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Review article

Targeting histone deacetylase 1: Inhibition and activation as promising therapeutic strategies for diverse disorders

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ABSTRACT

Epigenetic regulation plays a crucial role in several pathological conditions. Dysregulation of histone deacetylase (HDAC) enzymes has been implicated in the onset and progression of numerous diseases, including cancer, inflammatory disorders, and neurodegenerative conditions. Most known HDAC inhibitors (HDACi) are classified as "pan-inhibitors", targeting multiple HDAC isoforms indiscriminately. However, the growing demand for isoform-selective ligands has emphasized the need for more targeted therapeutic strategies. Among HDAC isoforms, HDAC1 has emerged as a particularly promising target for pharmacological intervention. This review provides a comprehensive overview of current HDAC1-selective ligands, including inhibitors and activators, highlighting their potential as useful therapeutic tools. The most promising class I of HDACi currently in clinical trials is discussed.

1. Introduction

Histone deacetylases (HDACs) are a class of enzymes mainly involved in epigenetic modifications and a wide range of biological processes, including gene transcription, protein folding, and cytoskeleton organization [1]. Notably, HDACs play a crucial role in cellular proliferation and transcriptional repression by removing the lysine acetyl group from histones, thereby compacting the chromatin structure and regulating gene expression [2]. Beyond histones, HDACs modulate non-histone proteins, including hormone receptors, chaperones, and cytoskeletal proteins, thereby further extending their influence on cellular functions [3]. Over the years, multiple HDAC isoforms have been identified in mammals and classified into four classes, as summarized in Table 1 [4].

Among these isoforms, HDAC1 has emerged as a key therapeutic target in cancer, inflammatory diseases, and neurodegenerative disorders [5–7]. Primarily localized in the nucleus, HDAC1 plays a pivotal role in regulating angiogenesis, inflammatory signaling, and redox homeostasis [8]. Studies have demonstrated its involvement in endothelial cell proliferation by regulating crucial cell cycle regulators. Moreover, HDAC1 modulates endothelial cell inflammation by influencing the production of chemoattractant cytokines and the expression of cell adhesion molecules (CAMs) [8]. Additionally, it downregulates antioxidant enzymes and reduces nitric oxide production, effects linked to its regulation of nitric oxide synthase 3 expression and activity [8].

Beyond its role in inflammation, HDAC1 has been implicated in neuropathic pain by promoting glial cell activation, leading to persistent and severe pain signals [9]. In oncology, the dysregulation of HDAC1 and other HDAC isoforms has been closely associated with cancer onset and progression [10–12]. Notably, HDAC1 overexpression has been observed in multiple tumor types, including gastric, breast, prostate, pancreatic, and colon cancers, underscoring its significance in tumorigenesis and cellular proliferation [13,14]. In recent years, epigenetic regulation has gained attention in research on neurodegenerative diseases, with HDAC1 identified as a crucial factor in protecting neurons from DNA damage in Alzheimer's disease (AD) [15]. Activation of HDAC1 has been shown to mitigate DNA damage by preventing aberrant cell cycle re-entry [3], a hallmark of neurodegeneration. Given its diverse roles in disease pathology, inhibition and activation of HDAC1 have emerged as promising therapeutic strategies for intervention in several pathological conditions. This review provides a comprehensive overview of HDAC1-selective ligands, including inhibitors and activators, published primarily between 2018 and early 2025, with a focus on the most recent advances in medicinal chemistry and pharmacology.

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Table 1
Classification of the HDAC family.

HDAC class	Member	Cellular Localization
Class I	HDAC 1, 2, 3, 8	Nucleus
Class IIa	HDAC 4, 5, 7, 9	Nucleus/Cytoplasm
Class IIb	HDAC 6, 10	Cytoplasm
Class III (SIRT)	SIRT 1, 2, 3, 4, 5, 6, 7	Nucleus/Cytoplasm/Mitochondria
Class IV	HDAC 11	Nucleus/Cytoplasm

2. HDAC inhibitors: from pan-selective to isoform-specific ligands

The involvement of epigenetic regulation in cancer progression represents a promising target for developing novel anti-cancer drugs [16,17]. However, more known HDAC inhibitors (HDACi) are defined as "pan-inhibitors" as they do not demonstrate selectivity and target all HDAC isoforms. So, a different series of HDAC class-selective inhibitors were further investigated [18].

Currently, five HDACi have been approved by the Food and Drug Administration (FDA) for the treatment of various hematological and solid tumors (Fig. 1) [19–21]. Vorinostat (SAHA), belinostat (PXD-101), and panobinostat (LBH589) are pan-inhibitors, and romidepsin (FK228), a class I inhibitor, is approved for the treatment of cutaneous T cell lymphoma, peripheral T-cell lymphoma, and multiple myeloma [22–25]. In 2024, the FDA approved givinostat for the treatment of Duchenne muscular dystrophy (Fig. 1) [26]. The tolerability of the pan-HDACi is impaired by dose-limiting side effects like fatigue, diarrhea, vomiting, anorexia, asthenia, weight loss, and thrombocytopenia [27–29]. For instance, belinostat (PXD-101), approved for peripheral T-cell lymphoma, exerted significant side effects, including genotoxicity and potential male infertility, hepatotoxicity, tumor lysis syndrome, gastrointestinal toxicity, and embryo-fetal harm [30–34]. Therefore, developing selective HDACi could be a valuable strategy to minimize the side effects of pan-inhibitors.

The development of isoform-selective inhibitors is challenging and could be considered a good strategy to obtain new anti-cancer drugs with an improved safety profile and minor side effects. Even though there are different structural motifs for HDACi, most ligands are characterized by a common pharmacophore consisting of a zinc-binding group (ZBG), a linker, and a cap group (CAP), as illustrated in Fig. 2.

However, to rationally design selective HDAC1 inhibitors, it is essential to consider not only the pharmacophore elements but also the structural and spatial constraints that distinguish HDAC1 from closely related isoforms [35]. Subtle yet critical differences in the architecture of the active site regions provide opportunities for the rational design of

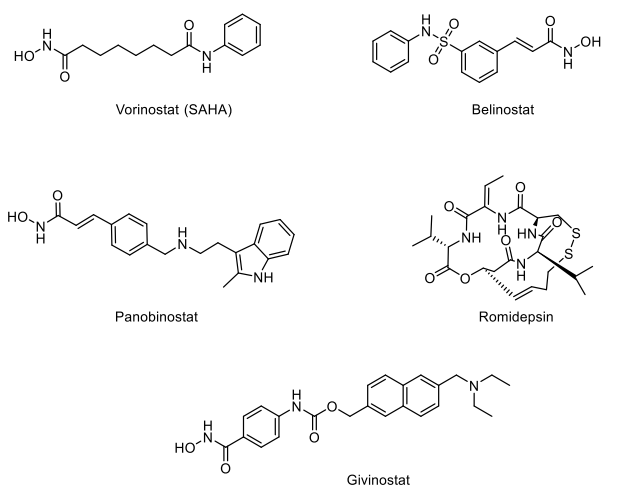


Fig. 1. FDA-approved HDAC inhibitors.

Fig. 2. Structural features for HDACis.

selective inhibitors.

Currently, several human HDAC1 crystal structures (4BKX, 6Z2J, 6Z2K, 7AO8, 7AO9, 7AOA, 7SME, 8VOJ, 8VPQ, 8VRT, and 5ICN) are available in the Protein Data Bank, all of which are characterized by the presence of a zinc ion in the binding site. For drug design, numerous ZBGs were employed, and the most commonly used were the hydroxamic acid and benzamide functional groups. Preclinical research is underway to discover novel HDACi targeting the HDAC1 isoform [36].

In 2016, Wagner et al. reported the structure-activity and structure-kinetic relationships of a series of selective *ortho*-aminoanilide inhibitors of HDACs 1 and 2 [37]. Compounds BRD4884 and BRD7232 demonstrated inhibitory activity towards HDAC1 and HDAC2 in the micromolar range, as reported in Fig. 3. However, these ligands exhibit kinetic selectivity for HDAC1 over HDAC2, indicating that while a kinetically selective HDAC1 inhibitor with high target engagement is attainable, a selective HDAC2 inhibitor with a comparable binding kinetics profile remains elusive. This study proved that the binding kinetics of HDACi can be changed for individual isoforms to modulate the target residence time [37].

Recently, the synthesis of a novel fluorinated aminophenyl-benzamide-based compound, named CBUD-1001 (Fig. 4), as a potent HDAC1 inhibitor was reported by Kim et al. [38]. The effectiveness of the compound CBUD-1001 in inhibiting HDACs was evaluated, and the results showed that it possesses good inhibitory activity against HDAC1 (IC_{50} = 28.1 nM). The activity of CBUD-1001 was also assessed against HDAC2 and HDAC3 with IC_{50} values of 158 nM and 404 nM, respectively [38]. The anti-cancer activity of HDAC1 was investigated in colorectal cancer (CRC) cells, revealing that HDAC1 regulates the proliferation and survival of CRC cells. Then, CBUD-1001 can induce the apoptotic death of CRC cells, which may be used as a therapeutic tool for CRC treatment [38].

Jiao and coworkers synthesized different benzoheterocyclic-containing benzamide derivatives [39]. Some of these ligands inhibited the activity of HDAC1 with IC_{50} values in the micromolar range. They could delay the proliferation of different cancer cells without having toxic effects on normal cells and human Ether-à-go-go-related gene (hERG) K^+ ion channels [39]. Compound **1** has emerged as the most promising compound of the series (Fig. 4) (IC_{50} = 0.64 μM), exhibiting good selectivity for HDAC1 over HDAC2 (IC_{50} = 2.10 μM), HDAC6 (IC_{50} > 10 μM), and HDAC8 (IC_{50} > 10 μM). The docking results indicated that compound **1** could insert into HDAC1 active sites as its benzamide group chelates the Zn^{2+} very well. Moreover, it was orally active and showed excellent *in vivo* antitumor activity in the human colon carcinoma mouse model. Further studies on compound **1** are in progress to better define its *in vivo* profile.

