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REVIEW ARTICLE

The Pharmacological and Chemical Profile of Vorinostat (SAHA): A Comprehensive Review

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The Pharmacological and Chemical Profile of Vorinostat (SAHA): A Comprehensive Review

SUMMARY

Vorinostat (N-hydroxy-N'-phenyloctanediamide) is an HDAC inhibitor that targets HDAC enzymes. In 2006, the U.S. Food and Drug Administration (FDA) approved vorinostat for use as a third-line treatment in patients with refractory and relapsed cutaneous T-cell lymphoma (CTCL). Vorinostat inhibits HDAC enzymes by chelating the zinc ion located in the catalytic site, leading to the reprogramming of gene expression. This process results in cell cycle arrest, suppression of proliferation, and induction of apoptosis in transformed cells. Current studies continue to investigate its potential applications against various cancer types, HIV, and parasitic infections. This article compiles and summarizes literature data on the synthesis, structure–activity relationships, physicochemical properties, as well as the pharmacological characteristics, mechanism of action, and pharmacokinetic profile of vorinostat.

Keywords: *Vorinostat, HDAC inhibitor, synthesis, structure–activity relationships, pharmacokinetics*

Vorinostat (SAHA)' ın Farmakolojik ve Kimyasal Profili: Kapsamlı Bir İnceleme

ÖZ

Vorinostat (N-hidroksi-N'-feniloktandiamid), histon deasetilaz (HDAC) enzimlerini hedef alan HDAC inhibitörleri sınıfında yer alır. 2006 yılında, dirençli ve nükseden kutanöz T-hücreli lenfoma (CTCL) hastalarında üçüncü basamak tedavide kullanılmak üzere Amerika Birleşik Devletleri Gıda ve İlaç Dairesi (FDA) tarafından onay almıştır. Vorinostat, katalitik bölgede yer alan çinko iyonunu şelatlayarak HDAC enzimlerini inhibe eder ve bu durum gen ekspresyonunun yeniden düzenlenmesine yol açar. Bu süreç, hücre döngüsünün durmasına, proliferasyonun baskılanmasına ve transforme hücrelerde apoptozun indüklenmesine neden olur. Güncel araştırmalar; ilacın farklı kanser türleri, HIV ve paraziter enfeksiyonlara karşı potansiyel kullanımını incelemeye devam etmektedir. Bu makale, vorinostatın sentezi, yapı-aktivite ilişkileri, fiziko-kimyasal özelliklerinin yanı sıra farmakolojik özellikleri, etki mekanizması ve farmakokinetik profiline dair literatür bilgilerini bir araya getirerek özetlemektedir.

Anahtar Kelimeler: *Vorinostat, HDAC inhibitörü, sentez, yapı-etki ilişkileri, farmakokinetik*

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INTRODUCTION

Epigenetics describes heritable modifications that influence gene expression without involving changes to the DNA sequence. Studies show the onset and progression of cancer involve epigenetic modifications (Gu et al., 2024; Kanwal, Gupta, & Gupta, 2015). Epigenetic modifications can occur through three different biological pathways, most notably histone acetylation and deacetylation controlled by histone acetyltransferases (HATs) and histone deacetylases (HDACs), in addition to genome methylation and small interfering RNA (siRNA)-mediated mechanisms (Kanwal et al., 2015; Zain & O'Connor, 2010). Epigenetic modifications, due to their reversible nature, represent excellent targets in anticancer drug discovery (Gu et al., 2024).

Histone deacetylases (HDACs) function as key epigenetic regulators by catalyzing the removal of acetyl groups from lysine residues on histone proteins, thereby promoting chromatin compaction and transcriptional repression (Marks et al., 2001b). Dysregulated HDAC activity is associated with uncontrolled cell proliferation, impaired differentiation, and tumor progression. Therefore, HDACs have attracted significant interest as molecular targets for anticancer drug development (Gregoretti, Lee, & Goodson, 2004). To date, 18 isoforms of HDAC are present in humans, primarily classified into two main groups according to their catalytic mechanisms and cofactor dependencies: the zinc-dependent and the nicotinamide adenine dinucleotide (NAD^+) dependent enzymes (Curcio, Rocca, Alcaro, & Artese, 2024). The classification of the HDAC family is presented in Table 1.

Table 1. The classification of the HDAC family

HDAC family							
Zinc-dependent				NAD^+-dependent			
Class I	**Class II**		**Class IV**	**Class III (SIRT-7)**			
HDAC1 HDAC2 HDAC3 HDAC8	Class IIa HDAC5 HDAC7 HDAC9	Class IIb HDAC6 HDAC10	HDAC11	Subclass I	Subclass II	Subclass III	Subclass IV
				SIRT 1 SIRT 2 SIRT 3	SIRT 4	SIRT 5	SIRT 6 SIRT 7

HDAC inhibitors (HDACis) are generally classified into four main structural groups: hydroxamic acids such as Trichostatin A (TSA), Vorinostat (SAHA), cyclic tetrapeptides such as Romidepsin (FK228), benzamides like Entinostat (MS-275), and fatty acids like Valproic acid (VPA) and Phenylbutyrate (Figure 1.). Among these, hydroxamic acid derivatives have received particular attention due to their strong zinc-binding capacity and potent inhibitory effects (Bozdağ-Dündar, 2023; Güngör and Bozdağ-Dündar, 2025; Peng, Sun, Kuang, & Chen, 2020).

Vorinostat, also known as suberoylanilide hydroxamic acid (SAHA), is a hydroxamate-based inhibitor with activity against class I, II, and IV HDACs. Chemically, it is a dicarboxylic acid diamide composed of suberic/octanedioic acid linked to aniline and hydroxylamine, with the IUPAC name N-hydroxy-N'-phenyloctanediamide (NCBI, 2026). Vorinostat, marketed under the trade name Zolinza®, was approved by the U.S. Food and Drug Administration (FDA) in October 2006 as the first HDAC inhibitor for the treatment of cutaneous T-cell lymphoma (CTCL) following failure of at least two prior systemic therapies. CTCLs, such as mycosis fungoides and Sézary syndrome, represent non-Hodgkin lymphomas marked by malignant T-lymphocyte proliferation in the skin (Mann, Johnson, Cohen, Justice, & Pazdur, 2007; Olsen et al., 2007).

