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Identification of 4-hydroxyquinolines inhibitors of p300/CBP histone acetyltransferases

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ABSTRACT

We identified a series of 4-hydroxyquinolines bearing a C1 to C15 alkyl chain at the C2 position and a carbethoxy/carboxy group at the C3 position of the quinoline nucleus (MC compounds), endowed with selective inhibitory activity against the p300/CBP HAT enzymes. Enzyme inhibition was investigated using in vitro HAT assays and by western blot analysis of cellular lysates to examine the acetylation levels of histone H3 and α-tubulin. When tested in U937 cells, some compounds displayed pro-apoptotic or cytodifferentiating properties.

In the nucleus of eukaryotic cells, DNA is highly compacted and organized into chromatin by both histone and non-histone proteins. The fundamental repeating unit of chromatin is the nucleosome, which consists of 147 base pairs of DNA wrapped 1.6 times around an octamer of core histone proteins H2A, H2B, H3, and H4.[1,2]

Histones undergo extensive post translational modification at specific amino acids within the histone tails. These modifications include acetylation, phosphorylation, methylation, ubiquitynation, sumoylation, and ADP-ribosylation.[3,4]

The functional implications of reversible acetylation–deacetylation have been most widely studied. Histone acetylation occurring at the ε-amino group of lysine residues in the N-terminal tails of core histones mediates conformational changes in nucleosomes. Two superfamilies of enzymes are involved in this process: histone acetyltransferase (HAT) and histone deacetylase (HDAC), which catalyze respectively the addition to and removal of acetyl units of histones.[5,6]

The HAT enzymes may be classified into two categories depending upon their cellular localization: type A or nuclear and type B or cytosolic enzymes. The nuclear HATs can be grouped into several families based on sequence similarity, including the GNAT (GCN5-related N-acetyltransferase) family, the MYST (named after its founding members, in particular MOZ, YBF2/SAS3, SAS2, and TIP60) family, the p300/CBP family, some nuclear receptor coactivators (like SRC-1, ACTR, TIF2), and other general transcription factors (such as TAFII-p250, the TFIIIC family, and others).[7,8]

In addition to histones, over 40 trascription factors and 30 other nuclear, cytoplasmic, and viral proteins have been shown to be acetylated in vivo.

Similarly to HDACs, HATs are typically found in cells in large multiprotein complexes, but unlike HDACs they exhibit robust catalytic activity as purified proteins. Each HAT complex may regulate a distinct set of genes and thereby specific cellular functions. For example, the members of GNAT family (including transcriptional coactivators, GCN5 and p300/CREB-binding protein-associated factor (PCAF)) regulate cellular growth and development. The MYST HATs are involved in a wide range of regulatory functions including

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transcriptional activation, and are important for cell growth and cell cycle regulation. The ubiquitously expressed members of the p300/CBP family are considered as global transcriptional coactivators, and have a critical role in cell cycle regulation, cellular differentiation and apoptosis.[9]

Dysfunction of HAT enzymes is often associated with several diseases, including cancer. Nevertheless, the role of HATs in cancer is not straightforward as these enzymes can act either as tumor suppressors or activators depending on the type and development stage of tumors. A global loss of H4K16 acetylation has been linked to tumorigenesis,[10] and gene targeting in mice revealed that MOZ is essential for the generation and maintenance of hematopoietic stem cells and for the appropriate development of myeloid, erythroid, and B lineage cell progenitors.[11] p300 and CBP are considered to be tumor suppressors: indeed, their expression decreases in hepatocarcinogenesis.[12] p300/CBP mutations have been found in several human leukemias, and missense or truncating mutations in p300 have been reported in colorectal, gastric, breast, and epithelial carcinomas.[13–15] On the other hand, MOZ can generate fusion genes with other HAT proteins, such as MOZ-TIF2, MOZ-CBP, and MOZ-p300, in acute myeloid leukemia (AML) by chromosomal translocation.[11,16–18]

Mistargeted and deregulated HAT activities of GCN5/PCAF and p300 have also been reported to play an important role in genetic diseases and in human colorectal, breast, and pancreatic cancers.[13,14,19] Reduced cellular levels of p300 or activity has been proposed to diminish stress-induced cardiac hypertrophy and development of heart failure.[20] Thus, small chemical inhibitors of HAT enzymes (HAT inhibitors, HATi) represent novel candidates for drug development.