Quinazolinyl-containing benzamide products were recently synthesized and assessed for their *in vitro* HDAC inhibitory activity [40]. *N*-(2-aminophenyl)-4-((quinazolin-4-ylamino)methyl)benzamide (**2**) (Fig. 4) bested the class I selective HDACi entinostat (MS-275) in both HDAC1 enzymatic inhibitory and cellular anti-proliferative activities *versus* several cancer cell types (Hut78, K562, Hep3B, and HCT116 cells) without effects on normal cells. Specifically, compound **2** inhibited HDAC1 (IC_{50} = 0.21 μM) more effectively than HDAC2 (IC_{50} = 2.50 μM), HDAC6 (IC_{50} > 10 μM), and HDAC8 (IC_{50} > 10 μM), demonstrating a satisfactory safety profile. Also, it showed encouraging oral pharmacokinetic properties and relevant anticancer activity in a non-small cell lung cancer mouse model [40].

Among the new HDAC1 ligands, the synthesis of *N*-(2-aminophenyl)-benzamide inhibitors were described by Gerokonstantis et al. [41]. The

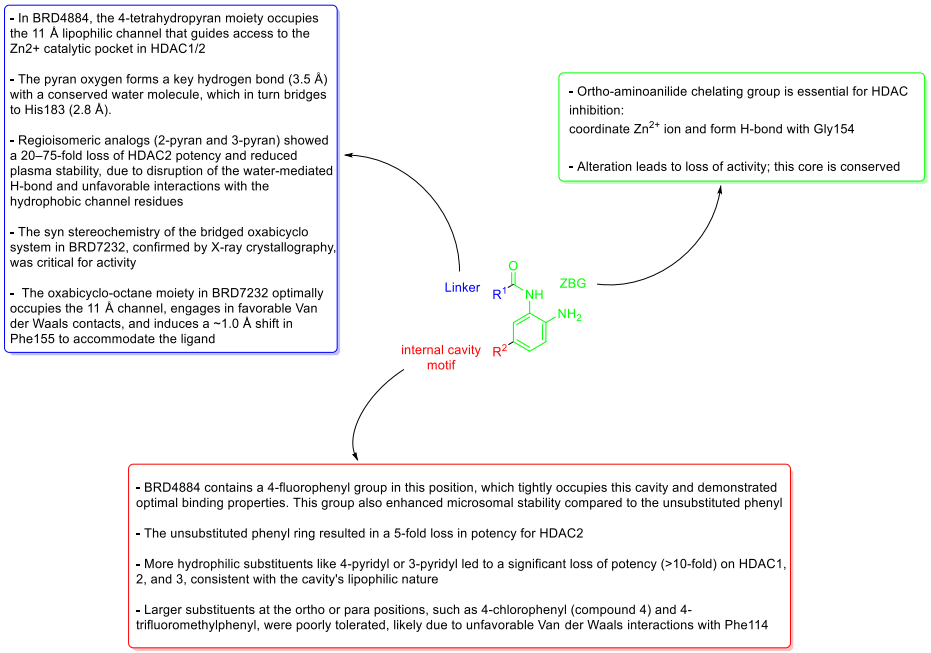


Fig. 3. BRD4884 and BRD7232 structure–activity relationships and IC_{50} values.

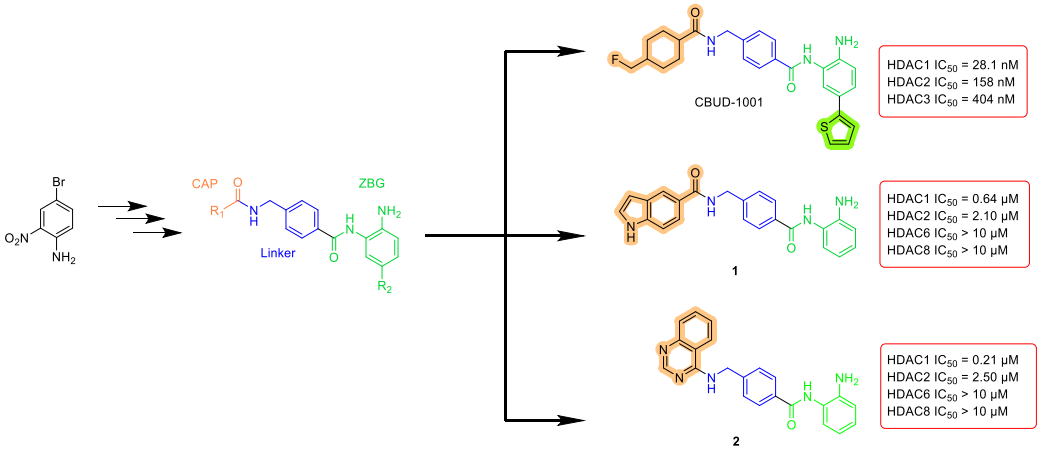


Fig. 4. Novel benzamide derivatives with HDAC1 inhibitory activity.

novel ligands presented amino acids, such as pyroglutamic acid or proline, or heterocyclic carboxylic acids as CAPs, and the 4-(benzyloxy) phenylmethylamine moiety as a linker. Structure–activity relationship (SAR) studies led to the definition of compounds that inhibit the HDAC1 enzyme in a nanomolar range. The novel benzamides were evaluated for their ability to inhibit the human HDAC1, HDAC2, and HDAC6 isoforms *in vitro*. Compounds bearing furan-2-carboxylic acid, 2-picolinic acid, or indole-2-carboxylic acid (Fig. 5, compounds **3**, **4**, and **5**, respectively) were identified as HDAC1 inhibitors (IC_{50} = 111, 200, and 182 nM, respectively) [41].

The involvement of HDAC1 in the pathogenesis of Rheumatoid Arthritis (RA) was reported. A selective HDAC1 inhibitor, named TTA03-107, was identified (Fig. 6) [42]. This selective HDAC1 inhibitor (HDAC1 IC_{50} = 3.22 nM) can suppress the production of inflammatory cytokines. TTA03-107 also suppressed the differentiation of T helper 17 cells (Th17). These results suggest that TTA03-107 can attenuate the

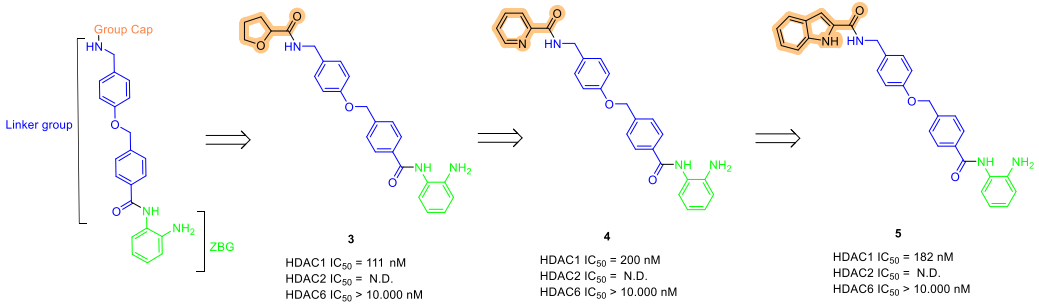


Fig. 5. Structures of novel *N*-(2-aminophenyl)-benzamide HDAC1 inhibitors with the 4-(benzyloxy)phenylmethylamine moiety as a linker.

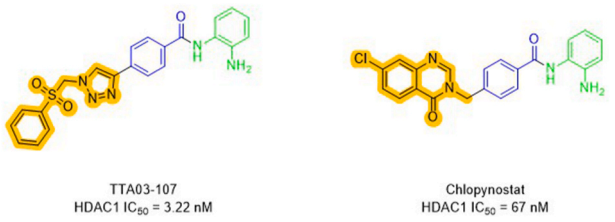


Fig. 6. Structures of TTA03-107 and chlopynostat.

development of arthritis in experimental RA models by inhibiting the differentiation and activation of macrophages and Th17 cells [42].

More recently, HDAC1 inhibition was described as capable of reactivating the STAT4/p66Shc apoptotic machinery in patients with chronic lymphocytic leukemia (CLL), and the compound chlopynostat was identified as a potent HDAC1 inhibitor with this pharmacological profile (Fig. 6) [43]. Chlopynostat showed a selective *h*HDAC1i profile (IC_{50} = 67 nM) respect to *h*HDAC6 (IC_{50} = >10,000 nM), *h*HDAC8 (IC_{50} = >10,000 nM) and *h*HDAC10 (IC_{50} = 1149 nM). The key structural characteristics of chlopynostat were the presence of a specific CAP, combined with the *o*-amino benzamide as the ZBG, and the benzyl group as a linker. In molecular docking studies, the authors highlighted that *o*-amino benzamide ZBG could discriminate between class I and class II isoforms. At the same time, the hydroxamic acid in ZBG seems to confer a pan-inhibition profile. Additionally, the benzyl linker appears to be important, as the flexible alkyl spacer is present in pan-inhibitors like vorinostat (SAHA).

Among the molecules described, selectivity involves the use of *ortho*-aminoanilide and benzamide scaffolds, which display high affinity for HDAC1 and HDAC2 but are poorly tolerated by other isoforms, such as HDAC6 and HDAC8. This selectivity is primarily attributed to the structural configuration of the catalytic pocket [44]. Specifically, the active sites of HDAC6 and HDAC8 possess a more constricted sub-pocket around the Zn^{2+} ion, often referred to as the "foot pocket" or "selectivity pocket", which limits the accommodation of bulky groups such as benzamides [45]. In contrast, HDAC1 and HDAC2 contain a larger and more flexible region adjacent to the metal center that can readily accommodate the planar, bidentate-binding benzamide moiety [46]. This structural feature allows ortho-aminoanilide inhibitors to establish stabilizing hydrogen bonds and metal chelation within HDAC1, while inducing steric clashes or suboptimal orientation in HDAC6 and HDAC8. Crystallographic analyses have confirmed that residues such as His141, Phe150, and Gly149 in HDAC1 contribute to forming a more permissive binding environment, whereas the corresponding residues in HDAC6 and HDAC8 impose steric hindrance [47]. Furthermore, selectivity can be enhanced by exploiting the variable surface loops (L1 and L2 regions) that line the rim of the active site, which differ among isoforms in both length and amino acid composition. CAPs with steric bulk or polar substituents can be strategically designed to interact with these loops, improving selectivity via induced-fit binding or enhanced residence time. For example, in HDAC6, the L2 loop forms a narrow tunnel that restricts the binding orientation of certain ligands, making it less accessible to inhibitors tailored for HDAC1. These differences can be visualized through comparative homology modeling and have been leveraged in hit-to-lead optimization programs [48].