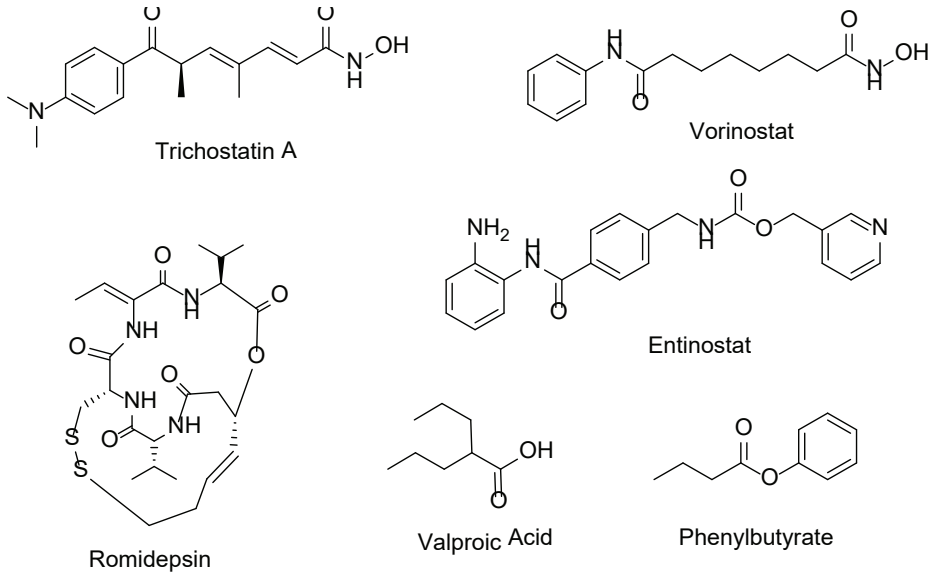


Figure 1. Chemical structures of various HDAC

Vorinostat inhibits HDAC enzymes by chelating the zinc ion located at the bottom of the catalytic site, consequently preventing deacetylation of the ε-amino groups of lysine residues in both histones and transcription factors (Marks, Richon, Breslow, & Rifkind, 2001a; Xu, Parmigiani, & Marks, 2007). This inhibition leads to chromatin relaxation and subsequent activation of gene transcription. Elevated levels of hyperacetylated histones and transcription factors are associated with cell cycle arrest, reduced proliferative capacity, and enhanced apoptosis in transformed cells (Eckschlager, Plch, Stiborova, & Hrabeta, 2017; West & Johnstone, 2014).

Vorinostat has been evaluated in multiple preclinical and clinical studies across a broad range of hematologic and solid malignancies, including breast cancer, lymphoma, glioblastoma multiforme, non-small cell lung cancer (NSCLC), and head and neck squamous cell carcinoma (Buglio et al., 2008; Duvic & Vu, 2007; Siegel et al., 2009a). Although it has shown significant therapeutic efficacy in hematologic cancers, its clinical benefits as monotherapy in solid tumors remain limited. Consequently, ongoing studies are exploring combination therapies to enhance its therapeutic potential (Eckschlager et al., 2017; Peng et al., 2020). As a milestone compound in epigenetic drug discovery, vorinostat continues to serve as a reference molecule for the design and development of next-generation HDAC-targeted anticancer drugs (Peng et al., 2020).

PHARMACOLOGY AND MECHANISM

Vorinostat (SAHA), a Zn^{2+}-dependent hydroxamic acid–based, broad-spectrum inhibitor of HDAC activity, effectively targets class I and class II enzymes, while exhibiting no inhibitory activity against class III HDACs, as class III enzymes are not Zn^{2+}-dependent. The pan-inhibition of Class I and II HDACs by vorinostat can be attributed to their catalytic pocket, particularly the presence of a Zn^{2+}-containing active site and a hydrophobic access channel. This structural similarity allows vorinostat to adopt a comparable binding mode within both classes (Herrera-Martínez et al., 2020; Marks et al., 2001b; Dailymed, 2024). Based on crystallographic studies, vorinostat applies its effect by directly binding to the Zn^{2+} ion at the HDAC catalytic site via its hydroxamate group (Micheletti, Boga, Drius, Bordoni, & Calonghi, 2024).

The HDAC pharmacophore includes three domains: a cap group (a phenyl ring with a tertiary amine substituent, extending from the domain), a zinc binding group (ZBG), and a carbon linker. As shown in Figure 2, vorinostat binds to the active sites

of multiple HDAC enzymes. Its hydroxamic acid group (zinc-binding group, ZBG) chelates the zinc ion within the catalytic site, the cap functions as a surface recognition motif that blocks the entrance of the active site, and the linker connects the ZBG to the cap (Bozdağ-Dündar, 2023; Güngör & Bozdağ-Dündar, 2025; Paul-Satyaseela et al., 2017; Peng et al., 2020). Vorinostat is regarded as a pan-HDAC inhibitor because it interacts with all HDAC isoforms (Banerjee, Moore, Broker, & Chow, 2018), with reported IC_{50} values of 258, 921, 350, 493, 378, 28.6, 344, 243, 316, 456, and 362 nM for HDAC1–11, respectively (Hanessian et al., 2010). Analysis of the IC_{50} profile indicates that vorinostat shows its highest selectivity toward HDAC6, followed next by HDAC8 (Negmeldin, Knoff, & Pflum, 2018). In the case of HDAC2, its aliphatic chain aligns within the aromatic tunnel formed by Phe155 and Phe210, while the terminal amide group engages in hydrogen-bonding interactions mediated by conserved water molecules (Tamanini et al., 2022). Regarding its interaction with HDAC6, enhanced selectivity arises from favorable engagement of the enzyme's hydrophobic regions. Therefore, this feature has guided the design of new analogues optimized for HDAC6 selectivity (Olaoye et al., 2021). For HDAC8, the hydroxamate group of vorinostat forms hydrogen bonds with H142, H143, and Y306, residues essential for the enzyme's catalytic function, and simultaneously coordinates the catalytic zinc ion, completing its distorted square-pyramidal coordination geometry (Finnin et al., 1999; Tabackman, Frankson, Marsan, Perry, & Cole, 2016). Unlike most HDACs, HDAC10 functions primarily as a polyamine deacetylase rather than a histone deacetylase, and it contains a characteristic electrostatic gatekeeper residue that shapes substrate recognition. Consequently, vorinostat engages the active site of HDAC10 in a manner that differs from its binding to other isoforms. In addition, the hydroxamate group can undergo a Lossen rearrangement, generating a reactive isocyanate able to alkylate cellular components, which may lead to genotoxicity (Goulart Stollmaier, Watson, & Christianson, 2024).