In comparison to the great number of known inhibitors of HDACs,[21,22] a limited number of HATi has been described to date (Fig. 1), with various degrees of selectivity and cell permeability. They can be grouped into three different classes: (i) the synthetic peptide-CoA-based bisubstrate inhibitors (Lys-CoA, specific for p300, and H3-CoA-20, specific for PCAF),[23] and their cell permeable versions LysCoA-SS-R10 and H3-CoA-20-TAT,[24] (ii) the natural products anacardic acid (AA),[25] garcinol,[26] and curcumin[27,28] that were described as potent p300/PCAF (AA and garcinol) or p300-selective (curcumin) inhibitors, (iii) some small molecules, such as the GCN5 inhibitor butyrolactone MB-3,[29] a group of isothiazolones that act as p300/PCAF inhibitors with interesting anticancer properties,[30] as well as some AA[31,32] and garcinol analogues (LTK compounds).[33]

We have undertaken a series of studies involving the design, synthesis, and biological validation of small molecule modulators of epigenetic targets;[34–38] we have recently employed a phenotypic screening assay in yeast to identify two quinolines, namely MC1626 and MC1752 (Fig. 2), which are active at submillimolar/millimolar range.[39–41]

In order to improve their HAT inhibiting activity, we introduced some chemical features typical of AA and MB-3 into the quinoline nucleus, obtaining the 3-carboxy-4-hydroxy-2-pentylquinoline MC1823 (**4**, Fig. 2) with 10/20-fold increased human HAT inhibitory activity with respect to the prototypes MC1626 and MC1752.[40]

Since **4** in human HAT inhibitory assay (U937 cell nuclear extracts) proved to be more potent than AA (% of inhibition at 50 μM: 30 (**4**) and 15 (AA)) and a few less active than MB-3 (44% of inhibition at 50 μM), used as reference drugs,[40] we re-examined two **4**-related quinolines (**1** and **7**, cited as compounds **15** and **8** in ref.[40] respectively) previously found inactive in the phenotypic screening in *Saccharomyces cerevisiae*. In addition, we prepared additional 4-hydroxyquinolines with 3-carboxy/3-carbethoxy functions at the C3 position, and differently sized alkyl chains (C1 to C15 carbon units) at the C2 position (Fig. 2), for testing them against several human HAT enzymes.

The 3-carbethoxy-4-hydroxyquinolines **1**, **3**, **5**, and **7** were obtained by reaction of the appropriate ethyl β-oxoester with isatoic anhydride in presence of sodium hydroxide as catalyst, according to the method described in Ref. 40. Alkaline hydrolysis of the above esters with 4 N KOH afforded the 4-hydroxy-3-quinolincarboxylic acids **2**, **4**, **6**, and **8** (Scheme 1).[40]

The new compounds have been tested on human HAT enzymes belonging to the p300/CBP (p300 and CBP) and GNAT (GCN5 and PCAF) families, in comparison with AA and MB-3 as reference drugs (Table 1) using in vitro HAT assays. Moreover, compounds **1–8** have been validated in living cells by examining the effects on histone H3 and α-tubulin acetylation both in human leukemia U937 and HEK-TE cells (Fig. 3). Finally, the effects of **1–8** on cell cycle, apoptosis induction, and granulocytic differentiation in U937 cell line have been determined (Fig. S1 in Supplementary material, Figs. 4 and 5).

