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Concise Syntheses and Antitumor Activities of α-Hydroxy(mercapto)amide Derivatives

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A novel process for preparing α-hydroxy(mercapto)-*N*-[6-(3-phenylureido)hexyl]amide derivatives was described and three new compounds **8-10** were synthesized. The antitumor activities on Hut102, MCF7 and HepG2 of the compounds **7-10** were assayed. The results showed that the target compounds **7-10** exhibited some antitumor activities against tumor cell lines.

Keywords: Histone deacetylase inhibitors, α-Hydroxy(mercapto)amide, Drug design, Antitumor activity.

INTRODUCTION

Histone acetylation and histone deacetylation are essential for chromatin remodeling and regulation of gene transcription in eukaryotic cells. Histone deacetylases and histone acetyltransferases are two classes of enzymes that catalyze the deacetylation and acetylation of lysine residues located in the NH_2 terminal tails of core histones[1,2]. Perturbations of this balance in the form of histone deacetylation are often observed in human tumors[3]. Aberrant activation of histone deacetylases results in the transcriptional repression of oncoprotein and is linked to the malignant phenotypes of tumors[4]. Thus, Histone deacetylase inhibitors have become promising anticancer agents in recent years. They have shown ability to block angiogenesis and cell cycling, as well as initiate differentiation and apoptosis[5-6]. At present, many of the histone deacetylases inhibitors such as suberoylanilide hydroxamic acid (SAHA), trichostatin A (TSA), Panobinostat (LBH 589) and MC 1568 have been reported (Fig. 1a) and the histone deacetylases inhibitors have potent anticancer effects *in vitro* and *in vivo*[7-8]. Among them, in 2006, Zolinza (SAHA, vorinostat) became the first histone deacetylases inhibitor to acquire FDA approval and is used for the management of the cutaneous manifestations of T-cell lymphoma[9]. On the whole, the classic pharmacophore

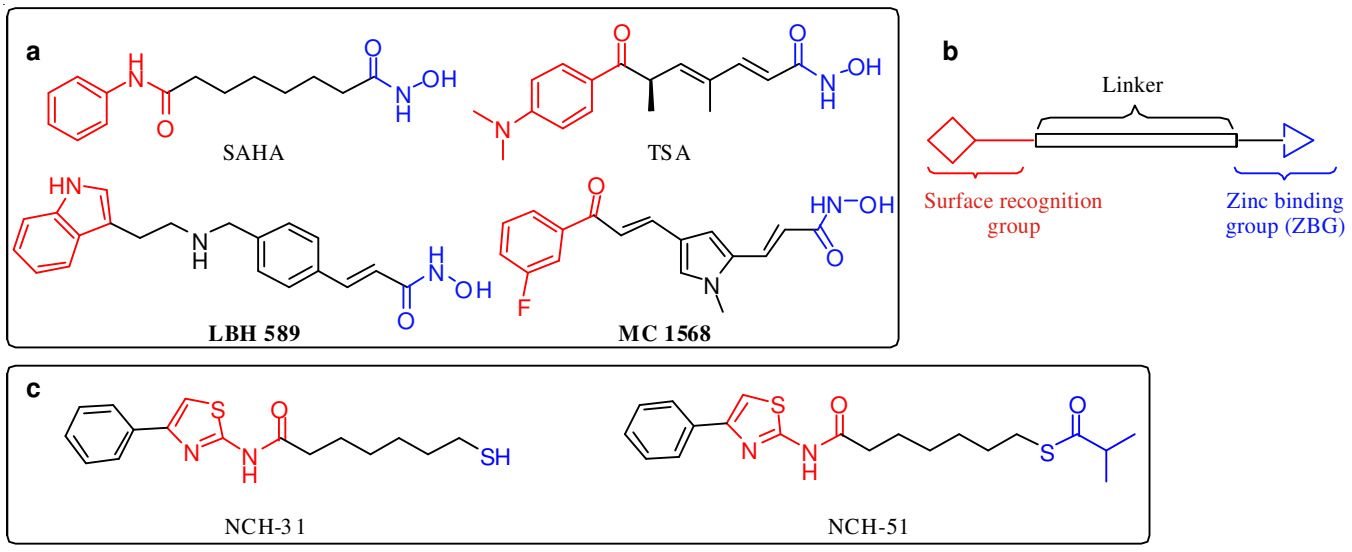


Fig. 1. Small molecule histone deacetylases inhibitors; (a) Selected examples of histone deacetylases inhibitors; (b) Pharmacophoric model of histone deacetylases inhibitors; (c) Structures of NCH-31 and NCH-51