Overall, these compounds demonstrate diverse chemotypes that are capable of achieving HDAC1-selective inhibition with varying degrees of potency and isoform discrimination. However, beyond their structural features, it is critical to understand the therapeutic rationale for targeting HDAC1 selectively over other class I isoforms. Although the pharmacological distinction between HDAC1-selective and nonselective inhibitors is often subtle due to the high sequence homology within class I HDACs, accumulating evidence suggests that selective HDAC1 inhibition may offer specific therapeutic advantages. HDAC1 and HDAC2 frequently co-localize within multiprotein complexes; however, genetic studies have shown that HDAC1 and HDAC2 possess non-redundant functions in specific cellular contexts [49]. For instance, HDAC1 deletion in mice leads to early embryonic lethality, whereas HDAC2 knockout results in postnatal lethality due to cardiac and neural defects, indicating distinct biological roles despite partial functional compensation [50]. *In vitro* and *in vivo* studies have further highlighted the therapeutic relevance of HDAC1 selectivity. The HDAC1-preferential inhibitor TTA03-107 demonstrated potent anti-inflammatory effects in rheumatoid arthritis models, selectively inhibiting HDAC1 (IC_{50} = 3.22 nM) without affecting HDAC2 or HDAC3, and significantly reduced cytokine production and Th17 cell differentiation *in vivo*, suggesting functional superiority over broader inhibitors in this disease setting [42]. Moreover, selective inhibition of HDAC1 with ortho-aminoanilide derivatives has been associated with reduced inhibition of hERG K^+ ion channels and lower toxicity in cardiomyocyte assays compared to pan-HDACi, which are known to exhibit cardiotoxicity and genotoxicity as dose-limiting side effects. This emerging profile of HDAC1-selective inhibitors suggests the potential for achieving a more favourable therapeutic index, particularly in chronic or systemic diseases that require long-term administration. Thus, the pursuit of HDAC1-selective ligands is not only a chemical design challenge but also a clinically relevant objective for minimizing off-target effects while preserving efficacy in disease-specific contexts.

2.1. *Hit-to-lead optimization: challenges in HDAC1 ligand development*

The development of HDAC1-selective inhibitors from early hits requires precise structural refinement to overcome the intrinsic homology among class I HDAC isoforms, particularly HDAC1 and HDAC2. Selectivity is typically achieved through the rational modulation of ligand–protein interactions in regions that diverge slightly between isoforms [14]. One well-established approach utilizes *ortho*-aminoanilide-based scaffolds, which interact with the catalytic zinc ion through a bidentate chelation mode, while offering chemical flexibility for optimizing the CAP. Substitution at the CAP region with bulky or polar moieties has been shown to exploit subtle differences in the L1 and L2 surface loops of HDAC1, enhancing isoform discrimination. Notably, ligands such as

BRD4884 and BRD7232 demonstrate kinetic selectivity, a prolonged residence time on HDAC1 relative to HDAC2, despite moderate differences in binding affinity [37]. This kinetic bias has been correlated with enhanced pharmacodynamic effects in cellular models. Beyond structural tailoring, kinetic optimization has emerged as a key parameter. Compounds exhibiting slow dissociation kinetics from HDAC1 can maintain durable target engagement, even when equilibrium binding constants are modest. Techniques such as surface plasmon resonance (SPR) and isothermal titration calorimetry (ITC) are increasingly utilized to guide this optimization phase [51]. Ligands such as CBUD-1001, compound 1, and compound 2 exemplify how isoform selectivity can be achieved through the strategic modification of the CAP and linker domains [40,52]. These compounds display submicromolar IC_{50} values for HDAC1 and up to 10-fold selectivity over HDAC2 and HDAC3, with documented antitumor efficacy in preclinical models. Their favourable ADMET profiles, characterized by improved microsomal stability, reduced inhibition of hERG K^+ ion channels, and limited cytotoxicity in non-malignant cells, further support their advancement. Overall, successful hit-to-lead optimization for HDAC1 inhibitors requires an integrative approach combining structure-based design, kinetic profiling, and early assessment of pharmacokinetic and safety parameters (Fig. 7). These efforts collectively support the progression of HDAC1-selective chemotypes with improved efficacy and reduced off-target liabilities.

2.2. Selective HDAC1 vs. pan-HDAC inhibitors: preclinical model comparisons

2.2.1. Cancer models

In medulloblastoma models, the HDAC1/2-selective inhibitor mocetinostat (MGCD0103) significantly suppressed tumor growth and prolonged survival in mice, demonstrating robust monotherapeutic efficacy [50]. Remarkably, mocetinostat (MGCD0103) elicited only marginal side effects and outperformed the pan-HDAC inhibitor vorinostat (SAHA) in terms of therapeutic response [53]. Similarly, the rationally designed HDAC1-selective benzamide CBUD-1001 showed potent antiproliferative activity against colorectal cancer cells, concurrently reversing epithelial-to-mesenchymal transition (EMT) markers [38]. These findings highlight the potential of HDAC1-selective agents to minimize the off-target toxicities commonly associated with broad-spectrum hydroxamate inhibitors [38].

2.2.2. Inflammatory and autoimmune models

Selective HDAC1 inhibition appears to preserve anti-inflammatory efficacy while markedly reducing systemic toxicity. In mouse models of rheumatoid arthritis, the HDAC1-selective compound TTA03-107 dramatically attenuated disease severity and inflammatory cytokine levels (TNF-α, IL-1β, IL-17A), primarily by inhibiting M1 macrophage polarization and Th17 cell differentiation [42,54]. Notably, TTA03-107 conferred these benefits without overt adverse effects *in vivo*, contrasting sharply with pan-HDAC inhibitors, which frequently cause weight loss, fatigue, gastrointestinal symptoms, and biochemical disturbances in similar models. Multiple reviews underscore that the broad activity of pan-HDACi contributes significantly to their toxicity in chronic inflammatory settings [42]. These findings suggest that, in contexts where both pan-HDACi and HDAC1-selective agents exhibit therapeutic efficacy, the latter may offer a superior safety [42,54].

2.2.3. Neurological and other disease models

Selective HDAC1 inhibition has shown promise in neurological models, although pan-HDACi occasionally yield greater effects. In a zebrafish model of Parkinson's disease (PD), the class I-selective inhibitor entinostat (MS-275) restored dopaminergic markers (e.g., tyrosine hydroxylase) and normalized cellular metabolism after neurotoxic insult, partially recapitulating the neuroprotective properties of broader HDAC inhibition [55]. However, neither entinostat (MS-275) nor selective HDAC6 inhibitors fully rescued locomotor impairments, indicating that combinatorial HDAC targeting may be necessary in some neurodegenerative contexts [55]. In pulmonary hypertension, pan-HDAC inhibitors such as vorinostat (SAHA) and trichostatin A (TSA) reversed disease pathology in hypoxic rodents, whereas HDAC1/2-selective inhibitors (e.g., romidepsin (FK228), CAY10398) exhibited only modest effects *in vivo* [56]. Nevertheless, under *ex vivo* conditions, selective HDAC1/2 inhibition was comparably anti-proliferative and pro-apoptotic to pan-HDAC inhibitors [56]. These results suggest that while broad inhibition may be required for maximal therapeutic impact in certain complex diseases, HDAC1-specific inhibition remains biologically active and may contribute to overall efficacy.

2.2.4. Efficacy vs. toxicity trade-off

Collectively, preclinical data indicate that HDAC1-selective inhibitors frequently match the therapeutic efficacy of pan-HDACi in both oncologic and inflammatory models [53,57]. Several studies directly compare isoform-selective HDAC1/2 inhibitors to pan-HDACi, reporting similar levels of tumor cytotoxicity and cell differentiation [53,57]. Crucially, selectivity appears to mitigate toxicity: for example, mocetinostat (MGCD0103) was well-tolerated and demonstrated a more favourable side effect profile than vorinostat (SAHA), while maintaining or surpassing antitumor activity [53]. Similarly, TTA03-107 effectively reduced arthritis symptoms without the anorexia, weight loss, or organ damage associated with pan-HDACi [54]. Authors of neuroblastoma studies likewise advocate for selective HDAC1/2 strategies to minimize patient toxicity [57].

