (Z-L-Am7(S-)-QA)$_2$ (**4**) (0.38 g, 0.86 mmol, 86%). Analytical RP HPLC, retention time 7.88 min, purity 100%. HRMS (FAB, *m*/*z*): $(M + H)^+$ found: 873.3457 (calcd for $C_{48}H_{53}N_6O_6S_2$: 873.3468).

4.7. HDACs preparation and enzyme activity assay

In a 100-mm dish, 293T cells ($1–2 \times 10^6$) were grown for 24 h and transiently transfected with 10 μg each of the vector pcDNA3-HDAC1 for human HDAC1, pcDNA3-HDAC4 for human HDAC4, or pcDNA3-mHDA2/HDAC6 for mouse HDAC6, using the LipofectAMINE2000 reagent (Invitrogen). After successive cultivation in DMEM for 24 h, the cells were washed with PBS and lysed by sonication in lysis buffer containing 50 mM Tris–HCl (pH 7.5), 120 mM NaCl, 5 mM EDTA, and 0.5% NP40. The soluble fraction collected by micro centrifugation was precleared by incubation with protein A/G plus agarose beads (Santa Cruz Biotechnologies, Inc.). After the cleared supernatant had been incubated for 1 h at 4 °C with 4 μg of an anti-FLAG M2 antibody (Sigma–Aldrich Inc.) for HDAC1, HDAC4 and HDAC6, the agarose beads were washed three times with lysis buffer and once with histone deacetylase buffer consisting of 20 mM Tris–HCl (pH 8.0), 150 mM NaCl, and 10% glycerol. The bound proteins were released from the immune complex by incubation for 1 h at 4 °C with 40 μg of the FLAG peptide (Sigma–Aldrich Inc.) in histone deacetylase buffer (200 μL). The supernatant was collected by centrifugation. For the enzyme assay, 10 μL of the enzyme fraction was added to 1 μL of fluorescent substrate (2 mM Ac-KGLGK(Ac)-MCA) and 9 μL of histone deacetylase buffer, and the mixture was incubated at 37 °C for 30 min. The reaction was stopped by the addition of 30 μL of trypsin (20 mg/mL) and incubated at 37 °C for 15 min. The released amino methyl coumarin (AMC) was measured using a fluorescence plate reader. DTT was added simultaneously with drugs to the enzyme solutions. The 50% inhibitory concentrations (IC_{50}) were determined as the means with SD calculated from at least three independent dose response curves.

4.8. The p21 promoter assay

The human wild-type p21 promoter luciferase fusion plasmid, WWP-Luc, was a kind gift from Dr. B. Vogelstein. A luciferase reporter plasmid (pGW-FL) was constructed by cloning the 2.4 kb genomic fragment containing the transcription start site into *Hin*dIII and *Sma*I sites of the pGL3-Basic plasmid (Promega Co., Madison, WI). Mv1Lu (mink lung epitherial cell line) cells were transfected with the pGW-FL and a phagemid expressing neomycin/kanamycin resistance gene (pBK-CMV, Stratagene, La Jolla, CA) with the Lipofectamine reagent (Life Technology, Rockville, MD USA). After the transfected cells had been selected by 400 μg/mL Geneticin (G418, Life Technology), colonies formed were isolated. One of the clones was selected and named MFLL-9. MFLL-9 expressed a low level of luciferase, of which activity was enhanced by TSA in a dose-dependent manner. MFLL-9 cells (1×10^5) cultured in a 96-well multi-well plate for 6 h were incubated for

18 h in the medium containing various concentrations of drugs. The luciferase activity of each cell lysate was measured with a LucLite luciferase Reporter Gene Assay Kit (Packard Instrument Co., Meriden, CT) and recorded with a Luminescencer-JNR luminometer (ATTO, Tokyo, Japan). Data were normalized to the protein concentration in cell lysates. Concentrations at which a drug induces the luciferase activity 10-fold higher than the basal level are presented as the 1000% effective concentration (EC_{1000}).

Conflict of interest

The authors declare that they have no conflict of interest.

Acknowledgments

This study was supported by Kitakyushu Foundation for the Advancement of Industry, Science and Technology (FAIS), Japan Student Services Organization (JASSO) and Saneyoshi Scholarship Foundation.

Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bioorg.2015.02.009.