Vorinostat binds to the HDAC enzyme, maintaining histone proteins acetylated, causing various cellular effects (Secrist, Zhou, & Richon, 2003; Xue et al., 2016). These effects may be transcriptional or non-transcriptional (Marks, 2010). Transcription-related effects include direct binding to and inhibition of the HDAC enzyme or indirectly altering the expression of various transcription factors, including p53, Bcl-6, E2F-1, YY-1, GATA-1, and Smad 7. Indirectly, SAHA acetylates the Bcl-6 transcriptional activator, which suppresses the transcriptional inhibition effect (Bereshchenko, Gu, & Dalla-Favera, 2002; Cortiguera et al., 2019). Furthermore, acetylation of lysine residues may lower the activity of pro-growth and pro-survival client proteins—for example, Bcr-Abl, mutant FLT-3, c-Raf, and AKT—in human leukemia cells (Bali et al., 2005). Among non-transcriptional effects, SAHA causes cell cycle arrest in malignant cell lines by inhibiting Cyclin/ cyclin-dependent kinase (CDK) complexes due to an increase in p21, thereby causing cell cycle arrest (Alqosaibi & Abdel-Ghany, 2023; Sandor et al., 2000). A similar effect is seen with decreased kinase activity due to decreased cyclins, affecting Rb dephosphorylation and, indirectly, E2F transcription activity (Zhao et al., 2005).

In hematological malignancies and solid tumors, vorinostat induces apoptosis via both transcription-dependent and transcription-independent pathways (Minucci & Pelicci, 2006; Silva, Cardoso, Belo, & Almeida, 2013). Vorinostat indirectly suppresses HIF-1 alpha and VEGF under hypoxic conditions, thereby limiting angiogenesis (Hutt, Roth, Vignaud, Cullin, & Bouchecareilh, 2014; Kim et al., 2001). It also acts as a STAT3 inhibitor by decreasing IL-10 and increasing IL-2 and IL-4 (Tiffon et al., 2011). Vorinostat is thought to be responsible for preventing damage to normal cells by targeting thioredoxin within these cells. HR23B acts as a biomarker indicating the therapeutic response of cutaneous T-cell lymphoma (CTCL) cells to vorinostat (Khan et al., 2010).

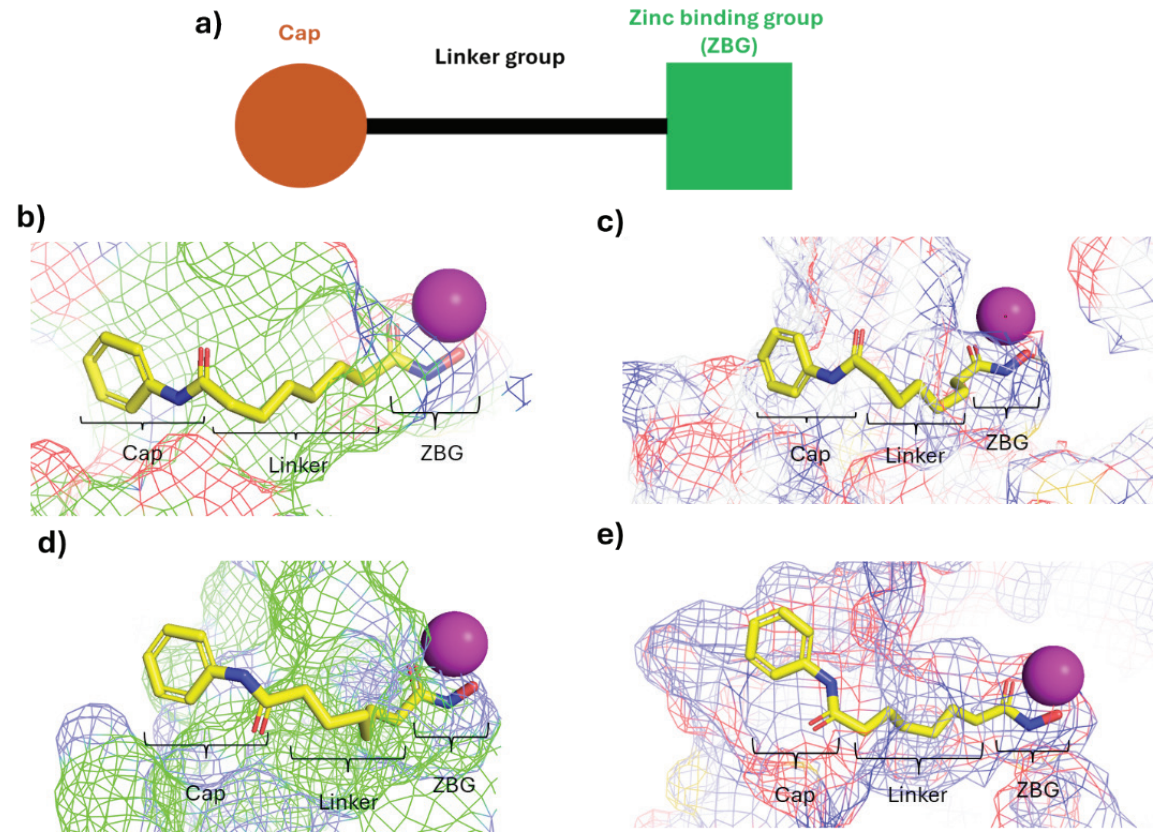


Figure 2. (a) Pharmacophore model of HDAC inhibitors; Three-dimensional images of the (b) HDAC2-SAHA interaction (Space-filling model); (c) HDAC6-SAHA interaction (Space-filling model); (d) HDAC8-SAHA interaction (Space-filling model); (e) HDAC10-SAHA interaction.