In conclusion, HDAC1-selective inhibitors can recapitulate the beneficial biological effects of broad-spectrum HDAC inhibition,

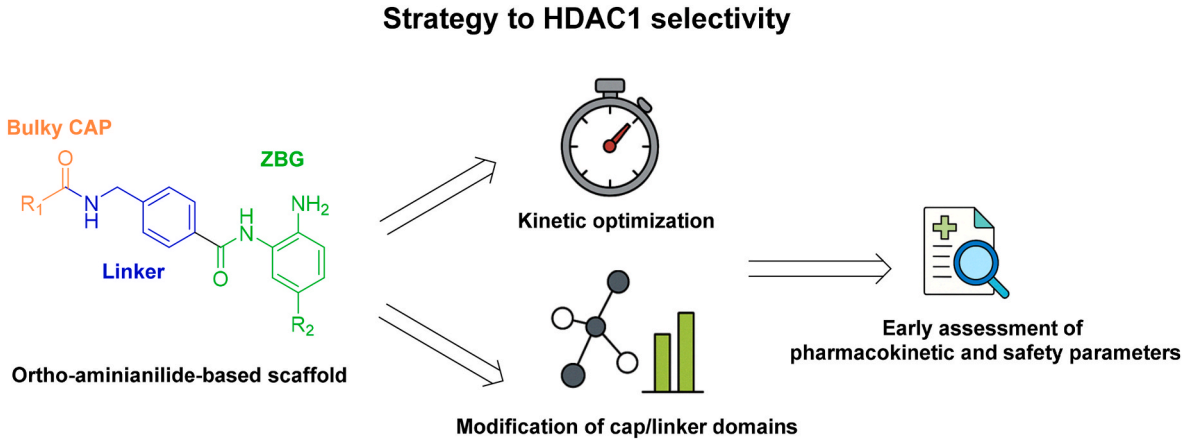


Fig. 7. Strategy to HDAC1 selectivity.

including tumor suppression and immunomodulation, while significantly reducing off-target toxicity. Although pan-HDACi may retain advantages in specific models (e.g., pulmonary hypertension) [57], many preclinical studies support HDAC1-selective inhibition as a safer and sufficiently efficacious alternative, offering hope for the future of cancer treatment [42,56].

3. HDAC1 activators

Genomic instability originates from a failure in the DNA damage response and repair and has been linked to age-related cognitive deficits and neurodegenerative disorders [58]. Preventing genomic instability may provide a protective strategy against several genotoxic stressors, thereby avoiding the neuronal death process [59]. The involvement of HDAC1 in the neurodegenerative process was reported. In a mouse model of stroke, it has been observed that the overexpression of catalytically active HDAC1 has a protective role against the neuronal damage caused by the p25/CDK5 complex [3]. Furthermore, the activity of HDAC1 was investigated in a mouse model of inducible p25/CDK5 characterized by some of the clinical symptoms of AD. This study detected an inhibition of the HDAC1 activity [60]. Therefore, HDAC1 plays a crucial role in neuroprotection by preserving the integrity of the human genome. Another important aberrant event occurring in AD physiopathology is the aggregation of Tau protein [61]. Tau is involved in various biological functions, such as synaptic transmission, DNA protection, and gene regulation, that are altered in neurodegeneration [62]. Siano et al. reported that Tau modulates the genes implicated in the glutamatergic synapse. In the early stages of AD, Tau destabilization leads to the accumulation of Tau monomers, resulting in neurotoxicity due to the pathological expression of glutamatergic genes. Conversely, in the late stage of AD pathology, a decrease in levels of glutamatergic genes was observed [63]. During the AD progression, Tau-dependent gene expression is likely compromised by aggregation, suggesting that aggregation induces a loss of function in nuclear Tau [64]. The mechanisms that regulate this function are still unknown. However, it was reported that Tau interacts with Tripartite Motif Containing 28 (TRIM28), a scaffold protein that cooperates with transcription factors and epigenetic remodelers. The interaction between TRIM28 and Tau is notably correlated to the pathological transport of Tau into the nucleus and with chromatin modifications [65]. Recently, a mechanism involving the competitive activity of HDAC1 on the interaction between Tau and TRIM28 was discovered [66]. The results suggest that HDAC1 displacement from the nucleus mediated by Tau upregulation could affect the alterations in disease-related gene expression observed in tauopathies. Moreover, HDAC1 and HDAC2 also have a role in regulating memory functions [67]. Several studies have demonstrated a correlation between HDAC1 and HDAC2 expression, showing that HDAC1 levels increase in response to HDAC2 knockdown or knockout [68]. Overall, this evidence highlights the potential therapeutic role of HDAC1 activation in treating aging and neurodegenerative disorders. Thus, small-molecule activators of HDAC1 were identified through high-throughput screening, and among them, the compound 5104434 (Fig. 8) was selected [69,70]. In 2021, Patnaik *et al.* evaluated the SARs of screened compounds and identified exifone as a potent HDAC1 activator (Fig. 8) [71].

Exifone, also known as 2,3,3′,4,4′,5′-hexahydroxybenzophenone or Adlone®, belongs to the family of benzophenones. It was first synthesized in France in 1970, and its initial therapeutic application was in disorders of blood microcirculation [72]. Afterwards, the neuroprotective effects of exifone were investigated in several preclinical studies and clinical trials. Then, it was approved as a neuroprotective drug in 1988 to treat cognitive deficits in elderly patients with both AD and PD [73]. Although exifone did not exhibit significant toxicity in preclinical and clinical studies, several cases of reversible liver damage were reported following its introduction to the market. Therefore, its marketing registration was deleted in 1990 [74,75]. Over the years, several studies have further investigated the profile of exifone. Exifone has shown free radical scavenging properties and antioxidant activity [76]. It is supposed that it may activate glucose and oxygen metabolism in neuronal cells [77]. Moreover, it was found that exifone can reduce DNA damage *in vivo* in an AD mouse model and further linked the fundamental mechanisms of the DNA damage response pathway and repair to HDAC1 activity. Exifone acts as a potent small-molecule activator of HDAC1, enhancing deacetylase activity in a concentration-dependent manner, and serves as a non-essential activator. *In vitro* enzymatic assays demonstrated that exifone activates HDAC1 with an EC_{50} of 20 nM, while HDAC2 is activated at an EC_{50} of 80 nM, indicating approximately 4-fold selectivity for HDAC1. No significant activation was observed for HDAC8 or SIRT1 at relevant concentrations, confirming the compound's specificity among class I HDACs [71]. To date, the mechanism of HDAC1 activation and the binding site of exifone are still unknown. Thus, developing novel small molecules like exifone could serve as a starting point for creating new HDAC1 activators as neuroprotective agents.

Various exifone derivatives have been synthesized in recent years to obtain analogs with an improved pharmacological profile. The exifone's toxic effects appear to be related to electrophilic oxidation products such as quinone or iminoquinone [78]. In particular, the transient reactive *o*-quinone species could cause *in vivo* toxicity by irreversibly binding the $–NH_2$ and –SH residues of proteins, thus forming toxic conjugates. First, in 1995, Largeron et al. proposed the electrochemical and chemical syntheses of novel 1,4-benzoxazine derivatives (I and II) (Fig. 8). These ligands showed structural similarities with exifone, demonstrating lower hepatotoxicity and improved antioxidant activity compared to it [78]. With the same aim, the authors synthesized a series of 8-alkylamino-substituted-1,4-benzoxazines (**6**) [77] and a series of 2-alkylamino-substituted-1,4-benzoxazines (**7**) (Fig. 9) [79].

The potential neuroprotective action of all 1,4-benzoxazine derivatives was investigated *in vitro* by evaluating their protective effects against L-homocysteic acid (L-HCA) cytotoxicity and their safety index. More interesting compounds (**6a**, **6b**, **7a**) compared with exifone are reported in Table 2. In summary, the results of these studies identified some 1,4-benzoxazine derivatives that showed neuroprotective activity without the toxic effects of exifone.

Moreover, the *in vivo* neuroprotective effects of the selected compounds were evaluated using an animal model of excitotoxic brain lesions in neonatal mice, induced by intracerebral administration of *S*-bromowillardiine. These 1,4-benzoxazine derivatives exhibited protective effects comparable to established agents, highlighting their promising therapeutic potential for the treatment and prevention of neurodegenerative disorders [77,79].

Another HDAC1 activator is compound 5104434 (Fig. 8), which belongs to the cyclohexanedione class. Similarity between compound 5104434 and exifone in their chemical structures has been observed. The effectiveness of compound 5104434 was first demonstrated and reported by Tsai et al. [69]. *In vitro*, treatment of primary cortical neurons subjected to oxygen–glucose deprivation (OGD) with compound 5104434 at 2.5 μM partially restored HDAC1 enzymatic activity, while 25 μM fully rescued activity to baseline levels measured via immunoprecipitation-enzyme assays. Notably, biochemical profiling confirmed that compound 5104434 selectively activates HDAC1 without significant effects on HDAC2, HDAC3, or HDAC8. Further

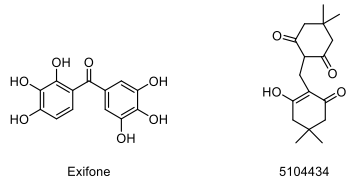


Fig. 8. Chemical structures of HDAC1 activators.

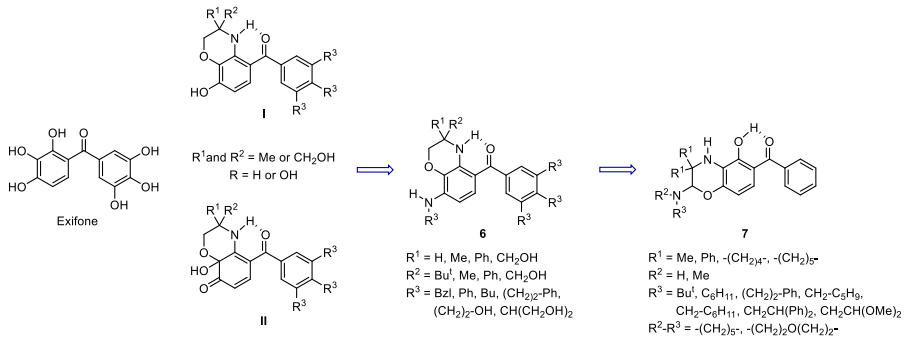
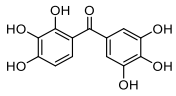
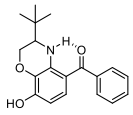
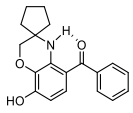
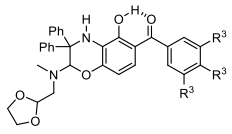


Fig. 9. Exifone derivatives with neuroprotective effects.

Table 2
In vitro neuroprotective activity estimated through their protective effects against L-HCA cytotoxicity[a].