for histone deacetylases inhibitors consists of three distinct structural motifs: the zinc-binding group (enzyme binding), a hydrophobic linker and a surface recognition group[10,11] (Fig. 1b). Typically, the common zinc-binding group of histone deacetylases inhibitors is the hydroxamate moiety. Study on the structural modifications of the hydro-xamate zinc-binding group of histone deacetylases inhibitors has recently attracted extensive attention. Kozikowski and coworkers reveals that mercaptoacetamide-based histone deacetylases inhibitors, in which the hydroxamate moieties of SAHA enzyme binding domain were replaced by mercaptomethyl amide, would probably avoid the dose-dependent toxicity associated with the hydro-xamate-based inhibitors[12]. Compounds containing a sulfydryl or isobutyryl sulfydryl in enzyme binding domain were both potent histone deacetylases inhibitors[13] (Fig. 1c). To search for novel antitumor hits, our research was initially based on the structure of SAHA. According to the strategy of bioisosteric replacement, the surface recongnition and enzyme binding domain were modified with phenylureido and α-hydroxy-(mercapto), respectively. Herein we wish to disclose our preliminary efforts on this subject.

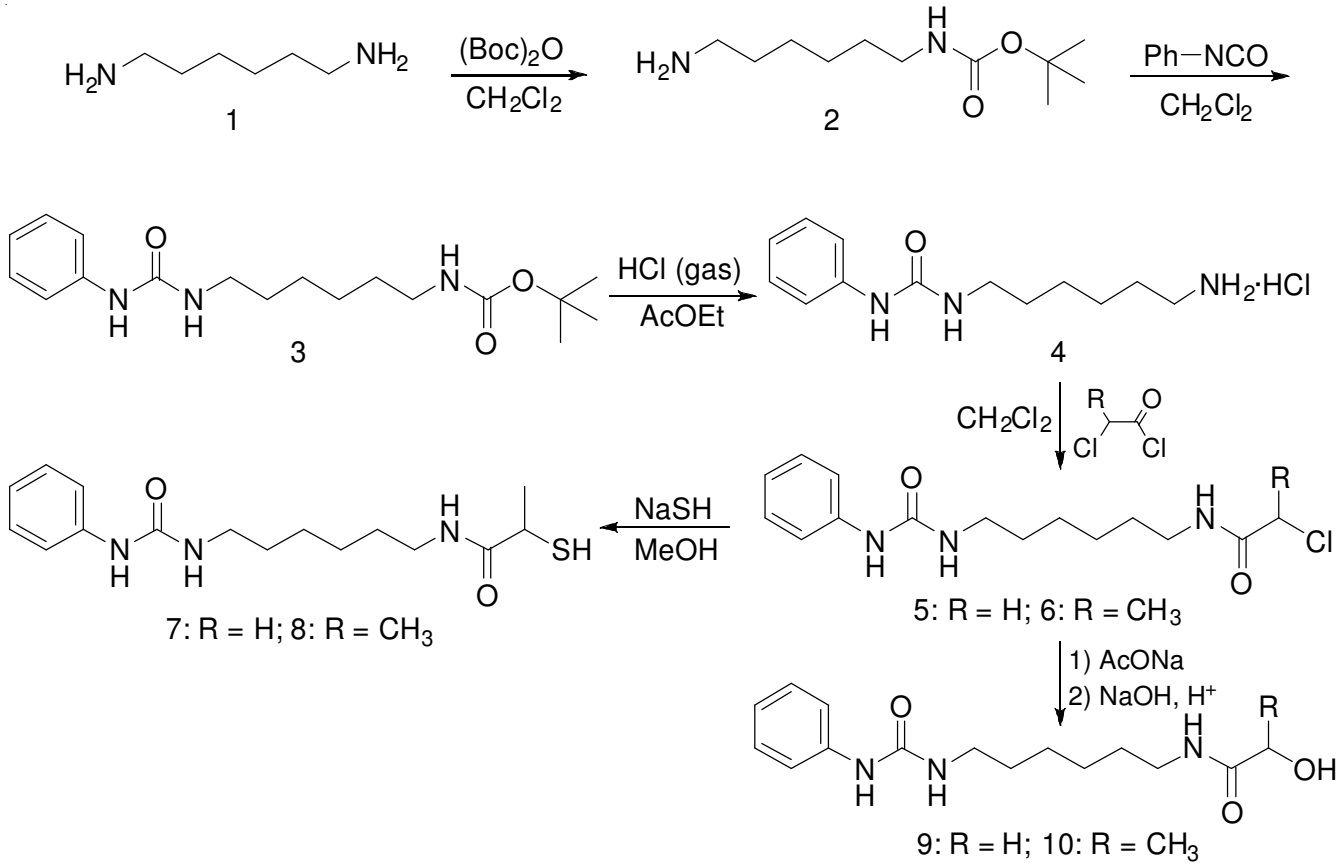
EXPERIMENTAL

Unless otherwise noted, reagents were purchased from commercial suppliers and used without further purification, as all solvents were redistilled before use. NMR spectra were recorded on a Mercury-Plus 400 spectrometer in $CDCl_3$ or DMSO-d_6 with TMS as the internal reference, the chemical shifts were reported in δ ppm. MS spectra were determined using a TraceMS 2000 or Waters 2Q4000 LC/MS organic mass spectrometer. Elemental analyses were performed on a Vario EL III elemental analysis instrument. Melting points were measured on a Buchi B-545 melting point apparatus and are uncorrected. Purity of all compounds was checked by TLC on precoated silica gel G plates (Kiesel gel 0.25 mm, 60G F_{254}, Qingdao, China).