An *in vitro* study showed that vorinostat prevents cancer development in human gastric cancer cells, possibly because of the restoration of expression of the gastric tumor suppressor RUNX3, causing a significant reduction in apoptosis (Huang, Ida, Ito, Zhang, & Ito, 2007). A different *in vitro* study showed that vorinostat increases intracellular reactive oxygen species (ROS) in lung cancer cells, leading to increased programmed cell death of cancer cells, while reducing ROS levels in healthy lung cells, thereby inhibiting programmed cell death (You & Park, 2017).

Vorinostat is approved by the FDA to be administered orally for the third-line clinical treatment of relapsed and refractory CTCL patients. According to an *in vivo* and in *vitro* study, Cisplatin (CDDP) and SAHA had a synergistic anticancer effect when given in combination, thus holding therapeutic promise for clinical management of castrate-resistant prostate cancer (CRPC) (Chang et al., 2023). In a clinical study conducted on 16 HIV-infected and aviremic individuals, it was successful in reversing latent infection safely and repeatedly; however, additional research is necessary to determine whether it can permanently and effectively reduce HIV infection (Archin et al., 2017). Also, by inhibiting HDACs, which play a critical role in gene expression and parasite survival, vorinostat has shown promising activity in both *in vitro* and, in some instances, *in vivo* studies against parasitic pathogens causing malaria, leishmaniasis, schistosomiasis, and amoebiasis (Herrera-Martínez et al., 2020).

In both *in vitro* and *in vivo* models, vorinostat demonstrates potent anti-neoplastic activity in various breast cancer cells. Its mechanisms include inhibition of proliferation, migration, and invasion,

induction of differentiation and apoptosis, and cell cycle arrest, either alone or alongside standard anticancer agents. Although vorinostat shows potential in breast cancer treatment, additional investigations are necessary to fully evaluate its therapeutic effectiveness (Wawruszak et al., 2021).

Adverse reactions

In CTCL patients, vorinostat proved effective and was generally well tolerated in clinical studies. (Kim et al., 2018; Siegel et al., 2009b). Two clinical trials were done on 86 patients with CTCL to observe the drug's adverse reactions. Clinical studies have shown that oral administration of Zolinza at 400 mg once daily is associated primarily with gastrointestinal toxicity, and systemic adverse effects. These include nausea, vomiting, diarrhea, appetite loss, fatigue, chills, and weight reduction, as well as hematologic abnormalities, including thrombocytopenia and anemia. A limited number of patients experienced serious adverse events, including pulmonary embolism (4.7%), squamous cell carcinoma (3.5%), and anemia (2.3%).

In CTCL patients, vorinostat has demonstrated efficacy and was generally well tolerated in clinical studies (Kim et al., 2018; Siegel et al., 2009b). Two clinical trials involving 86 patients with CTCL evaluated the drug's adverse effects. Oral administration of Zolinza at 400 mg once daily was primarily associated with gastrointestinal and systemic toxicities, including nausea, vomiting, diarrhea, loss of appetite, fatigue, chills, and weight loss, as well as hematologic abnormalities such as thrombocytopenia and anemia. A small proportion of patients experienced serious adverse events, including pulmonary embolism (4.7%), squamous cell carcinoma (3.5%), and anemia (2.3%).

A range of single but serious adverse events was also reported. These included gastrointestinal hemorrhage, thromboembolic stroke, ischemic stroke, myocardial infarction, streptococcal bacteremia, and T-cell lymphoma. In addition, 9.3% of patients who were administered a 400 mg dose once daily discontinued the medication due to adverse effects. Additionally, in the clinical trial, 10.5% of patients needed dose adjustments, and 69% of CTCL patients exhibited increased serum glucose levels (Kim et al., 2018; Siegel et al., 2009b).

In clinical studies, proteinuria was recorded as an abnormal lab result with 51.4% of the patient population. However, it remains uncertain whether this finding holds clinical significance. Dehydration was another serious adverse reaction observed. Therefore, patients were advised to maintain a minimum daily fluid intake of two liters for enough hydration. Adverse reactions were more common in patients without CTCL, and the serious ones were not seen in CTCL patients, including single events of asthenia, blurred vision, vasculitis, tumor hemorrhage, urinary retention, hyponatremia, renal failure, hypertension, hemoptysis, and Guillain-Barré syndrome (Dailymed, 2024).

Doses

ZOLINZA capsules have received FDA approval in a 100 mg dose. The product is supplied as hard gelatin capsules that are white and opaque, bearing the imprint "568" above "100 mg" in black ink. A daily dose of 400 mg taken with food is recommended. If disease progression does not occur and unacceptable toxicity is absent, treatment can be continued at the same dose. In cases of treatment intolerance, the dose may be reduced to 300 mg once daily, with additional adjustment to a five-day-per-week dosing schedule if necessary. Among patients with mild to moderate hepatic dysfunction (bilirubin 1 to 3 x ULN or AST greater than ULN), the initial dose may be decreased to 300 mg taken once daily with food. Patients with severe hepatic impairment (bilirubin greater than 3 x ULN), however, no appropriate dose can be defined because a lack of evidence (Dailymed, 2024).

