

Novel Histone Acetyltransferase (HAT) Inhibitors for Treating Diseases

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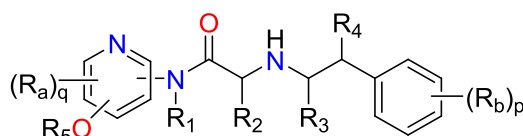
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Important Compound Classes.



Title. P300/CBP HAT Inhibitors and Methods for their Use

Patent Publication Number. WO 2020/176558 A1

Publication Date. September 3, 2020

Priority Application. US 62/811,143 and US 62/879,852

Priority Date. February 27, 2019 and July 29, 2019

Inventors. Wilson, J. E.

Assignee Company. Constellation Pharmaceuticals Inc., USA

Disease Area. Cancer, cardiac diseases, metabolic diseases, fibrotic diseases, inflammatory diseases, viral infections, and neurological disorders

Biological Target. Histone acetyltransferase (HAT)

Summary. Chromatin is a complex combination of DNA and protein that makes up chromosomes. It is found inside the nuclei of eukaryotic cells and is divided between heterochromatin (condensed) and euchromatin (extended) forms. The major components of chromatin are DNA and proteins. Histones are the chief protein components of chromatin, acting as spools around which DNA winds. The functions of chromatin are to package DNA into a smaller volume to fit in the cell to strengthen the DNA to allow mitosis and meiosis and to serve as a mechanism to control expression and DNA replication. The chromatin structure is controlled by a series of post-translational modifications to histone proteins, notably histones H3 and H4, and most commonly within the "histone tails" which extend beyond the core nucleosome structure. Histone tails tend to be free for protein–protein interaction and are also the portion of the histone most prone to post-translational modification. These modifications include acetylation, methylation, phosphorylation, ubiquitinylation, and SUMOylation. These epigenetic marks are written and erased by specific enzymes that place the tags on specific residues within the histone tail, thereby forming an epigenetic code, which is then interpreted by the cell to allow gene specific regulation of chromatin structure and thereby transcription.

Covalent modification of histones is a fundamental mechanism of control of gene expression and is one of the

major epigenetic mechanisms at play in eukaryotic cells. Distinct classes of enzymes, namely, histone acetyltransferases (HATs) and histone deacetylases (HDACs), acetylate or deacetylate specific histone lysine residues.

Histone acetyltransferases (HATs) catalyze the acetylation (transfer of an acetyl group) on a ϵ -amino group of a target lysine side chain within a substrate histone and HDACs catalyze the removal of acetyl group from lysine residues. Subsequently, acetylated core histones were shown to preferentially associate with transcriptionally active chromatin. HATs are categorized into four major families based on primary sequence homology, shared structural features and functional roles: Gen5/PCAF (General control nonrepressed protein 5 and p300 and CBP associated factor); MYST (named for founding members MOZ, Ybf2/Sas3, Sas2, and Tip60); p300/CBP (protein of 300 kDa and CREB Binding Protein); and Rtt109 (Regulator of Tyl Transposition gene production 109).

The present application describes a series of novel histone acetyltransferase (HAT) inhibitors for the treatment of diseases including, cancer, cardiac diseases, metabolic diseases, fibrotic diseases, inflammatory diseases, viral infections, and neurological disorders. Further, the application discloses compounds, their preparation, use, pharmaceutical composition, and treatment.