Synthesis of α-hydroxy(mercapto)amides: The title compounds were synthesized by a convenient five-steps procedure as outlined in **Scheme-I**.

Preparation of *tert*-butyl 6-aminohexylcarbamate (2)[14,15]: To a solution of hexane-1,6-diamine (60 g, 0.516 mol) **1** in CH_2Cl_2 (200 mL) was added $(Boc)_2O$ (22.5 g, 0.103 mol) during 0.5 h at 0 °C, then the mixture was stirred at room temperature for 5 h, extracted with CH_2Cl_2 (150 mL × 3), dried with anhydrous magnesium sulfate, filtered off with suction. The combined organic layer was concentrated on a rotary evaporator to give colourless oil **2** in yield 96 % (21.5 g). The product was used directly for next reaction without purification.

Preparation of *tert*-butyl 6-(3-phenylureido)hexylcarbamate (3)[16,17]: To a solution of intermediate **2** (0.5 g, 2.31 mmol) in CH_2Cl_2 (6 mL) was added isocyanatobenzene (0.33 g, 2.77 mmol) at 0 °C, then the mixture was stirred at room temperature for 4 h, extracted with CH_2Cl_2 (50 mL × 3), dried with anhydrous magnesium sulfate, filtered off with suction. The combined organic layer was concentrated on a rotary evaporator, purified by chromatography on silica using petroleum ether/ethyl acetate (15:1, v/v) as eluent to give white solid **3** in yield 95 % (0.73 g). m.p. 97-99 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.26 (s, 4H, $CCCH_2CH_2CC$), 1.36 (s, 9H, 3 × CH_3), 1.41(s, 4H, CCH_2CCCH_2C), 2.88 (dd, J_1 = 6.4



Scheme-I: Synthetic route of α-hydroxy(mercapto) amide derivatives

Hz, J_2 = 10.6 Hz, 2H, N(CO)NCH$_2$), 3.04 (dd, J_1 = 6.4 Hz, J_2 = 10.6 Hz, 2H, O(CO)NCH$_2$), 6.08 (t, J = 5.6 Hz, 1H, PhN(CO)NH), 6.76 (t, J = 5.6 Hz, 1H, O(CO)NH), 6.85-7.37 (m, 5H, PhH), 8.35 (s, 1H, PhNH); EI MS: *m/z* (%) 336 ([M + 1]$^+$, 1), 335 (M$^+$, 4), 279 (10), 206 (3), 143 (12), 119 (2), 93 (100).