Compound		Protection *vs* 2 mM L-HCA		Safety index	
		PC_{50}/(μM)		MTC/PC_{50}	
		MTT	LDH	MTT	LDH
Exifone		<10	<10	<1	<1
6a		15.8	14.4	>15.8	>17.4
6b		2.5	4.0	>100	62.5
7a		0.1	1.0	200	>250

[a] MTC, maximum tolerated concentration; PC_{50}, concentration producing 50 % protection; MTT, 3-(4,5- dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide; LDH lactate dehydrogenase.

studies performed in a human neural blastoma cell line, SH-SY5Y, have shown that compound 5104434 provides specificity and selectivity in activating HDAC1. Moreover, it exhibited neuroprotective effects in a mouse model of neurodegeneration [80]. Experimental results suggest that it may promote enzymatic activity in a dose-dependent manner *in vitro*. *In vivo*, administration of compound 5104434 at 30 mg/kg/day i.p. in a rat model of cerebral ischemia significantly restored HDAC1 activity in brain tissues, reduced infarct volume, neuronal apoptosis, DNA damage, and oxidative stress markers; behavioral assessments also showed improved neuromuscular, balance, and forepaw strength functions [80]. In particular, the administration of compound 5104434 attenuated ischemia-induced neuronal morphological collapse, reduced neuronal loss and apoptosis, and significantly decreased DNA strand breaks and associated oxidative damage. These protective effects suggest that HDAC1 activation may enhance genomic stability under pathological stress conditions [81,82]. These data provide compelling quantitative and functional support for compound 5104434 as a selective HDAC1 activator with robust *in vitro* and *in vivo* neuroprotective effects. Nevertheless, the mechanism of action of compound 5104434 on HDAC1 activation is still uncertain.

Other HDAC1 activators have been patented by Tsai et al. The new ligands were designated as deacetylase-activating compounds ("DACs") for the treatment of neurological disorders (Fig. 10) [70]. Examining the chemical structures, these compounds exhibited several structural similarities, suggesting specific SARs to activate HDAC1. These compounds, identified through targeted screening of HDAC1, exhibit effective working concentrations in the 5–10 μM range, demonstrating a dose-dependent activation of HDAC1 *in vitro* in a microfluidics-based assay. Additional confirmation in HEK293T cells revealed that 10 μM DAC-003 maintains deacetylation of key histones (H3K56, H4K12, H3K14) after 20 h, confirming functional HDAC1 activation and prevention of Ac–H4K12 accumulation (via western blot). Cytotoxicity at these working concentrations was minimal (<10 % reduction in cell survival), suggesting a favourable safety profile. The results highlighted that these compounds could activate HDAC1 in cells. Specifically, DAC-001, DAC-002, DAC-003, DAC-009, and DAC-012 displayed significant protection against DNA breaks [70]. HT-22 cells, a hippocampal neuron-derived cell line, were employed as a model of neurodegeneration. Cell viability was assessed using CellTiter-Glo assays, which revealed that DAC-003 and DAC-012 are protective against oxidative stress. The potential neuroprotective effect of "DACs" was investigated in a neuronal excitotoxicity model. The data showed that the compounds have a protection trend, and among them, the most interesting was DAC-001.

Moreover, several natural metabolites that act as allosteric activators of non-sirtuin HDACs *in vitro* have been identified *in vitro*. These metabolites include different CoA derivatives like acetyl-CoA, butyryl-CoA, idrossimetilglutaril-CoA, and malonyl-CoA, as well as NADPH (but not $NADP^+$, NADH, NAD^+). They are all characterized by an adenosine phosphate moiety. Remarkably, even though free CoA and butyrate generally inhibit HDAC, butyryl-CoA (Fig. 11) stimulated HDAC 1 and 2 activities following a mixed activation kinetic [81]. By analyzing different engineered HDAC1 mutants, it has been suggested that HDAC activity can be decoupled from "activatability" by these CoA derivatives [83]. Supplementary studies are required to identify the residues involved in binding between activators and HDACs.

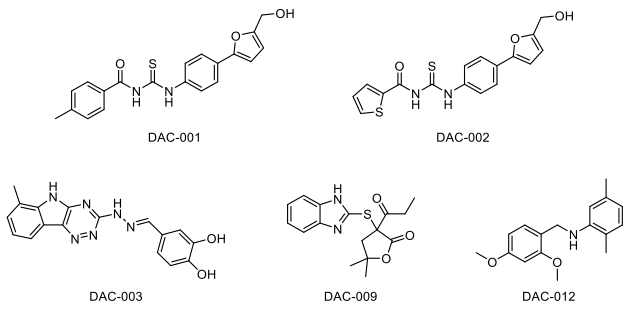


Fig. 10. DACs compounds' structures.

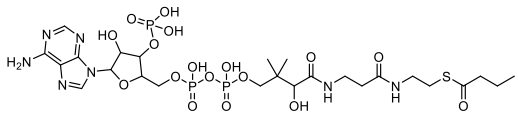


Fig. 11. Butyryl-CoA structure.

4. Clinical trials and future perspectives

To date, no HDAC1-selective inhibitor has advanced into clinical trials, despite growing preclinical evidence supporting its potential as a therapeutic target in oncology, inflammatory, and neurodegenerative diseases. The clinical landscape of HDAC-targeted therapies is still dominated by pan-HDACi or compounds with preferential, but not exclusive, activity against class I HDACs [84]. The clinical investigation of HDAC1 modulation has primarily relied on class I-selective HDACi, including entinostat (MS-275), mocetinostat (MGCD0103), pracinostat (SB939), and quisinostat (JNJ-26481585). These agents inhibit HDAC1 and HDAC2 with varying degrees of selectivity and are often considered the most pharmacologically relevant tools for probing HDAC1-associated biology in humans. Several of these compounds have entered early-phase clinical trials for the treatment of hematologic malignancies (e.g., myelodysplastic syndromes, acute myeloid leukemia) and solid tumors (e.g., breast, lung, ovarian cancer) [85]. A selection of the most relevant HDACi acting on HDAC1 in clinical trials is reported (Fig. 12).

Despite favourable preclinical profiles, the clinical translation of these agents has encountered significant challenges. In Phase I/II studies, entinostat (MS-275) demonstrated epigenetic reprogramming activity, including increased histone H3 and H4 acetylation, as well as the re-expression of tumor suppressor genes; however, its clinical efficacy was limited by dose-limiting gastrointestinal and hematological toxicities [86–88]. Pracinostat (SB939), which exhibits improved oral bioavailability and a longer plasma half-life, failed to significantly enhance clinical outcomes when combined with azacitidine in randomized trials for acute myeloid leukemia, leading to trial discontinuation [89–91]. Mocetinostat (MGCD-0103), another class I-selective agent, demonstrated promising anti-tumor activity and an acceptable safety profile in early trials, particularly in patients with refractory lymphomas. However, further development has been constrained by modest response rates and nonspecific toxicities [92]. A central pharmacological obstacle is the difficulty in achieving actual HDAC1 selectivity. HDAC1 and HDAC2 share greater than 85 % sequence identity in their catalytic domains and are frequently co-recruited into multi-subunit transcriptional repression complexes such as NuRD, Sin3A, and CoREST [93]. As such, compounds that target HDAC1 often exhibit near-equal activity against HDAC2, making it challenging to dissect their contributions to therapeutic outcomes and side effect profiles. Moreover, compensatory upregulation of HDAC2 upon HDAC1 inhibition, and vice versa, has been observed in various preclinical models, further complicating isoform-specific targeting strategies [94]. Another barrier to clinical progress is the lack of validated pharmacodynamic biomarkers for HDAC1 activity *in vivo*. While histone hyperacetylation (e.g., H3K9ac, H4K12ac) is commonly used as a readout of HDAC inhibition, it is a non-specific marker that does not distinguish between HDAC isoforms [95]. This limitation hampers patient stratification, response monitoring, and dose optimization in clinical trials. Future strategies should incorporate chromatin immunoprecipitation-based profiling, transcriptomic signatures, and functional genomic approaches to identify HDAC1-specific biomarkers and more accurately predict therapeutic responsiveness [96,97]. Additionally, toxicological concerns remain a significant limitation for the clinical development of HDAC inhibitors. Pan-HDACi are often associated with cardiotoxicity, thrombocytopenia, fatigue, and gastrointestinal symptoms, partly due to their broad inhibition of class II and HDAC6 isoforms, which are involved in non-epigenetic cellular functions such as cytoskeletal remodeling and protein degradation [98]. Although class I-selective inhibitors are hypothesized to exhibit an improved safety profile, emerging data suggest that dual HDAC1/2 inhibition may still affect critical pathways in non-malignant tissues, especially in chronically treated patients. In light of these considerations, current clinical efforts can be viewed as a transitional phase, bridging non-selective HDAC inhibition and the future development of highly specific HDAC1-targeted therapies. In conclusion, while no HDAC1-selective inhibitors are currently undergoing clinical trials, class I HDAC inhibitors provide partial insight into the therapeutic relevance of HDAC1 modulation. The next generation of clinical candidates will need to address the intertwined challenges of isoform specificity, safety, and the integration of translational biomarkers. A shift toward precision pharmacology and rational combination regimens, guided by systems biology and tumor epigenomic profiling, will be essential to fully unlock the therapeutic potential of HDAC1 in cancer and other complex diseases. Instead, HDAC1 activators are beginning to gain attention for the treatment of neurodegenerative diseases, although no such compounds have yet reached clinical evaluation. The selective enhancement of HDAC1 activity may offer a protective strategy against oxidative DNA damage in conditions such as AD, but its clinical translation remains a challenge. In future clinical programs, a stronger emphasis on biomarker-driven patient selection, transcriptional profiling, and dynamic pharmacodynamic markers (e.g., chromatin accessibility, histone occupancy) will be essential. Only through such precision strategies can HDAC1-targeted therapies fulfill their translational promise.