Definitions. R_1 , R_3 and R_4 = H or C_{1-4} alkyl;

R_2 = phenyl or 5- to 6-membered heteroaryl, each of which is optionally substituted with 1 to 3 groups selected from R_c ;

R_5 = C_{1-6} alkyl substituted with 4- to 6-membered heterocyclyl or 5- to 6-membered heteroaryl, wherein each of said 4- to 6-membered heterocyclyl or 5- to 6-membered heteroaryl are optionally substituted with 1 to 3 groups selected from R_d ;

R_a , R_b , R_c and R_d = halo, CN, oxo, NO_2 , C_{1-6} alkyl, C_{2-6} alkenyl, C_{1-6} alkoxy, halo(C_{1-6} alkoxy), halo(C_{1-6} alkyl), $-C_{1-6}$ alkylOR $_e$, $-C(O)R_f$, $-C(O)OR$, $-C_{1-6}$ alkylC(O)OR $_e$, $-C(O)N(R_e)_2$, $-C(O)NR_eC_{1-6}$ alkylOR $_e$, $-OC_{1-6}$ alkylN(R_e) $_2$, $-C_{1-6}$ alkylC(O)N(R_e) $_2$, $-C_{1-6}$ alkylN(R_e) $_2$, $-N(R_e)_2$,

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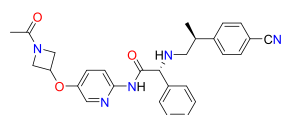
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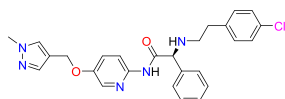
–C(O)NR_eC_{1–6}alkylN(R_e)₂, –NR_eC_{1–6}alkylN(R_e)₂,
 –NR_eC_{1–6}alkylOR_e, –SOR_e, –S(O)₂R_e, –SON(R_e)₂, –SO₂N(R_e)₂,
 –O(C_{3–6})cycloalkyl, –O–C_{1–4}alkylaryl, –C_{1–6}alkyl-(C_{3–6})cycloalkyl,
 –C_{1–6}alkylaryl, –C_{1–6}alkylheteroaryl, –C_{1–6}alkylheterocyclyl, (C_{3–6})cycloalkyl,
 heterocyclyl, heteroaryl or aryl;

q = 0, 1, or 2; and p = 0, 1, 2, or 3.

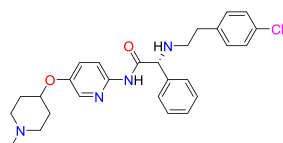
Key Structures.



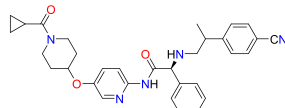
Compound 2



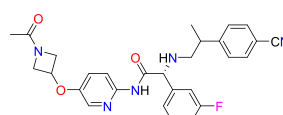
Compound 8



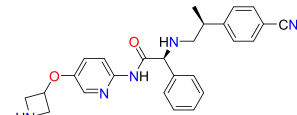
Compound 11



Compound 20



Compound 23



Compound 26

Biological Assay. The p300/CBP HAT scintillation proximity assay (SPA) was performed. The compounds described in this application were tested for their ability to inhibit HAT. The HAT IC₅₀ (μM) are shown in the following Table.

Biological Data. The table below shows representative compounds were tested for HAT inhibition. The biological data obtained from testing representative examples are listed in the following table.

Compound No.	Isomer	p300 HAT SPA IC ₅₀ (μM)
2	Isomer 1	0.0212
8	Isomer 2	0.0168
11	Isomer 1	0.0266
20	Isomer 2	0.0267
23	Isomer 1	0.0233
26	Isomer 2	0.014

Claims. Total claims: 44

Compound claims: 25

Pharmaceutical composition claims: 17

Method of treatment claims: 1

Use of compound claims: 1

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1. He, Z.; Wei, B.; Zhang, X.; Gong, Y.; Ma, L.; Zhao, W. *Eur. J. Med. Chem.* **2021**, *209*, 112861.
2. Gomathi, K.; Akshaya, N.; Srinaath, N.; Rohini, M.; Selvamurugan, N. *Int. J. Biol. Macromol.* **2021**, *170*, 326.
3. Wang, Y.; Xie, Q.; Tan, H.; Liao, M.; Zhu, S.; Zheng, L.; Huang, H.; Liu, B. *Pharmacol. Res.* **2021**, in press.
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Notes

The author declares no competing financial interest.