PHYSICOCHEMICAL CHARACTERISTICS

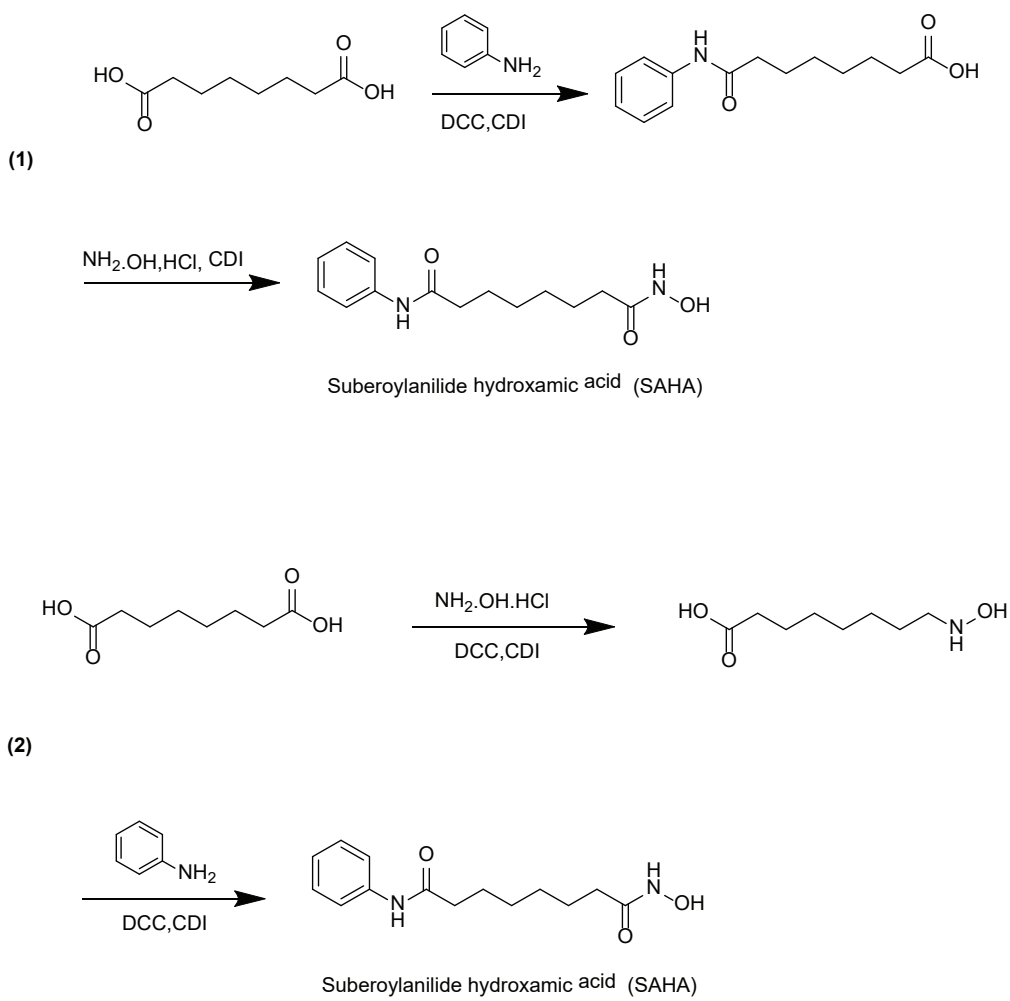
Vorinostat appears as a white colored solid powder that has a melting point of 159-160.5 °C. Vorinostat is a low-molecular-weight compound with a molecular weight of 264.32 g/mol and is represented by

the chemical formula $C_{14}H_{20}N_2O_3$. It is a hydrophobic acid with a pKa of approximately 9.2 (Clinical Pharmacology and Biopharmaceutics Review: Zolinza (Vorinostat), 2006; NCBI, 2026). Vorinostat's partition coefficient (Log P) in octanol and water is 0.96. Vorinostat is not optically active since it has no chiral centers (NCBI, 2026). Vorinostat shows poor aqueous solubility (0.2 mg/ml) (Mohamed et al., 2012a; Rompicharla et al., 2018) and thus poses a problem for parenteral administration (Cai et al., 2010).

Vorinostat exhibits limited solubility in water, alcohol, isopropanol, and acetone, while showing high solubility in dimethyl sulfoxide and no detectable solubility in methylene chloride (Bubna, 2015). Cyclodextrins increased the solubility of vorinostat in aqueous media. Future formulation development studies of vorinostat for parenteral use may aim to use HP-β-CD (Hydroxypropyl β-Cyclodextrin) to increase water solubility (Cai et al., 2010). Micellar PEG-b-PLA formulations of vorinostat have been designed, increasing the solubility of vorinostat in water by more than 40-fold, and both oral and IV formulations improved its overall pharmacokinetics in rats (Mohamed et al., 2012a).

Synthesis

The synthesis of vorinostat (SAHA) was carried out in two different ways (Scheme 1) (Vinayak Madhukar, Rahul, Hemant, & Sandeep, 2015).



Scheme 1. The synthesis of vorinostat (SAHA)

In the first method (1), suberic acid was coupled with aniline in the presence of coupling reagents such as N,N'-dicyclohexylcarbodiimide (DCC) or carbonyldiimidazole (CDI) to obtain suberanilic acid. The remaining carboxylic acid group was then activated with CDI and condensed with hydroxylamine hydrochloride to yield suberoylanilide hydroxamic acid.

In the second method (2), suberic acid was first converted to N-hydroxy-7-carboxy heptanamide using hydroxylamine hydrochloride and coupling agents (DCC, CDI). The resulting intermediate was subsequently condensed with aniline to afford suberoylanilide hydroxamic acid.

Structure-activity relationship

The discovery of a new anti-cancer drug that affects MELC cells, along with the discovery of DMSO, compound **a**, was significant. Before the discovery of vorinostat, it was synthesized based on developing and examining the effects of several compounds. Initially, the structures of simple linear and cyclic amides were examined, and compound **b**, and their activity increased five times. Then, a compound containing acetamide on both sides of it was synthesized, compound **c**. After examining its effect, it was observed to be ten times more active than the simple acetamides. Thus, it was determined that a chain length of six was optimal. It was concluded that acetamide groups alone did not bind well, so by adding a methyl group to both acetamide groups, compound **d**, the activity of the compound increased tenfold compared to bis-acetamide alone. Since the target of DMSO was thought to be a metal enzyme, the methyl groups were replaced by the hydroxyl groups, compound **e**. Moreover, it was discovered that the synthesized compound was more potent. However, the probability of a protein having two metal ion binding sites so far apart is very low. Therefore, instead of two hydroxamic acids, a hydroxamic acid was placed on one side and a phenyl ring on the other, compound **f**. Thus, it was thought that the phenyl ring would bind to the hydrophobic region, allowing the hydroxamic acid to coordinate more strongly to the metal binding site; it was then proved to be correct. Suberoylanilide hydroxamic acid (SAHA) inhibited HDAC enzymes 6 times more actively than suberoyl-bis-hydroxamic acid (SBHA). Subsequently, many molecules were synthesized by changing the link group length, but a 6-carbon length was optimal. Similarly, different and larger hydrophobic rings were introduced instead of the phenyl ring. While the binding activity to the enzyme increased, cytotoxicity also increased in *in vivo* experiments (Figure 3.) (Fischer & Rotella, 2017; Marks & Breslow, 2007).