When tested at 50 μM against immunoprecipitated p300 HAT from U937 cell nuclear extracts, all the compounds **1–8** showed high inhibitory activity, regardless of the presence of carbethoxy or carboxy group at C3, and of C1, C5, C10, or C15 carbon unit chain at C2. The most potent compounds were the 2-methylquinolines **1** and **2**, which displayed approximately 3-fold higher inhibition

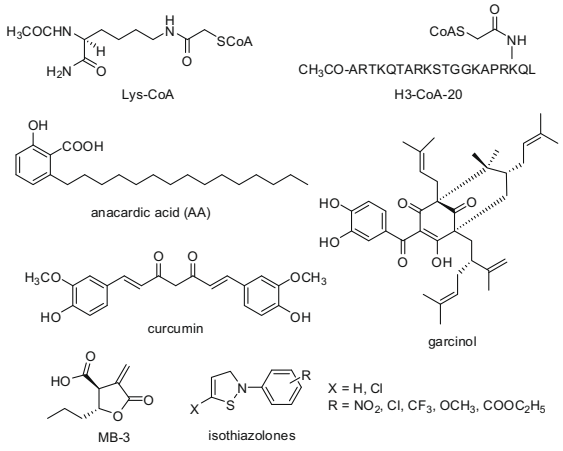


Figure 1. Known HAT inhibitors.

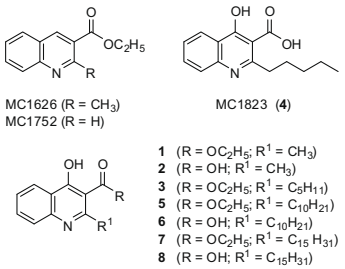
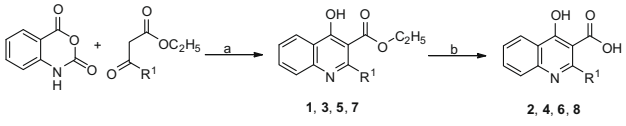


Figure 2. Novel quinoline-based HAT inhibitors.



Scheme 1. Reagents and conditions; (a) NaOH, dioxane, reflux; (b) 4 N KOH, EtOH, reflux.

Table 1
Effects of MC compounds (50 μM) on four different human HAT enzymes[a]

Compound	R	R_1	% HAT remaining activity			
			p300-IP	CBP-GST	GCN5	PCAF-GST
Control (DMSO)			100	100	100	100
1	OC_2H_5	CH_3	16.4	13.4	97.4	81.7
2	OH	CH_3	11.4	20.5	97.4	104.2
3	OC_2H_5	C_5H_{11}	47.7	91.2	101.8	100.0
4	OH	C_5H_{11}	82.0	19.0	98.0	102.8
5	OC_2H_5	$C_{10}H_{21}$	39.1	93.4	93.4	90.1
6	OH	$C_{10}H_{21}$	53.9	13.2	95.4	91.5
7	OC_2H_5	$C_{15}H_{31}$	39.8	116.5	96.8	82.4
8	OH	$C_{15}H_{31}$	46.9	14.4	103.3	62.7
AA			53.1	44.0	112.6	52.1
MB-3			58.6	45.9	54.5	76.8

[a] Values are means ± SD determined from at least three experiments.