Preparation of 1-(6-aminohexyl)-3-phenylurea hydrochloride (4)[18]: In a 250 mL three neck round bottom flask, intermediate **3** (5.5 g, 0.016 mol) and ethyl acetate (150 mL) were added. HCl (gas) was passed in reaction mixture at room temperature, the mixture was stirred for 5 h, which was concentrated on a rotary evaporator to give white solid **4**, yield 97 % (4.35 g). m.p. 154-156 °C. ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm): 1.32 (s, 4H, CCCH$_2$CH$_2$CC), 1.41 (s, 2H, NCCH$_2$), 1.55 (s, 2H, (CO)NCCH$_2$), 2.77 (dd, J_1 = 13.2 Hz, J_2 = 6.8 Hz, 2H, NCH$_2$), 3.06 (dd, J_1 = 13.2 Hz, J_2 = 6.8 Hz, 2H, (CO)NCH$_2$), 6.41 (t, J = 5.2 Hz, 1H, PhN(CO)NH), 6.84-7.39 (m, 5H, PhH), 7.87 (s, 2H, NH$_2$), 8.76(s, 1H, PhNH); EI MS: *m/z* (%) 236 ([M + 1]$^+$, 1), 235 (M$^+$, 3), 219(1), 183(10), 149(4), 143(12), 93(100).

Preparation of 2-chloro-N-[6-(3-phenylureido)hexyl] acetamide (5)[19]: To a solution of intermediate **4** (2.0 g, 7.36 mmol) in CH$_2$Cl$_2$ (50 mL) was added Et$_3$N (2.23 g, 22.1 mmol). The mixture was stirred at room temperature for 1 h, then 2-chloroacetyl chloride (1.0 g, 8.85 mmol) was dropwise added at 0 °C. The resulting mixture was stirred at room temperature for 5 h, extracted with CH$_2$Cl$_2$ (60 mL × 3), dried with anhydrous magnesium sulfate, filtered off with suction. The combined organic layer was concentrated on a rotary evaporator, triturated with ethyl acetate (5 mL). The precipitate was filtrated and dried with vacuum to give white solid **5**, yield 73 % (1.67 g). m.p. 139-141 °C. ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm): 1.29 (s, 4H, CCCH$_2$CH$_2$CC), 1.43 (s, 4H, CCH$_2$CCCH$_2$C), 1.51 (d, J = 6.8 Hz, 3H, CH$_3$), 3.99 (dd, J_1 = 11.6 Hz, J_2 = 5.6 Hz, 4H, CH$_2$CCCCCH$_2$), 4.43 (dd, J_1 = 12.6 Hz, J_2 = 6.8 Hz, 1H, ClCH), 6.08 (t, J = 5.6 Hz, 1H, PhN(CO) NH), 6.84-7.37 (m, 5H, PhH), 8.18 (s, 1H, NH(CO)C), 8.35 (s, 1H, PhNH); EI MS: *m/z* (%) 313([M + 2]$^+$, 1), 311 (M$^+$, 3), 219(6), 174(12), 162(13), 128(21), 119(25), 106(22), 98(16), 93(100).

Preparation of 2-chloro-*N*-[6-(3-phenylureido)hexyl] propanamide (6): In the same way as compound **5**, intermediate compound **6** was synthesized. white solid, Yield: 71 %, m.p. 142-144 °C. ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm): 1.29 (s, 4H, CCCH$_2$CH$_2$CC), 1.43 (s, 4H, CCH$_2$CCCH$_2$C), 1.51(d, J = 6.8 Hz, 3H, CH$_3$), 3.99 (dd, J_1 = 11.6 Hz, J_2 = 5.6 Hz, 4H, CH$_2$CCCCCH$_2$), 4.43 (dd, J_1 = 12.6 Hz, J_2 = 6.8 Hz, 1H, ClCH), 6.08 (t, J = 5.6 Hz, 1H, PhN(CO)NH), 6.84-7.37 (m, 5H, PhH), 8.18 (s, 1H, NH(CO)C), 8.35 (s, 1H, PhNH); EI MS: *m/z* (%) 313 ([M + 2]$^+$, 1), 311 (M$^+$, 3), 219(6), 174(12), 162(13), 128(21), 119(25), 106(22), 98(16), 93(100).

