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# Novel Sustainable-by-Design HDAC Inhibitors for the Treatment of Alzheimer's Disease

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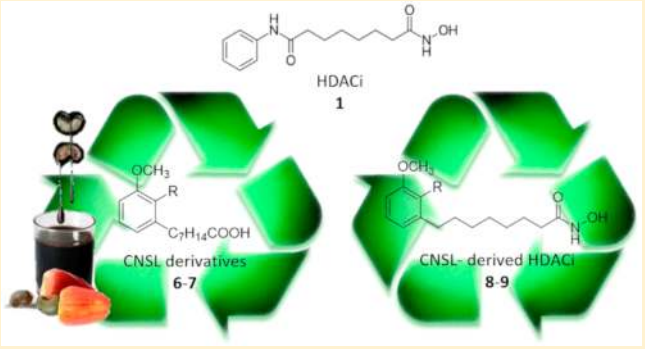
Supporting Information

**ABSTRACT:** Alzheimer's disease (AD) represents a global problem, with an estimation of the majority of dementia patients in low- and middle-income countries by 2050. Thus, the development of sustainable drugs has attracted much attention in recent years. In light of this, taking inspiration from the HDAC inhibitor vorinostat (**1**), we develop the first HDAC inhibitors derived from cashew nut shell liquid (CNSL), an inexpensive agro-food waste material. CNSL derivatives **8** and **9** display a HDAC inhibitory profile similar to **1**, together with a more promising safety for **9** compared to **1**. Moreover, both compounds and particularly **9** were able to effectively modulate glial cell-induced inflammation and to revert the pro-inflammatory phenotype. All these results demonstrate that the use of inexpensive food waste materials could be successfully applied for the development of accessible and sustainable drug candidates for the treatment of AD.




**KEYWORDS:** *Neurodegenerative drug discovery, sustainable drugs, immunomodulation, food waste*

Alzheimer's disease (AD) is the most common form of dementia and a global health problem. In fact, if AD was initially thought of as the epidemic of the developed world, with its aging population, nowadays it particularly impacts low- and middle-income countries.[1]

There is no definitively established cause nor a cure for AD, with available treatments ultimately failing to modify disease progression.[2] In addition, if we want to guarantee universal coverage and equity of access to treatments to the global AD population, the medications must be affordable and accessible to avoid overwhelming developing countries' health systems.[3] This clearly adds lines of complexity to AD drug discovery, which is already one of the most formidable challenges for the pharmaceutical community.[4] However, it is something we must focus on, so as to ensure that we "leave no one behind" in the battle for a cure.[5]

In AD most cases occur in patients with no known family history and are not linked to a genetic cause; thus, AD is mostly sporadic. Mutations in specific genes can only explain 5−10% of the cases.[6] The genes implicated in early onset familial AD are those encoding for amyloid precursor protein (APP), presenilin 1, and presenilin 2. The gene implicated in

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the pathogenesis and the risk of developing sporadic AD is apolipoprotein E ε4 (APOE ε4).[7] The sporadic nature of the disease, the differential susceptibility and disease course in males and females, as well as the late age onset and the influence of lifestyles, highlight that genetic causes alone fail to explain AD etiology and reinforce the hypothesis that epigenetics might play a key role.[8,9] Evolving lines of research indicate that pharmacologically targeting epigenetic mechanisms, namely, DNA methylation, histone acetylation/deacetylation, or noncoding RNA, may be of potential benefit in AD. Particularly, restoring the perturbed acetylation homeostasis of the neurodegenerative state by histone modification has become one of the most significant research hot spots.[10] Indeed, if epigenetic treatments represent fewer than 2% of current drugs in Alzheimer's trials, Alzheimer's Drug Discovery Foundation (ADDF) considers this as an emerging area holding great promise.[11] One of the two epigenetic drugs currently in AD clinical trials is HDAC inhibitor (HDACi) vorinostat (**1**, Figure 1), a drug approved

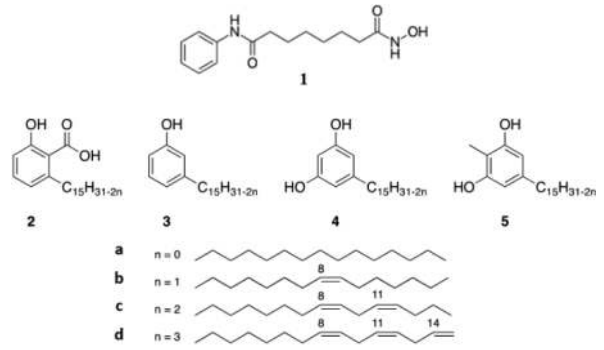


**Figure 1.** Chemical structures of HDACi **1** and CNSL derivatives **2**–**5**.

for the treatment of subcutaneous T cell lymphoma. Its therapeutic potential in AD is based on in vivo animal studies suggesting that its specific inhibition of class I histone deacetylases (HDACs) and HDAC6 (class IIb) could be most beneficial in treating dementia.[12]