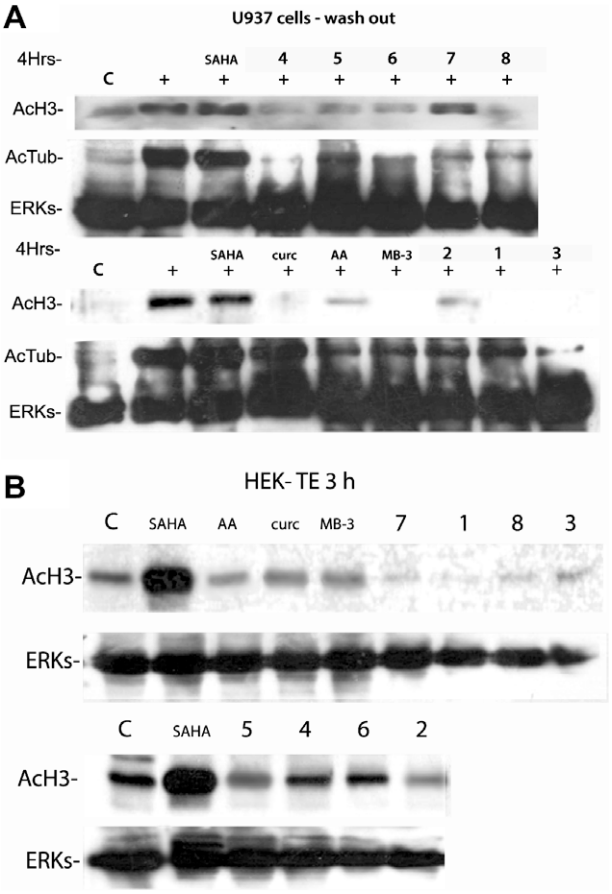


Figure 3. (A) Effects of compounds **1**–**8** (100 μM) on histone H3 and α-tubulin acetylation in SAHA-pretreated U937 cells. (B) Effects of compounds **1**–**8** (100 μM) on histone H3 acetylation level in HEK-TE cells.

compared to AA and MB-3. The other quinolines showed a p300 inhibitory activity comparable to those of the reference drugs, with the exception of **4** which was less active. When we carried out assays with the recombinant GST-CBP fusion protein, at 50 μM high inhibitory activity was registered with the carboxylic acid derivatives (**2**, **4**, **6**, and **8**), whereas the corresponding ethyl esters were inactive. An important exception was the 3-carbethoxy-4-hydroxy-2-methylquinoline **1**, which was as active as (if not more than) the related carboxylic acid **2**. When tested against GCN5 and PCAF HAT enzymes, at 50 μM all compounds **1–8** displayed low (**1**, **5**–**7** against PCAF-GST) or no activity, the only active quinoline being compound **8**, which showed 37.3% of PCAF-GST inhibitory activity at 50 μM.

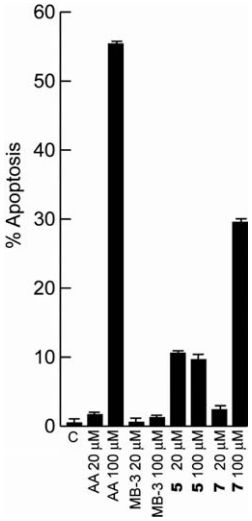


Figure 4. Apoptosis induction of **5** and **7** at 20 and 100 μM in U937 cells (Annexin V/PI method).

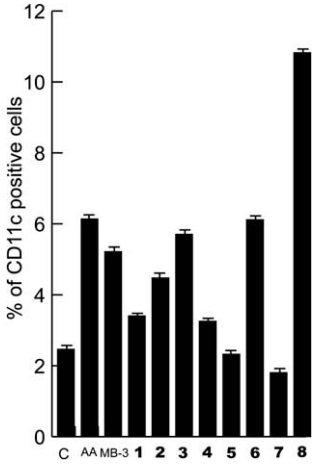


Figure 5. Granulocytic differentiation induced by compounds **1**–**8** (20 μM) in U937 cells (CD11c method).

Western blot analyses were performed on U937 cell lines to study the effects of **1–8** on the acetylation levels of histone H3 as well as of the non-histone substrate α-tubulin (Fig. 3A). Since the U937 cells show only weak basal acetylation levels for both the substrates, we pre-treated the cells with the well-known HDAC inhibitor SAHA (suberoylanilide hydroxamic acid, 2 h, 5 μM, '+' in Fig. 3A)[42,43] to increase the acetylation amounts of histone H3 and α-tubulin. After wash out, we determined the effects of **1-8**, used at 100 μM, on acetylation levels after 4 h of treatment. AA, curcumin, and MB-3 (all at 100 μM) were used as reference drugs. As depicted in Figure 3A, the tested quinolines induced hypoacetylation on both the histone and non-histone substrates. In the acetyl-H3 assay, the majority of the tested compounds showed high hypoacetylating activity comparable to that of curcumin and MB-3. In contrast, **7** had no detectable effects, while **2** and AA caused moderate reduction in H3 acetylation (Fig. 3A).