Preparation of 2-mercapto-*N*-[6-(3-phenylureido)-hexyl]acetamide (7)[20]: To a solution of intermediate **5** (0.2 g, 0.64 mmol) in MeOH (15 mL) was added NaSH (54 mg, 0.96 mmol), the mixture was refluxed for 3 h. The reaction mixture was cooled to room temperature, evaporated in vacuum, purified by chromatography on silica using chloroform/methanol (10:1, v/v) as eluent to give white solid **7** in yield 75 % (0.15 g). m.p. 127-129 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 1.28 (m, 4H, CCCH$_2$CH$_2$CC), 1.41 (m, 4H, CCH$_2$CCCH$_2$C), 2.72 (t, J = 7.8 Hz, 1H, SH), 3.05 (m, 4H, CH$_2$CCCCCH$_2$), 3.58 (s, 2H, CH$_2$S), 6.10 (t, J = 5.4 Hz, 1H, PhN(CO)NH), 6.87-7.37 (m, 5H, PhH), 7.97 (t, J = 5.4 Hz, 1H, NH(CO)C), 8.37 (s, 1H, PhNH). ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 169.42, 155.20, 140.61, 128.62, 120.89, 117.51, 38.96, 38.79, 29.7, 29.0, 27.1, 26.1. LC MS calcd. 309.4, found 309.7 [M], 332.6 [M + Na]$^+$. Anal. calcd. for C$_{15}$H$_{23}$N$_3$O$_2$S (%): C, 58.22; H, 7.49; N, 13.58. Found (%): C, 58.17; H, 7.32; N, 13.37.

Preparation of 2-mercapto-*N*-[6-(3-phenylureido)hexyl]-propanamide (8): In the same way as compound **7**, the target compound **8** was synthesized. white solid, Yield: 69 %, m.p. 128-130 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 1.28 (m, 4H, CCCH$_2$CH$_2$CC), 1.32 (d, J = 6.8 Hz, 3H, CH$_3$), 1.41 (m, 4H, CCH$_2$CCCH$_2$C), 2.79 (d, J = 8.5 Hz, 1H, SH), 3.02 (m, 4H, CH$_2$CCCCCH$_2$), 3.41 (dd, J_1 = 7.0 Hz, J_2 = 8.5 Hz, 1H, SCH), 6.09 (t, J = 4.0 Hz, 1H, PhN(CO)NH), 6.85-7.38 (m, 5H, PhH), 7.91 (t, J = 5.1 Hz, 1H, NH(CO)C), 8.35 (s, 1H, PhNH); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 172.98, 155.74, 141.13, 129.13, 121.42, 118.11, 40.08, 39.17, 36.83, 30.26, 29.45, 26.60, 22.69; LC-MS calcd. for [C$_{16}$H$_{25}$N$_3$O$_2$S + 1]$^+$, 324, found, 324.1. [2 × C$_{16}$H$_{25}$N$_3$O$_2$S + Na]$^+$, 669, found, 669.3. Anal. calcd. for C$_{16}$H$_{25}$N$_3$O$_2$S: C, 59.41; H, 7.79; N, 12.99. Found: C, 59.37; H, 7.72; N, 13.07.

Preparation of 2-hydroxy-*N*-[6-(3-phenylureido)hexyl]-acetamide (9)[21]: To a solution of **5** (0.5 g, 1.6 mmol) in DMF (10 mL) was added CH$_3$COONa (0.26 g, 3.2 mmol). The mixture was stirred at 100 °C for 4 h, cooled to room temperature and extracted with ethyl acetate (50 mL × 3), dried with anhydrous magnesium sulfate, filtered off with suction. The combined organic layer was concentrated on a rotary evaporator to give residue. Therein NaOH (0.13 g, 3.2 mmol), H$_2$O (5 mL), acetone (5 mL) were added, the mixture was stirred at room temperature for 4 h. The resulting mixture was evaporated in vacuum to remove acetone, then H$_2$O (10 mL) was added, acidification by HCl to pH = 3, the precipitate was filtered and dried with vacuum to give white solid **9** in yield 80 % (0.37 g). m.p. 103-105 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 1.28 (m, 4H, CCCH$_2$CH$_2$CC), 1.42 (m, 4H, CH$_2$CCCH$_2$), 3.11 (m, 4H, CH$_2$CCCCCH$_2$), 3.78 (s, 2H, CH$_2$O), 5.44 (s, 1H, OH), 6.11 (t, J = 5.6 Hz, 1H, PhN (CO)NH), 6.85-7.23 (m, 5H, PhH), 7.70 (s, 1H, NH(CO)C), 8.37 (s, 1H, PhNH). ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 171.54, 155.18, 140.54, 128.58, 120.87, 117.54, 61.40, 38.93, 37.93, 29.68, 29.21, 26.08. LC MS calcd. 294.3, found 294.2 [M], 316.2 [M + Na]$^+$. Anal. calcd. for C$_{15}$H$_{23}$N$_3$O$_3$: C, 61.41; H, 7.90; N, 14.32. Found: C, 61.38; H, 7.82; N, 14.27.