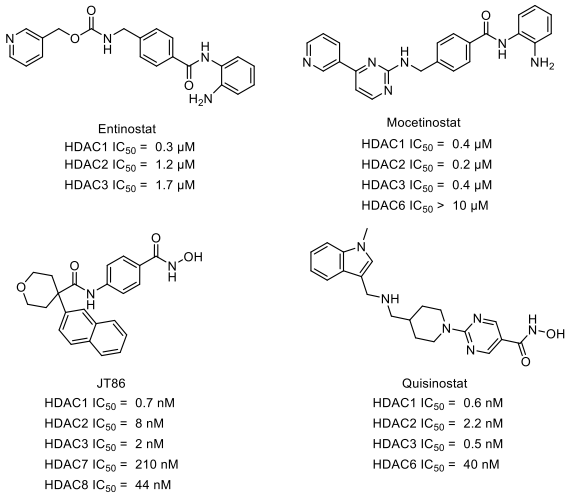


Fig. 12. HDACi in clinical trials.

4.1. Barriers to clinical translation of HDAC1-selective ligands

While several HDAC1-selective ligands have shown promise in preclinical models, their translation to clinical efficacy remains suboptimal. One major hurdle is the context-dependence of HDAC1 function. In cancer, HDAC1 may play divergent roles depending on the tumor type, genetic background, and stage of progression, acting either as a repressor of tumor suppressor genes or a facilitator of oncogenic programs. This duality complicates patient selection and biomarker-driven stratification in clinical trials. For example, high HDAC1 expression does not necessarily predict dependency or therapeutic vulnerability unless it is integrated with the epigenetic and transcriptomic context [99]. Furthermore, epigenetic compensation and redundancy pose intrinsic limits to selective inhibition. HDAC1 and HDAC2 often co-occupy chromatin and share substrates, so selective HDAC1 inhibition may be buffered by HDAC2 activity. Inhibitors must therefore achieve either high selectivity without loss of efficacy or co-inhibit both targets in a biased and safe manner. However, HDAC2 inhibition has been linked to

adverse effects on memory and neuronal survival, raising concerns about the broader class I HDAC inhibition [100]. Another obstacle is the limited *in vivo* exposure and poor pharmacokinetics of many HDAC1 inhibitors. Rapid hepatic metabolism, poor solubility, and low oral bioavailability have hindered the development of several candidates. Even when HDAC1 engagement is confirmed by pharmacodynamic markers (e.g., increased histone acetylation), target modulation does not always translate into durable biological responses, particularly in solid tumors with complex stromal environments. Additionally, resistance mechanisms can emerge rapidly through upregulation of compensatory chromatin modifiers (e.g., LSD1, EZH2) or activation of bypass pathways (e.g., PI3K, MAPK). These adaptations blunt the epigenetic reprogramming intended by HDAC1 inhibition and support the rationale for combination strategies. However, many HDAC1 inhibitors have unfavourable toxicity profiles when combined with cytotoxic or immunomodulatory agents at therapeutic doses [101]. Finally, clinical trial design must undergo a paradigm shift to fully realize the therapeutic potential of HDAC1-selective ligands [102]. Traditional trial frameworks often fail to capture the nuanced, context-dependent effects of epigenetic modulation, particularly in solid tumors and heterogeneous hematologic malignancies. Basket trials that enroll patients based on shared molecular features, such as HDAC1 overexpression, chromatin compaction patterns, or specific transcriptional signatures, could enable a more precise evaluation of drug activity across histologically diverse tumors [103]. Likewise, adaptive trial designs that allow for dynamic modification of study arms based on interim biomarker or efficacy data could enhance efficiency and reduce exposure to suboptimal regimens [104]. One of the significant limitations in current trials is the absence of robust, predictive pharmacodynamic biomarkers. Reliance on bulk histone acetylation levels as a surrogate readout of HDAC inhibition is inadequate, as it lacks specificity for HDAC1 and often fails to correlate with therapeutic outcomes. Furthermore, global histone acetylation changes can be influenced by multiple HDAC isoforms and may not reflect gene-specific chromatin remodeling events relevant to disease pathogenesis. Therefore, multiparametric biomarker strategies are urgently needed. Moreover, implementing liquid biopsy approaches, including circulating tumor DNA (ctDNA) and exosomal RNA profiling, may enable non-invasive, real-time monitoring of epigenetic target engagement and treatment response. Coupling these molecular readouts with advanced computational modeling and machine learning could further facilitate the personalization of HDAC1-based therapies, ultimately improving patient selection, dosing strategies, and clinical outcomes [105].

5. Computational strategies in HDAC inhibitors development

A significant challenge in developing effective HDACi lies in their selectivity. First-generation HDACi often lack specificity, as they target multiple HDAC isoforms and can potentially cause cellular toxicity. This lack of selectivity necessitates the development of more targeted inhibitors that specifically target the relevant HDAC isoforms involved in disease pathogenesis, thereby minimizing off-target effects. To address these challenges, computational methods have emerged as valuable tools in discovering and developing HDACi with the desired potency and/or selectivity [106].

Multiple studies have explored different classes of histone deacetylase 1 inhibitors (HDAC1i), their mechanisms of action, and drug design strategies, including computational approaches such as density functional theory (DFT), molecular dynamics (MD), machine learning (ML), and virtual screening (VS). More specific compounds are being researched to reduce side effects and improve efficacy. Some research focuses on the structural analysis of drug-HDAC interactions, while others assess the pharmacokinetic properties and toxicity of inhibitors. In this review, we report *in-silico* models examined to predict activity and guide the discovery of more effective drugs.

5.1. Virtual screening and molecular docking

VS and molecular docking are increasingly used as computational tools to identify potential enzyme inhibitors involved in disease, such as HDAC. HDAC1 is an enzyme involved in the progression of various types of tumors, making it a promising target for pharmacological intervention.

The VS involves docking a large set of molecules by simulating their interaction with the crystallographic structure of HDAC1. A typical VS workflow (Fig. 13) includes specialized software for molecular docking, which can predict the optimal orientation and binding affinity of each compound within the enzyme's active site [105–107]. When the database of molecules to dock has a large dimensionality (thousands of molecules to be tested), it is often preferred to perform a preliminary filtration. A quick approach is evaluation by pan assay interference compounds (PAINS), which can be performed using RDKit [14] or the online tool SwissADME [107]. Alternatively, preliminary filtering using a pharmacophoric model can be employed to identify hits that best match the pharmacophore. Sirous et al. successfully screened a database consisting of 736,160 molecules. They initially generated the various conformers of different molecules and then selected only those whose conformers best fit the pharmacophoric model [14].

MD simulations are usually used to refine further the selection, which assesses the conformational stability of the protein-ligand complex in a simulated environment. The workflow can be complemented by molecular mechanics generalized Born surface area (MM-GBSA) analysis, performed before and/or after MD. MM-GBSA analysis provides a more accurate calculation of free energy in small molecule-protein complexes than molecular docking because it combines the molecular mechanical (MM) energies with the continuum solvent generalized Born (GB) model for polar solvation, as well as a solvent-accessible surface area (SASA) for the non-polar solvation term.

Finally, it is essential to assess the pharmacokinetic properties of

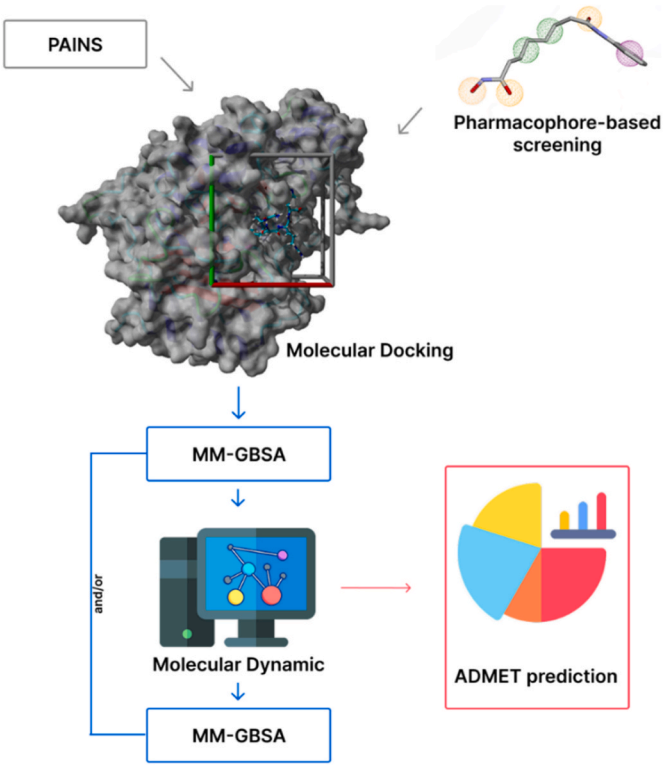


Fig. 13. Typical workflow employed in VS of large molecule databases. As an example, the structure of the HDAC1 5ICN crystal, suitable for molecular docking and vorinostat (SAHA)-based for pharmacophore screening, is shown in the figure.

compounds by *in-silico* prediction of ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) properties. The efficacy of a drug depends not only on its intrinsic activity but also on its ability to overcome biological barriers without undergoing metabolism. Therefore, assessing the ADMET profile is crucial in the early stages of drug discovery, increasing the likelihood of clinical success. Today, *in-silico* techniques enable the rapid prediction of safety, pharmacokinetics, bioavailability, and toxicity, thereby reducing the need for expensive experimental testing. Important pharmacokinetic properties, such as compliance with the Lipinski rule, polar surface area (PSA), blood-brain barrier (BBB) penetrability, and gastrointestinal (GI) absorption, can be predicted using the QikProp module integrated into the Schrödinger suite and the SwissADME online tool [14,106–108].