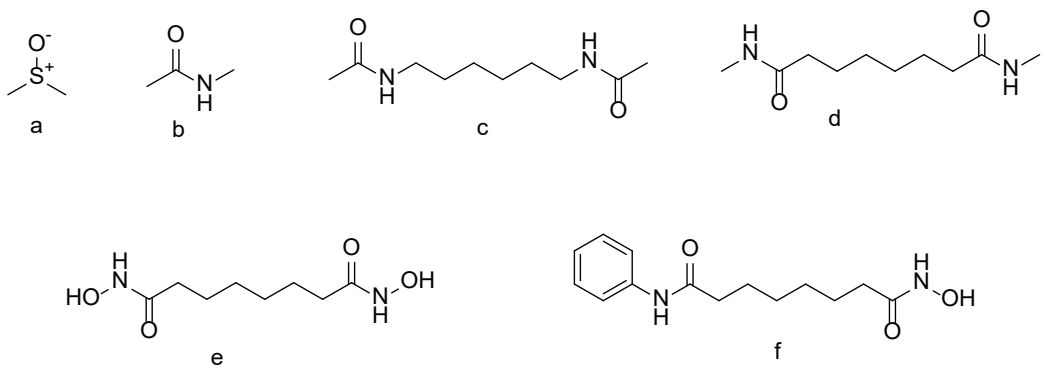


Figure 3. Chemical structures of **a** dimethylsulfoxide (DMSO), **b** N-methylacetamide, **c** hexamethylene bis-acetamide, **d** suberoyl-bis-N-methylamide, **e** suberoyl-bis-hydroxamic acid (SBHA), **f** suberoanilide hydroxamic acid (SAHA)

QUANTIFICATION METHODS

Various methods were developed for the quantification of vorinostat. LC-MS/MS is one of the methods that provides accurate and validated measurements at low nanomolar levels. In a research, a rapid isocratic LC/MS method was developed to determine vorinostat in rat serum and urine. Therefore, the aim of this study was sample preparation to facilitated by precipitating proteins using ice-cold acetonitrile, with daidzein employed as an internal reference compound. Chromatographic separation was accomplished on a Phenomenex LunaR C18 column using a fast isocratic elution mobile phase. Detection utilized mass spectrometry with positive-ion electrospray ionization (ESI+) and Selected Ion Monitoring detection. Analytical calibration curves demonstrated excellent linearity (r^2>0.99), ranging from 0.05 to 50 µg/mL in serum and 0.5 to 25 µg/mL in urine. Vorinostat exhibited good matrix stability when subjected to three repeated freeze–thaw procedures and maintained in the autosampler for 24 h. Consequently, this study aimed to assess the *in vivo* pharmacokinetic behavior of vorinostat in a preclinical rat study (Mohamed et al., 2012b).

In 2011, a new patent application was published detailing two new analytical methods for vorinostat quality control. The main focus of this patent is the detection and quantification of impurities of vorinostat during synthesis. In this context, the pattern application presents three main chromatographic approaches. The first method is based on gradient elution, where the mobile phase composition is changed over time to meet high-resolution requirements. In this method, four impurities were targeted and separated using an aqueous phase and an organic phase on a reversed-phase C18 column. The second method's mobile phase contains alcohol. Therefore, earns the flexibility to operate in both isocratic and gradient modes. On the other hand, the third method consists of a phosphate salt, a phosphoric acid, or an anhydride as a mobile phase. These impurities are N, N'-diphenyl-octanediamide, N'-phenyl-octanediamide, 7-(phenylcarbamoyl) heptanoic acid (suberanilic acid) and N-hydroxy-N,N-di-(N'-phenyl-octanediamide) amine. All three methods are utilize High-Performance Liquid Chromatography (HPLC) separation followed by either a UV and/or visible spectrophotometer, a fluorescence spectrophotometer, a differential refractometer, an electrochemical detector, a mass spectrometer, a light scattering detector, or a radioactivity detector (Vijayakumar, Vele, Singh, & Vishe, 2011).

PHARMACOKINETICS AND BIOAVAILABILITY

Absorption

Although intravenous (IV) formulations were used in clinical research, administered either as a three-day schedule (75–900 mg/m²/day every 21 days) or as a five-day schedule over three consecutive weeks (300 mg/m² with escalation to 600 and 900 mg/m²), only the oral formulation has received FDA approval (Kelly et al., 2005). When vorinostat is given orally in doses between 200 and 600 mg, the plasma concentration of the drug varies proportionally to the dose given (Kelly et al., 2005). When vorinostat is given on an empty stomach in doses between 200 and 600 mg, its bioavailability is 43%, the amount of absorption increased slightly with ingestion after a meal, and the time to peak the maximum concentration in the blood was prolonged (Rubin et al., 2006). Absorption and bioavailability do not differ significantly if taken before or after food, but taking vorinostat after food may prevent side effects that may occur during absorption in the digestive system (Bubna, 2015; Kelly et al., 2005). Vorinostat's half-life is between 60 and 100 min, the presence of a hydroxamate zinc-binding group in its structure causes rapid metabolism and conversion to inactive metabolites, resulting in a short half-life in the circulatory system (Du, Musson, & Wang, 2006; Kenny, Ude, Docherty, & Marmion, 2020; Liu et al., 2014; Rubin et al., 2006). Mean pharmacokinetic parameters and 90% confidence

intervals of vorinostat measured over 8 days following twice-daily (bid) oral administration are given in Table 2. Mean plasma concentrations of vorinostat following oral administration with—200 mg once or twice daily, 300 mg twice daily, 400 mg once or twice daily, or 600 mg once daily—on cycle 1, day 9 are shown in Figure 4 (Kelly et al., 2005).

Table 2. Mean pharmacokinetic parameters and 90% confidence intervals of vorinostat measured over 8 days following twice-daily (bid) oral administration (Plasma concentrations are expressed as the free base).