Preparation of 2-hydroxy-N-[6-(3-phenylureido)hexyl]-propanamide (10): In the same way as compound **9**, the target compound **10** was synthesized. white solid, Yield: 76 %, m.p. 102-103 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 1.21 (d, J = 6.8, 3H, CH$_3$), 1.28 (m, 4H, CCCH$_2$CH$_2$CC), 1.44 (m, 4H, CCH$_2$CCCH$_2$C), 3.08 (m, 4H, CH$_2$CCCCCH$_2$), 3.94 (dd, J_1 = 6.0, J_2 = 12.0 Hz, 1H, COCH), 5.42 (s, 1H, OH), 6.11 (t, J = 5.2 Hz, 1H, PhN(CO)NH), 6.86-7.39 (m, 5H, PhH), 7.67 (s, 1H, NH(CO)C), 8.37 (s, 1H, PhNH). ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 174.27, 155.17, 140.55, 128.58, 120.87, 117.54, 67.23, 38.92, 38.00, 29.68, 29.15, 26.03, 21.11. LC MS calcd. 308.4, found 308.2 [M], 330.2 [M + Na]$^+$. Anal. calcd. for C$_{16}$H$_{25}$N$_3$O$_3$: C, 62.52; H, 8.20; N, 13.67. Found: C, 62.48; H, 8.15; N, 13.63.

Assay of antitumor activities: The cytotoxic activity of synthesized α-hydroxy (mercapto)-*N*-[6-(3-phenylureido)-hexyl]amide compounds **7-10** were evaluated against a panel of human cell lines, with SAHA and 5-Fu as the reference control. The cancer cell lines were cultured in Dulbecco's modified Eagle's medium (DMEM) supplement with 10 % fetal bovine serum (FBS). Approximately 4×10^3 cells, suspended in DMEM medium, were plated onto each well of a 96-well plate and incubated in 5 % CO_2 at 37 °C for 24 h. The subject compounds at indicated final concentrations were added to the culture medium and the cell cultures were continued for 72 h. Fresh MTT was added to each well at a terminal concentration of 0.5 mg/mL and incubated with cells at 37 °C for 4 h. The formazan crystals were dissolved in 100 µL DMSO each well and the absorbency at 492 nm (for absorbance of MTT formazan) and 630 nm (for the reference wavelength) was measured with the ELISA reader. All of the compounds were tested three times in each of the cell lines. The results expressed as IC_{50} (inhibitory concentration 50 %) were the averages of three determinations and calculated by Bliss method. The results were illustrated in Table-1 with Sorafenib as the positive control.

TABLE 1
ANTITUMOR ACTIVITIES OF THE COMPOUNDS **7-10** AGAINST THREE TUMOR CELL LINES *in vitro*

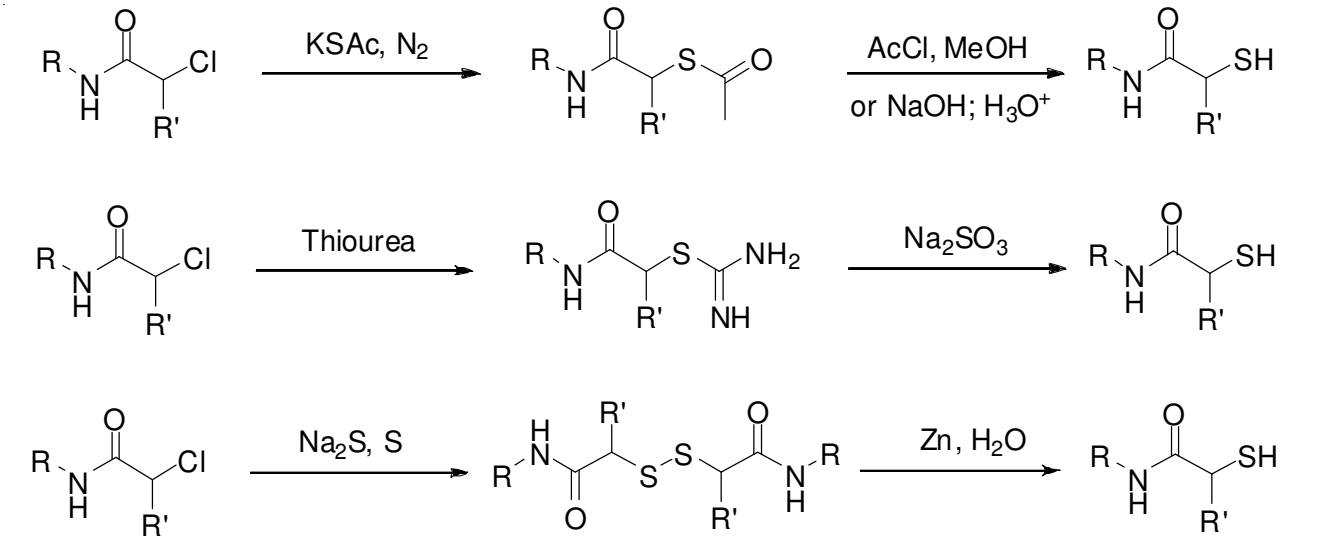
Compound	IC_{50}/nM		
	Hut102	MCF7	HepG2
7	43.6	28.3	31.2
8	56.9	24.4	25.1
9	57.0	37.1	29.7
10	94.6	26.4	43.8
SAHA	10.0	20.1	22.3
5-Fu	-[a]	15.5	16.2