Gopinathan et al. used a VS approach to search for HDAC1 inhibitors to treat glioblastoma. HDAC1 is overexpressed in glioblastoma cells, resulting in the downregulation of Neprilysin (NEP) levels. Therefore, searching for selective HDAC1 inhibitors would significantly benefit the pathology, leading to increased levels of NEP. Panobinostat (LBH589), melphalan, and tasimelteon have been identified as potential therapeutic agents for glioblastoma, capable of reducing the expression levels of the HDAC1 protein in cancer cell lines. Panobinostat (LBH589) showed potent cytotoxic action in the nanomolar range in both cell lines tested [106]. Further research has focused on developing benzamide-based analogs, a class of compounds with known HDAC inhibitory activity. Through VS and MD, it was possible to optimize the structure of these molecules, improving their affinity and selectivity for HDAC1. Six molecules (Fig. 14) that show excellent stability profiles and appropriate binding modes in the HDAC1 active site were identified. The authors highlight how these molecules could be considered encouraging models for further developing new benzamide chemotypes as HDAC1 inhibitors [107]. Bharadwaj et al. performed VS of phytocompounds from the PhytoHub database against the HDAC1 enzyme. Pinocembrin, a natural flavonoid, has been identified as a potential inhibitor of HDAC1, with a predicted binding energy of −7.99 kcal/mol and an inhibition constant of 1.38 μM predicted. Analysis of ADME properties showed a favourable pharmacokinetic profile. Pinocembrin could play a role in mitigating cancer cell progression through epigenetic chromatin remodeling. Still, the authors emphasize that further *in vitro* and *in vivo* research will be needed to validate its anticancer efficacy precisely [108].

5.2. 3D-QSAR-based virtual screening

Sirous et al. proposed a VS method based on the generation of a 3D-QSAR model. The research group worked on aminophenylbenzamide derivatives, compounds known for potent and selective inhibitory activity against HDAC1. Phase software was used to derive the 3D-QSAR model. Initially, a pharmacophoric hypothesis was generated based on 20 HDAC1 inhibitors with IC_{50} values of $\leq$10 nM, which were considered highly active. The resulting model was named ADDRR as it is defined by one hydrogen bond acceptor (A), two hydrogen bond donors (D), and two aromatic rings (R). According to the model, the identified positions are crucial for interaction with the active site of HDAC1, promoting zinc ion coordination, hydrogen bond formation, and pi-pi stacking interactions with key residues. The ADDRR model was employed as an alignment rule for generating the 3D-QSAR model using a comprehensive set of 370 benzamide derivatives, which were divided into training and test sets. Models containing one to seven factors were generated to avoid overfitting. The seven-factor model was chosen as the best because it had an excellent correlation coefficient ($R^2 = 0.96$) and high predictive ability ($Q^2 = 0.82$; $Q^2_{F3} = 0.89$). The 3D-QSAR model was validated using an external test set comprising 113 compounds, yielding a good correlation coefficient (r^2ext_ts = 0.79). In addition, the model's capabilities were tested through analysis against decoys. The decoy set consisted of 5,870 compounds (5,764 decoy molecules and 106 actives). The model demonstrated an excellent ability to discriminate between active and inactive compounds, supported by an enrichment factor (EF) of 48.33, a Güner-Henry (GH) score of 0.71, and an Area Under the Curve (AUC) value calculated from the Receiver Operating Characteristic (ROC) curve of 0.94. The results make the generated model a valuable tool for VS and rational design of selective HDAC1 inhibitors [109].

5.3. Investigate the binding mode and the binding site

Molecular docking studies were performed to investigate the binding mode of inhibitory HDAC1 molecules. Several studies highlight the importance of the coordination bond between the molecules and the zinc ion within the catalytic site. Other recurrent interactions in various studies include hydrogen bonds formed with the residues Asp99 and Gly149, as well as pi-pi interactions with the residue His178 [39–41,85,110]. Table 3 presents the details of all interactions reported in the examined articles, assuming that all molecules involve the chelation of zinc ions.

In addition to considering key residues in the interaction, the rational design of selective inhibitors for the HDAC1 isoform should consider structural differences in binding sites. The active site of HDAC8 is described as larger and having a greater surface opening than those of

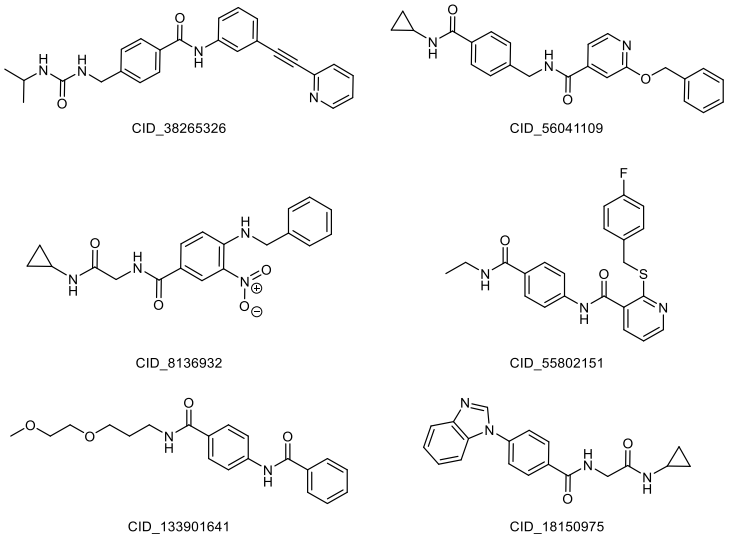


Fig. 14. 2D chemical structures of the six identified inhibitors.

Table 3
HDAC1i interactions reported in the examined studies.

Compound	Residue (type of interactions)	HDAC1 PDB ID	Reference
3c	Asp99 (hydrogen bond), Gly149 (hydrogen bond)	4BKX	[40]
11a	Asp99 (hydrogen bond), Gly149 (hydrogen bond)	4BKX	[40]
M1	Asp99 (hydrogen bond), Gly149 (hydrogen bond)	4BKX	[111]
M2	Asp99 (hydrogen bond), Gly149 (hydrogen bond)	4BKX	[111]
M3	Gly149 (hydrogen bond)	4BKX	[111]
M4	Asp99 (hydrogen bond), His178 (pi-pi interaction), Phe205 (pi-pi interaction)	4BKX	[111]
GK445	His140 (hydrogen bond), His141 (hydrogen bond), Tyr303 (hydrogen bond), Gly149 (hydrogen bond), His178 (pi-pi interaction), Leu271 (hydrogen bond)	5ICN	[41]
GK713	His140 (hydrogen bond), His141 (hydrogen bond), Tyr303 (hydrogen bond), Gly149 (hydrogen bond), His178 (pi-pi interaction), Glu98 (hydrogen bond), His28 (hydrogen bond)	5ICN	[41]
GK725	His140 (hydrogen bond), His141 (hydrogen bond), Tyr303 (hydrogen bond), Gly149 (hydrogen bond), His178 (pi-pi interaction), Tyr 204 (pi-pi interaction), Leu271 (hydrogen bond)	5ICN	[41]
AR-42	Asp99 (hydrogen bond), Phe150 (pi-pi interaction), Phe205 (pi-pi interaction)	homology model	[82]

HDAC1–3. In addition, the foot pocket, a cavity approximately 14 Å in diameter perpendicular to the hydrophobic tunnel of the active site, is narrower in HDAC8 due to the bulky side chain of the Trp141 residue in HDAC8 occupying this space. In contrast, in HDAC1–3, this pocket is more accessible. This difference in foot pocket space between HDAC8 and HDAC1 can be exploited for selectivity [112]. Although HDAC1 and HDAC3 are both class I isoforms and share 64 % sequence similarity, there are crucial structural differences in their binding site. One significant distinction is the presence of the Tyr107 residue in HDAC3, in contrast to the Ser113 present in HDAC1. This amino acid substitution in HDAC3 creates a steric hindrance that prevents bulky functional groups of inhibitors from accessing the active site, making it a key factor in the selectivity of HDAC3 inhibitors and limiting the binding of larger molecules that might otherwise also inhibit HDAC1. Ultimately, the foot pocket of HDAC3 is significantly smaller than that of other isoforms due to the pressure exerted by the side chain of Tyr107 on the adjacent Leu133 residue [47,112]. HDAC6, which is part of class IIb, is distinguished from HDAC1 by the presence of a much larger active site, which facilitates access of bulky inhibitors to the catalytic Zn^{2+} ion. A relevant structural feature of HDAC6 is the L1 loop pocket, which is rigid and well-defined, allowing the accommodation of large hydrophobic groups. In contrast, in class I HDACs, the L1 loop is displaced about 1 Å relative to HDAC6, which constricts the substrate binding pocket and makes it less suitable for binding bulky groups [113]. Class IIa HDACs possess a considerably larger active site cavity than class I HDACs, including HDAC1. The size difference is related to the fact that class IIa HDACs have a highly conserved histidine residue, which is located distant from the zinc ion. In class I HDACs, instead of the histidine residue, we find a tyrosine residue whose aromatic ring extends into the binding site, reducing its size [114].

5.4. Density functional theory (DFT) studies

DFT is a quantum chemical computational method that predicts and analyses the electronic properties of atoms and molecules based on electron densities. In contrast to other *in-silico* techniques, DFT provides details at the atomic level, including the electronic distribution in molecular orbitals and the electronic properties that influence interactions. This can help us understand the molecular mechanisms regulating the interaction between ligands and the enzyme more deeply [115].

Zhou et al. performed DFT-based QM/MM studies – specifically, Born-Oppenheimer *ab initio* QM/MM MD simulations – and reported an analysis of the structural and functional aspects of class I HDACs, focusing on the different π-stacking interactions between conserved residues. They observed that all class I HDACs could alter the chelation of zinc inhibitors through conserved tyrosine residues, specifically Tyr303 for HDAC1. By studying the pan-inhibitor vorinostat (SAHA), they observed that a conserved tyrosine residue promotes the hydroxyl hydrogen deprotonation reaction, enhancing the ability to chelate zinc and, thus, the ligand-protein interaction. In addition, Tyr303 plays a key role in stabilizing the reaction intermediate during the substrate deacetylation process [116].