Parameter*	**200mg**	**300mg**	**400mg**
AUC (ng/mL·1.saat)	74,374 ± 74,914	39,730 ± 23,694	77,334
C_{max} (ng/mL)	301 ± 152	263 ± 100	349 ± 127
T_{max}, min	120	53	150
$T_{1/2}$, min	122 ± 33.8	93.5 ± 25.2	100

*AUC, area under the plasma concentration; C_{max}, maximum plasma concentration; T_{max}, time to reach maximum concentration; $T_1/_2$, elimination half-life

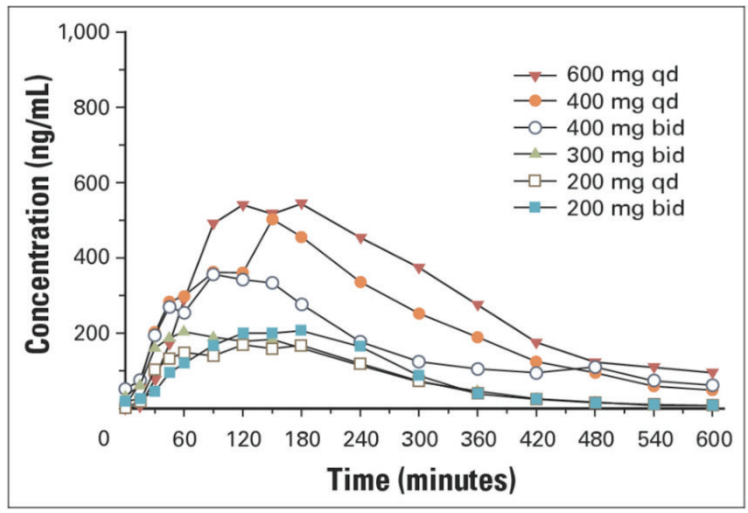


Figure 4. Mean pharmacokinetic parameters and 90% confidence intervals of vorinostat measured over 8 days following twice-daily (bid) oral administration

Distribution

Vorinostat approximately binds to human plasma proteins in a 71% across a range of concentrations of 0.5–50 μg/mL. *In vitro* investigations suggest that vorinostat neither inhibits the P-glycoprotein transport system nor is a human P-glycoprotein substrate. There is no data on whether vorinostat is distributed into human milk. Animal studies demonstrate that vorinostat is capable of crossing the placental barrier, with fetal plasma concentrations reaching up to 50% of those observed in maternal circulation (NCBI, 2026).

Metabolism and excretion

Vorinostat and its primary metabolites were determined in plasma and peripheral blood mononuclear cells (PBMCs). Vorinostat's epigenetic effect only applies intracellularly. Therefore, this approach was used to determine the concentration of vorinostat and its relationship with plasma and PBMS. Solid phase extraction (SPE) was used as the extraction technique in plasma, while liquid-liquid extraction was used in PBMS. Vorinostat was applied in three different therapeutic concentrations to healthy patients' blood samples. Results showed that recoveries varied from

88.6% to 114.4% of all analytes. And vorinostat showed proliferation in PBMS and sufficient HDAC activity. However, the method used for the extraction of plasma, SPE, is time-consuming and pricey. Additionally, vorinostat has been showing a stability problem in plasma (Liu et al., 2014).

Vorinostat undergoes rapid metabolic degradation to its inactive metabolites, which negatively affects its efficacy (pharmacokinetics and pharmacodynamics), and moreover, decreases the patient's compliance by taking more than one dose per day (Kenny et al., 2020). Vorinostat is converted to its inactive metabolites by two methods; the first metabolite is vorinostat O-glucuronide (M1), formed after glucuronidation by several uridine diphosphate glucuronosyl transferases (UGTs), including UGT1A1, UGT1A3, UGT1A7, UGT1A8, UGT1A9, UGT2B7, and UGT2B17. The second metabolite is 4-anilino-4-oxobutanoic acid (M2), an inactive carboxylic acid derivative, formed first by hydrolysis and then by β-oxidation (Figure 5.) (Du et al., 2006; Kenny et al., 2020; Liu et al., 2014). Vorinostat is neither metabolized by CYP enzymes nor has an effect on them (NCBI, 2026). Vorinostat is largely excreted by being converted into inactive metabolites in the liver, and less than 1% of the given portion of the dose is eliminated unchanged via the urine (Rubin et al., 2006). During the vorinostat, M1 and M2 sample preparation and storage phases, they were found to be stable in urine and serum (after freeze-thaw cycling and storage at -70 °C for more than 1 year), while vorinostat undergoes degradation in plasma due to coagulation proteins (Du et al., 2006). According to a study conducted in 2020, it is revealed that vorinostat releases nitric oxide (NO) by using Ruthenium (III) as an NO scavenger in *in vitro* environments (Kenny et al., 2020).

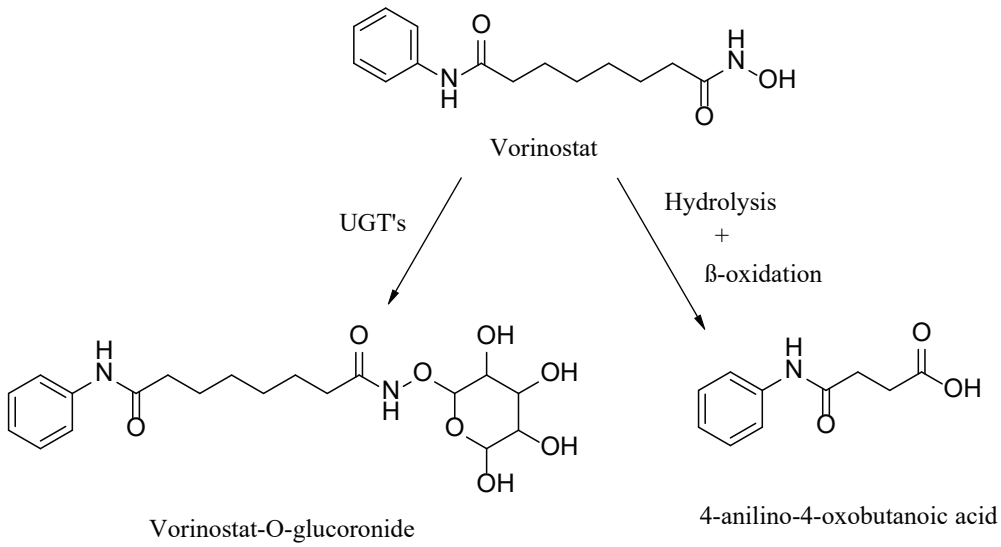


Figure 5. The metabolism of Vorinostat to its inactive metabolites, M1 (Vorinostat-O-glucuronide) and M2 (4-anilino-4-oxobutanoic acid)