[a]Not tested

RESULTS AND DISCUSSION

In the deprotection of **3**, typically methods including TFA and hydrochloric acid led to inconvenient workup and low yields (26 %). However, hydrogen chloride gas gave a clean ammonium salt 4 with 97 % yield. To obtain α-mercapto-*N*-[6-(3-phenylureido)hexyl]amides, a route involved rigorous conditions using expensive triphenylmethanol, TFA and Et_3SiH, was reported[12,22]. As outlined in **Scheme-I**, the mercaptopropionamide **7-8** are synthesized from 1,6-hexanediamine in this paper, obviating the need of fetid thioglycolic derivatives. There were three methods for α-sulfhydrylation of α-chloroamides: deacylation of acetylthio substituted intermediate[23], deamidination of carbamimidothioate[24] and reduction of disulfides which were obtained with sodium disulfide[25,26] **(Scheme-II)**. However, all have failed in the preparation of 7-8 after we tried the three routes. It worked well when treated with NaSH in refluxing methanol. Direct sulfhydrylation of our method has a superiorities of mild conditions, convenient operations and higher yields (the overall yield of **7** increase to 48 % from 16 % reported in literature), which provides a concise and efficient improvement. On the other hand, hydroxylations step-by-step afforded a rapid preparation of **9** or **10** using CH_3COONa and NaOH, subsequently.

Antitumor activity: The *in vitro* antitumor activities of the synthesized title compounds **7-10** against three human cancer cell lines, including Hut102, MCF7 and HepG2, were evaluated by MTT method. As shown in Table-1, the results



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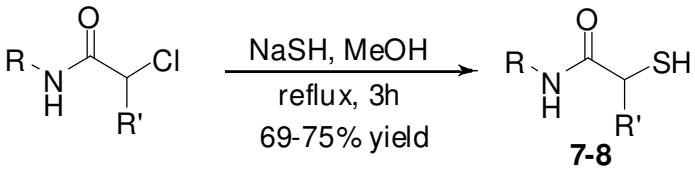

Scheme-II: Sulfhydrylation of α-chloroamides

indicated that title compounds **7-10** displayed a broad spectrum of antitumor activity. Although compounds **7-10** showed slightly weaker antitumor activity against Hut102, MCF7 and HepG2, they were in the same order of magnitude as the positive control. Nevertheless, replacement of the hydroxamate moieties with α-hydroxy(mercapto) amide led to a distinct decrease in activity. It could be concluded that the hydroxamate moieties played a crucial role in the antitumor activity. Probably the hydroxamate moieties can interact much more efficiently with a Hut102 Zn^{2+} ion. The structural optimization of SAHA was worth to further research.

Conclusion

In summary, four α-hydroxy(mercapto)-*N*-[6-(3-phenylureido)hexyl]amide derivatives were designed according to the strategy of bioisosteric replacement. Except **7** the other title compounds were newly synthesized. The titled compounds **7-10** were synthesized through a novel synthetic procedure with wild conditions and acceptable yields. Direct sulfhydrylation using NaSH from α-chloroamide will become an extremely useful synthetic method for α-mercaptoamides. The preliminary bioassay showed that all of the target compounds exhibited certain antitumor activities against Hut102, MCF7 and HepG2 cell lines.

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