With these concepts in mind and in conjunction with our studies aimed to explore the potential of cashew nut shell liquid (CNSL) for the production of AD drugs,[13] herein we focused on the development of **1**'s derivatives obtained from an inexpensive agro-food waste material. CNSL is a byproduct of the cashew kernel industry, extremely interesting in terms of waste valorization for the production of new chemicals.[14] Although one of its main components, i.e., anacardic acid (**2a**, Figure 1),[15] as well as some synthetic derivatives,[16−18] are well-known histone acetyltransferase inhibitors, to the best of our knowledge no report has never addressed the possibility to obtain AD-targeted HDACis from CNSL.

## DESIGN

We pursue the idea that CNSL is a valuable starting point in the search for cost-effective and sustainable HDACis against AD. Chemically, CNSL is a source of nonisoprenoid lipids, mainly anacardic acids (**2**), cardanols (**3**), cardols (**4**), and 2-methylcardols (**5**) (Figure 1). All of them share a phenolic structure, bearing a C15-alkyl side chain (with different degrees of unsaturation) in meta-position with respect to the hydroxyl group (see Figure 1).[19]

We were intrigued by the fact that the C8-acids **6** and **7** (Figure 2), easily obtained from CNSL by oxidative cleavage

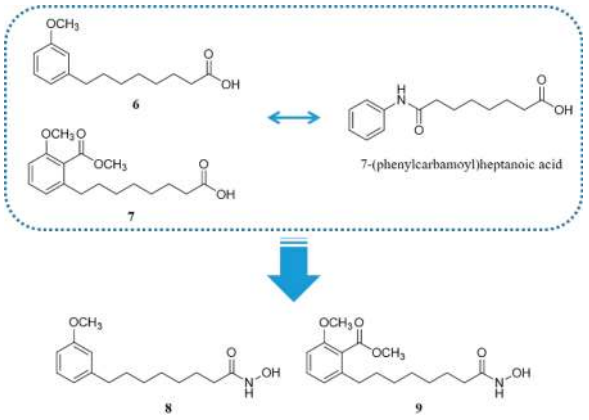


**Figure 2.** Design of CNSL derivatives **8** and **9**.

derivatization, might be an optimal starting point for the synthesis of hydroxamates inspired by **1**. Particularly, hydroxamates **8** and **9** (derived from **3** and **2**) bear clear chemical resemblance to **1**, including the metal binding moiety, the carbon linker, and the capping group. To this end, docking simulations were carried out to confirm the proper fit of the designed **8** and **9** at class I nuclear HDAC1 and class IIb HDAC6 isoforms, in comparison with **1**. Figure 3 depicts the best generated complexes for **8** as obtained for HDAC1 (A) and HDAC6 (B).

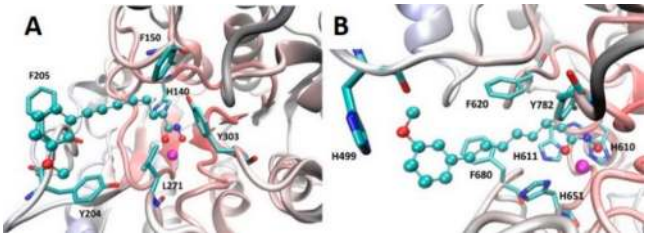


**Figure 3.** Main interactions stabilizing the putative complexes as computed for **8** within the binding pocket of HDAC1 (A) and HDAC6 (B).