Choubey et al. reported the identification of novel HDAC1 inhibitors using various computational approaches [117]. After VS of various compounds using an integrated approach of molecular docking and constructing a 3D-QSAR model, DFT studies were further performed to investigate the best hit. DFT has been used to study the electronic characteristics of ligands involved in the charge transfer process in receptor-ligand interactions [118]. Authors suggest that the ability of compounds to behave as electron acceptors is crucial for molecular interaction. Specifically, it was shown that when the oxygen atom of the carbonyl group of the ligand interacts with the residue His178 of HDAC1, the nitrogen atom N3 of His178 acts as an electron donor.

5.5. Machine learning (ML) approaches

Rourou et al. built 80 classification models using five different ML algorithms: decision tree (DT), random forest (RF), support vector machine (SVM), eXtreme Gradient Boosting (XGBoost), and deep neural network (DNN). The aim was to predict the activity of a compound based on its structural characteristics, represented by molecular fingerprints such as MACCS fingerprints, RDKit fingerprints, TT fingerprints, and ECFP4 fingerprints. The best-performing model was 15A_2, based on the XGBoost algorithm and ECFP4 fingerprints, with an accuracy of 88.08 % and an MCC value of 0.76 in the test set. In addition, clustering with the K-Means method revealed that *N*-(2-amino-phenyl)-benzamide groups are often present in highly active HDAC1i [119].

Krishna et al. employed a multi-step VS approach, beginning with an SVM model based on MACCS descriptors. This model effectively distinguishes between the active and inactive molecules of HDAC1. Subsequently, a pharmacophoric model based on ZBGs was generated, which demonstrated high sensitivity and specificity in discriminating between active and inactive compounds. VS, combined with molecular docking, identified three active compounds (Fig. 15) – BTB0359, SEW04788, and SP00930 – with IC_{50} ranging between 5 and 8 μM that showed antiproliferative activity *in vitro* and affected chromosome stability. Finally, MD analysis confirmed the stability of the protein-ligand complexes formed by the identified compounds [120].

6. Summary of investigations of selective HDAC1 inhibitors

Despite the growing body of preclinical evidence supporting the therapeutic relevance of HDAC1 inhibition, no highly selective HDAC1 inhibitor has yet entered clinical trials. Nonetheless, several class I-selective HDACi with partial preference for HDAC1 have advanced to early-phase clinical evaluation, providing indirect insight into the potential clinical utility of HDAC1 modulation [121]. Among these, entinostat (MS-275), mocetinostat (MGCD0103), pracinostat (SB939), and quisinostat (JNJ-26481585) have been most extensively studied [55,57]. These compounds exhibit nanomolar inhibitory activity toward HDAC1 and HDAC2 and have demonstrated varying degrees of efficacy

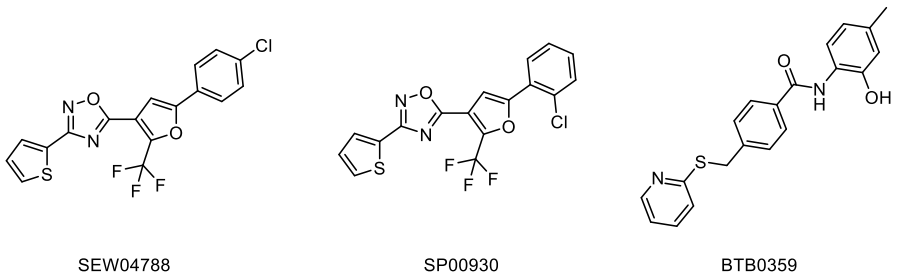


Fig. 15. 2D chemical structure of the three actives BTB0359, SEW04788, and SP00930.

across hematologic malignancies and solid tumors, including breast, lung, ovarian, and colorectal cancers. Mocetinostat (MGCD0103), a benzamide-based HDAC1/2-selective inhibitor, demonstrated promising antitumor activity in relapsed or refractory lymphomas and myelodysplastic syndromes, with reduced hematologic toxicity compared to pan-HDAC inhibitors, such as vorinostat (SAHA). In a Phase I trial, mocetinostat (MGCD0103) demonstrated durable responses and epigenetic target engagement, including increased histone acetylation and re-expression of tumor suppressor genes. However, further clinical development was limited by variable pharmacokinetics and non-specific side effects, partly attributable to its residual activity on HDAC2 and HDAC3 [91]. Similarly, entinostat has been evaluated in several Phase I and II clinical trials, particularly in combination with other agents such as immune checkpoint inhibitors or aromatase inhibitors [122]. Although it demonstrated the capacity to modulate immune responses and enhance tumor immunogenicity, its efficacy as monotherapy was limited, and dose-limiting toxicities (e.g., thrombocytopenia, neutropenia) remained a challenge. Pracinostat (SB939) and quisinostat (JNJ-26481585), two other class I HDAC inhibitors with activity on HDAC1, were tested in acute myeloid leukemia and other malignancies, but ultimately failed to meet clinical endpoints, highlighting the need for better isoform specificity and patient stratification [87].

One of the critical barriers to translating HDAC1-selective ligands into clinical use is the high degree of homology (over 85 %) between HDAC1 and HDAC2 within the catalytic domain, which complicates selective targeting. Most current inhibitors cannot fully discriminate between the two isoforms and often affect both simultaneously, leading to broader epigenetic effects and associated toxicity. Furthermore, HDAC1 and HDAC2 are frequently co-recruited into the same multiprotein complexes (e.g., NuRD, CoREST, SIN3A), making it difficult to isolate the functional contribution of HDAC1 inhibition *in vivo* [123].

To date, none of the novel HDAC1-selective chemotypes reported in preclinical studies, including compounds such as CBUD-1001, TTA03-107, and chlopynostat, have entered human trials [49,51]. These molecules have demonstrated potent isoform selectivity, reduced hERG K^+ ion channels inhibition, and improved safety in animal models; however, their clinical translation is hindered by issues related to metabolic stability, oral bioavailability, and lack of validated pharmacodynamic biomarkers to assess HDAC1-specific activity in patients. Conventional readouts such as histone H3 and H4 acetylation are not isoform-discriminative and therefore inadequate for assessing HDAC1-targeted therapy. Emerging strategies, including transcriptomic profiling, chromatin accessibility assays, and HDAC1-specific protein complexes, may offer future solutions for biomarker-driven patient selection. In summary, while no HDAC1-selective inhibitors are currently in clinical trials, ongoing investigations with class I-targeting agents underscore the therapeutic potential of this approach. The development of truly selective HDAC1 inhibitors with optimized pharmacokinetic profiles and validated biomarkers will be crucial to advancing this promising pharmacological strategy from the bench to the bedside.

7. Conclusions and future directions

Developing selective ligands for HDAC1, encompassing activators and inhibitors, represents a promising avenue and a significant opportunity for advancing therapeutic strategies across a broad spectrum of diseases, particularly those driven by epigenetic dysregulation. HDAC1 plays a multifaceted role in various cellular processes, including gene expression, differentiation, apoptosis, angiogenesis, and inflammatory signaling. Given its involvement in cancer progression, neurodegenerative disorders, and immune regulation, the ability to precisely modulate HDAC1 activity holds immense therapeutic potential.

One of the primary challenges in HDAC1-targeted drug development lies in achieving selectivity over other HDAC isoforms to minimize off-target effects. Many current HDAC inhibitors exhibit broad-spectrum activity, which can lead to unintended toxicities and limit their clinical applicability. Therefore, future efforts should focus on the rational design of isoform-specific modulators, guided by high-resolution structural insights and computational modeling. Advances in structural biology, including cryo-electron microscopy and X-ray crystallography, are crucial for elucidating the precise binding interactions between HDAC1 and small molecules, thereby enabling the development of more selective and potent compounds.

Beyond oncology, emerging evidence suggests that HDAC1 plays a neuroprotective role in mitigating DNA damage and oxidative stress in neurodegenerative diseases such as AD and PD. While HDAC inhibitors have been widely explored for their potential to reactivate silenced tumor suppressor genes in cancer therapy, selective HDAC1 activators may offer novel strategies to enhance neuronal resilience and repair mechanisms in neurodegeneration. Understanding the context-dependent functions of HDAC1, whether as a driver of pathological signaling in cancer or as a protective factor in neurodegeneration, will be key to optimizing therapeutic approaches.

Developing allosteric modulators and PROTAC (proteolysis-targeting chimera) technologies also presents new opportunities for fine-tuned control over HDAC1 activity. Allosteric inhibitors can provide an alternative to traditional active-site targeting, potentially enhancing selectivity and minimizing side effects. Meanwhile, PROTAC-based approaches could selectively degrade HDAC1 in pathological contexts, offering an innovative therapeutic strategy.

Future research should also explore the role of HDAC1 in inflammation and immune regulation, particularly in autoimmune diseases and chronic inflammatory conditions. Given its ability to regulate cytokine production, cell adhesion molecules, and immune cell activation, selective modulation of HDAC1 could pave the way for novel anti-inflammatory therapies.

In conclusion, the discovery and optimization of HDAC1-selective modulators, whether inhibitors, activators, or degraders, have the potential to revolutionize the treatment landscape for various diseases. Researchers can develop next-generation therapeutics with enhanced specificity, efficacy, and safety by integrating insights from structural, computational, and pharmacological domains. As our understanding of HDAC1 biology continues to expand, these advancements hold the potential to usher in more precise and personalized therapeutic

interventions.

CRediT authorship contribution statement

Giuliana Costanzo: Writing – original draft, Visualization, Investigation, Data curation. **Rocco Buccheri:** Writing – original draft, Visualization, Investigation, Data curation. **Giuseppe Cosentino:** Writing – original draft, Visualization, Investigation, Data curation. **Carlo Reale:** Writing – original draft, Visualization, Investigation, Data curation. **Sara Zuccalà:** Writing – original draft, Visualization, Investigation, Data curation. **Agostino Marrazzo:** Writing – review & editing. **Emanuele Amata:** Writing – review & editing. **Antonio Rescifina:** Writing – review & editing, Supervision, Project administration, Funding acquisition. **Lorella Pasquinucci:** Writing – review & editing, Supervision, Project administration, Funding acquisition, Conceptualization.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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