Toxicity

Elevations in serum enzyme levels were infrequently observed in clinical studies of vorinostat among individuals diagnosed with CTCL, with only occasional cases of mild increases reported. Minor elevations in serum alanine aminotransferase (ALT) were observed in approximately 15–45% of patients; however, ALT values exceeding five times the upper limit of normal (ULN) were uncommon, and no cases of hepatitis, jaundice, or clinically evident liver injury were reported in treated patients. Although the clinical use of vorinostat is limited, no evidence of significant liver damage has been reported in the current literature (NCBI, 2020). Since vorinostat is mostly excreted

through metabolism, it should be used with caution in patients with hepatic insufficiency (Ramalingam et al., 2010). As a result, a study is warranted to evaluate its effects in patients with hepatic insufficiency. Since only 1% is renally excreted, dose adjustment is unnecessary among patients with kidney insufficiency. However, patients with kidney insufficiency should be treated with caution as an increase in serum creatinine was observed in 45% of patients during clinical trials (Clinical Pharmacology and Biopharmaceutics Review: Zolinza (Vorinostat), 2006).

In conclusion, recent pharmacovigilance studies have highlighted that vorinostat and other HDAC inhibitors are associated with significant hematological, gastrointestinal, and cardiotoxic adverse effects, largely due to their non-selective inhibition of multiple HDAC isoforms (Li, Fu, & Wang, 2024).

Drug interactions

Vorinostat interactions with drugs metabolized by CYP enzymes are doubtful because it is neither a substrate nor a metabolite of these enzymes. However, SAHA interacts with coumarin-derivative anticoagulants (such as warfarin). As a result, patients may develop increases in prothrombin time (PT) or international normalized ratio (INR). Therefore, patients who take both medications need more regular monitoring of coagulation parameters. Vorinostat in combination with other histone deacetylase inhibitors may boost severe side effects such as thrombocytopenia and gastrointestinal bleeding, monitoring platelets every two weeks during the first two months is obligatory (Dailymed, 2024).

RESULTS

Vorinostat (suberoylanilide hydroxamic acid, SAHA) is recognized as a pioneering compound in the evolution of HDACis. Vorinostat promotes chromatin relaxation and tumor suppressor gene reactivation. These epigenetic changes contribute to cell cycle arrest, differentiation, and apoptotic cell death in malignant cells.

Vorinostat (SAHA) represents the prototypical zinc-dependent HDAC inhibitor and is widely used as a reference scaffold for structure–activity relationship studies. Its classical pharmacophore, comprising an aromatic cap group, a flexible aliphatic linker, and a terminal hydroxamic acid zinc-binding group (ZBG), enables high-affinity, nonselective inhibition of class I and II HDAC isoforms. The hydroxamic acid moiety is primarily responsible for SAHA's nanomolar potency, forming a bidentate chelate with the catalytic Zn^{2+} ion while engaging a conserved hydrogen-bonding network with key active-site residues. However, this same structural motif also underlies the compound's limited metabolic stability, as hydroxamate-based molecules are susceptible to enzymatic hydrolysis and rapid hepatic biotransformation, ultimately leading to short systemic exposure and reduced oral bioavailability.

Pharmacokinetic assessments following both single and multiple oral administrations have demonstrated that Vorinostat is rapidly absorbed, reaching its maximum plasma concentration (T_{max}) within approximately two hours post-dose. The compound exhibits a relatively short elimination half-life, generally ranging between 1.5 and 2 hours, reflecting its rapid systemic clearance. Vorinostat also exhibits high interindividual variability in systemic exposure parameters, such as AUC and C_{max}, suggesting that differences in metabolic capacity, plasma protein binding, and enzymatic activity (e.g., glucuronidation and β-oxidation) can significantly influence its pharmacokinetic profile and therapeutic response. Although vorinostat demonstrates favorable therapeutic activity in hematologic malignancies, especially cutaneous T-cell lymphoma (CTCL), its limited activity against solid tumors underscores the need for optimized formulations and combination strategies to enhance its therapeutic potential. Further studies focusing on formulation development, improved delivery systems, and pharmacokinetic modulation may contribute to increased bioavailability and clinical benefit.

CONCLUSION

Vorinostat (SAHA) is a prototypical zinc-dependent HDAC inhibitor that targets class I and II HDACs. In 2006, the U.S. Food and Drug Administration approved vorinostat as a third-line therapeutic option for patients with relapsed or refractory cutaneous T-cell lymphoma (CTCL). Vorinostat is characterized by a terminal hydroxamic acid zinc-binding group, enabling high-affinity but nonselective inhibition of class I and II HDAC isoforms. Vorinostat exerts its inhibitory effect on HDAC enzymes by chelating the catalytic zinc ion within the active site, thereby modulating gene expression. This mechanism leads to cell cycle arrest, reduced cellular proliferation, and the induction of apoptosis in malignant cells. Although vorinostat demonstrates clinical efficacy in hematologic malignancies, particularly cutaneous T-cell lymphoma, its limited activity in solid tumors highlights the need for improved formulations, delivery strategies, and pharmacokinetic optimization to enhance its therapeutic potential.

In conclusion, the pharmacological understanding gained from vorinostat has significantly shaped the optimization of HDAC inhibitors to achieve improved selectivity, stability, and safety. As a pioneering molecule, SAHA continues to inspire the design of next-generation therapeutics.

AUTHOR CONTRIBUTION STATEMENT

Z.O.: Literature review and manuscript writing. Z.A.: Study design, manuscript writing and editing. O.B.D.: Study design, supervision, and final review.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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