References

[1] K.V. Butler, A.P. Kozikowski, Curr. Pharm. Des. 14 (2008) 505–528.
[2] R. Breslow, P.A. Marks, R.A. Rifkind, B. Jursic, PTC Int. Appl. WO 93/07148, April 15, 1993.
[3] T. Suzuki, A. Kouketsu, Y. Itoh, S. Hisakawa, S. Maeda, M. Yoshida, H. Nakagawa, N. Miyata, J. Med. Chem. 49 (2006) 4809–4812.
[4] T. Suzuki, A. Kouketsu, A. Matsuura, A. Kohara, S. Ninomiya, K. Kohda, N. Miyata, Bioorg. Med. Chem. Lett. 14 (2004) 3313–3317.
[5] S.C. Mwakwari, W. Guerrant, V. Patil, S.I. Khan, B.L. Tekwani, Z.A. Gurard-Levin, M. Mrksich, A.K. Oyelere, J. Med. Chem. 53 (16) (2010) 6100–6111.
[6] D.F. Wang, O. Wiest, P. Helquest, H.Y. Lan-Hargest, N.L. Wiech, J. Med. Chem. 47 (2004) 3409–3417.
[7] N. Nishino, B. Jose, S. Okamura, S. Ebisusaki, T. Kato, Y. Sumida, M. Yoshida, Org. Lett. 5 (2003) 5079–5082.
[8] N. Nishino, G.M. Shivashimpi, P.B. Soni, M.P.I. Bhuiyan, T. Kato, S. Maeda, Tomonori G. Nishino, M. Yoshida, Bioorg. Med. Chem. 16 (2008) 437–445.
[9] G.M. Shivashimpi, S. Amagai, T. Kato, N. Nishino, S. Maeda, T.G. Nishino, M. Yoshida, Bioorg. Med. Chem. 15 (2007) 7830–7839.
[10] B. Jose, Y. Oniki, T. Kato, N. Nishino, Y. Sumida, M. Yoshida, Bioorg. Med. Chem. Lett. 14 (2004) 5343–5346.
[11] N. Nishino, D. Yoshikawa, L.A. Watanabe, T. Kato, B. Jose, Y. Komatsu, Y. Sumida, M. Yoshida, Bioorg. Med. Chem. Lett. 14 (2004) 2427–2431.
[12] N.M. Islam, T. Kato, N. Nishino, H.J. Kim, A. Ito, M. Yoshida, Bioorg. Med. Chem. Lett. 20 (2010) 997.
[13] M.A. Hoque, M.A. Islam, M.N. Islam, T. Kato, N. Nishino, A. Ito, M. Yoshida, Bioorg. Med. Chem. 22 (2014) 3862–3870.
[14] Y. Komatsu, K. Tomizaki, M. Tsukamoto, T. Kato, N. Nishino, S. Sato, T. Yamori, T. Tsuruo, R. Furumai, M. Yoshida, S. Horinouchi, H. Hayashi, Cancer Res. 61 (2001) 4459–4466.
[15] M.P.I. Bhuiyan, T. Kato, T. Okauchi, N. Nishino, S. Maeda, Tomonori G. Nishino, M. Yoshida, Bioorg. Med. Chem. 14 (2006) 3438–3446.
[16] M.S. Islam, M.P.I. Bhuiyan, M.N. Islam, T.K. Nsiama, N. Oishi, T. Kato, N. Nishino, A. Ito, M. Yoshida, Amino Acids 42 (2012) 2103.
[17] N. Suzuki, T. Suzuki, Y. Ota, T. Nakano, M. Kurihara, H. Okuda, T. Yamori, H. Tsumoto, H. Nakagawa, N. Miyata, J. Med. Chem. 52 (2009) 2909–2922.
[18] P. Jones, S. Altamura, P.K. Chakravarty, et al., Bioorg. Med. Chem. Lett. 16 (2006) 5948–35952.
[19] G.V. Kapustin, G. Fejer, J.L. Grounlund, D.G. McCafferty, E. Seto, F.A. Etzkorn, Org. Lett. 5 (2003) 3053–3056.
[20] J. Zain, D. Kaminetzky, O.A. O'Connor, Expert Rev. Hematol. 3 (2010) 187.
[21] M.A. Hoque, M.A. Islam, M.N. Islam, T. Kato, N. Nishino, A. Ito, M. Yoshida, Amino Acids 46 (2014) 2435–2444.
[22] M.A. Hoque, T. Arai, N. Nishino, H.J. Kim, A. Ito, M. Yoshida, Bioorg. Med. Chem. Lett. 22 (2012) 6770–6772.
[23] M.A. Hoque, M.A. Islam, M.N. Islam, T. Kato, N. Nishino, A. Ito, M. Yoshida, Bioorg. Med. Chem. 22 (2014) 3850–3855.
[24] V.M. Richon, S. Emiliani, E. Verdin, Y. Webb, R. Breslow, R.A. Rifkind, P.A. Marks, Proc. Natl. Acad. Sci. USA 95 (1998) 3003–3007.
[25] R. Furumai, A. Matsuyama, M. Kobashi, Cancer Res. 62 (2002) 4916.
[26] N. Nishino, B. Jose, S. Okamura, Org. Lett. 5 (2003) 5079.
[27] L. Shargel, Andrew B.C. Yu, Applied Biopharmaceutics and Pharmacokinetics, third ed., Prentice-Hall-International Inc., Limited, USA, 1993. pp. 77.