In acetyl-α-tubulin assay, all the tested compounds effectively decreased the acetylation levels of the substrate, with the exception of **1** and **5**, which produced only marginal decreases in tubulin acetylation, and curcumin was practically inactive using our experimental conditions (Fig. 3A).

Further western blot analyses were performed to investigate the effects compounds **1–8** at 100 μM in human immortalized kidney epithelial cells (HEK-TE), which are transformed but not tumorigenic. These cells show higher basal acetylation of histone H3 compared to U937 cells. Data reported in Fig. 3B confirmed the high hypoacetylating effects of most of our quinoline derivatives in this cell system following a 3-h of treatment.

Finally, the quinoline compounds **1–8** and the reference compounds, AA and MB-3, were tested on U937 cells to evaluate their effects on cell cycle, apoptosis induction, and granulocytic differentiation. When tested at 20 μM for 24 h, only **5** and **7** caused cell cycle arrest at the G1/S phase, with the total loss of cells in G2 phase (Fig. S1 in Supplementary material). The other compounds displayed no effects on cell cycle progression (data not shown). In the Annexin V/propidium iodide (PI) double staining apoptotic assay, again the only significant results were obtained with **5** and **7** at concentrations of 20 and 100 μM for 24 h. In particular, at 20 μM **5** and **7** were 1.4- to 18.3-fold more potent than AA and MB-3 in inducing apoptosis, whereas at 100 μM they were more efficient than MB-3 and 1.9- to 5.7-fold less active than AA.

Granulocytic differentiation was evaluated through the CD11c method, by treatment of the U937 cells with **1–8** (20 μM) for 24 h. Subsequently, the number of the CD11c positive/PI negative cells was determined. In this assay, some compounds (**3**, **6**) showed a cytodifferentiating activity similar to those of the reference drugs, whereas **8** was more efficient.

In conclusion, we identified a series of 4-hydroxyquinolines (compounds **1–8**) with differently sized (from C1 to C15 methylene units) alkyl chains at C2 and a carbethoxy/carboxy group at C3, that function as HAT inhibitors. Moreover, we tested the MC compounds in human leukemia U937 cell line to study their effects on apoptosis induction and granulocytic differentiation. When tested against four different HAT enzymes (p300, CBP, GCN5, and PCAF), compounds **1–8** displayed selective inhibition towards the members of the p300/CBP family of HATs. In particular, the 3-carbethoxy- and 3-carboxy-4-hydroxy-2-methylquinolines **1** and **2** were the most potent inhibitors of p300 and CBP, and 4- to 5-fold (p300 assay) or 2- to 3-fold (CBP assay) more effective than AA and MB-3 reference drugs. In the p300 assay the other compounds showed almost the same potency as the reference drugs, with the exception of **4** which was less effective. In contrast, in the CBP assay only the other 3-carboxy derivatives **4**, **6**, and **8** displayed high enzyme inhibition, whereas the corresponding ethyl esters were totally inactive. Despite the fact that the 2-methylquinoline compounds were the most potent in inhibiting the p300/CBP HATs, in human leukemia U937 cells the 2-decyl- and 2-pentadecylquinoline ethyl esters **5** and **7** showed the highest apoptosis induction, and the corresponding carboxylic acids **6** and **8** produced the highest fraction of CD11c positive/PI negative cells, perhaps due to better cell permeability resulting from the presence of a highly lipophylic alkyl chain at the C2 position of the quinoline nucleus. Studies are in progress to gain insights on structure-activity relationship of these novel p300/CBP-selective HAT inhibitors.

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