In both complexes, the zinc binding group shows the expected bidentate chelation further stabilized by polar interactions with His140 and Tyr303 (in HDAC1) as well as with His610 and Tyr782 (in HDAC6). The carbon linker is engaged in apolar contacts, which appear to be richer in HDAC6 (with His611, Phe620, His651, Phe680, and Leu749) than in HDAC1 (with Phe150, His178, and Leu271). Finally, the cap moiety contacts the cavity rim where it can elicit $\pi-\pi$ stacking reinforced by a H-bond with His499 in HDAC6 and with Tyr204 and Phe205 in HDAC1. The more hindered cap moiety of **9** does not elicit relevant additional contacts, but it might even interfere with the rim residues, a feature more pronounced in HDAC1 where it clashes against Pro29, due to the already documented greater narrowness of the HDAC1 cavity rim compared to HDAC6.[20] Notably, both compounds compare well with the corresponding complexes stabilized by **1**. As exemplified by Figure S1 for **8** within the HDAC6 binding site, the linkers and the two hydroxamic groups show superimposable binding modes. In contrast, the cap phenyl


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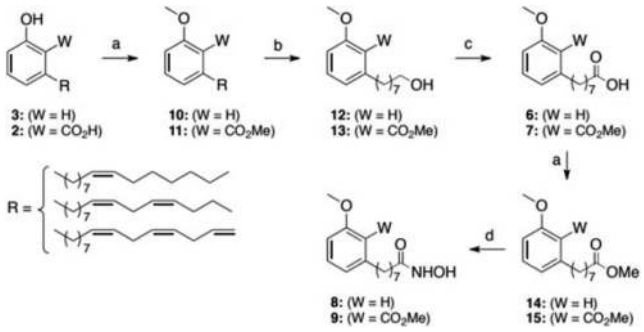
groups show different arrangements reasonably due to the effect of the amide function, which induces a more folded arrangement in the linker of **1**. Based on these results, both compounds were synthesized and biologically characterized.

## CHEMISTRY

Hydroxamates **8** and **9** were prepared by aminolysis exploiting the methyl esters **14** and **15** as starting reagents. The required methyl 8-(3-methoxyphenyl)octanoate (**14**) and methyl 8-(3-methoxy-2-carbomethoxyphenyl)octanoate (**15**) were synthesized through methylation of mixtures of unsaturated **2** and **3** isolated from CNSL.[13] Thus, individual reactions of **2** and **3** with iodomethane in acetone afforded the corresponding *O*-methoxycardanol **10** (92%) and methyl *O*-methoxyanacardate **11** (90%) mixtures. Next, treatment of **10** or **11** with ozone air in dichloromethane/methanol (1:1) at −70 °C, followed by reduction with sodium borohydride furnished the corresponding alcohols **12** (80%) or **13** (50%).

Treatment of **12** or **13** with PCC led to the aldehydes intermediates, which were oxidized by Jones Reagent to the acids **6** (96%) and **7** (70%). In turn, **6** and **7** were converted to the respective methyl esters **14** (74%) and **15** (70%) by treating with iodomethane in acetone. Despite its effectiveness, this synthetic sequence is clearly not compatible with sustainability criteria. In response to these concerns, greener methods for producing **14** and **15** are being developed. Finally, **14** and **15** were converted into target hydroxamates **8** and **9** following aminolysis with hydroxylamine generated *in situ* (Scheme 1).

**Scheme 1. Synthesis of Hydroxamates 8 and 9**




**HDAC Biochemical Assays.** Considering that the most promising HDACi for learning and memory indications exhibit the greatest selectivity for class I HDACs, targeted development of class I HDAC isoforms has been advocated for AD.[21] In addition, although not fully elucidated, HDAC6 has been suggested to play a role in AD-associated neurodegeneration.[22] Based on these considerations and on **1**'s class I HDAC/HDAC6 inhibitory profile, we preliminary verified the computationally predicted capacity of **8** and **9** to properly bind HDAC1 and HDAC6 through a biochemical assay.[23] Compounds **1** and **6** were used as positive and negative controls, respectively (Table 1). As expected, **1** modulated the activity of HDAC1 and 6 with roughly equivalent submicromolar potency. Both **8** and **9** exhibited a similar HDAC profile, with inhibitory potencies that were only slightly decreased (by 2.7- to 6.5-fold with respect to **1**). Thus, the obtained results support the starting idea that the insertion of the hydroxamate moiety on a CNSL backbone provides SAHA-like HDACis.

**Table 1. In Vitro Inhibition of HDAC1 and HDAC6**

| compound | $IC_{50}$ ± SEM [nM] HDAC1 | $IC_{50}$ ± SEM [nM] HDAC6 |
|---|---|---|
| **1** | 119.5 ± 5.6 | 41.9 ± 11.3 |
| **6** | <15% inhibition at 10 μM | <15% inhibition at 10 μM |
| **8** | 316.2 ± 37 | 190.1 ± 38.2 |
| **9** | 774.7 ± 14.4 | 215.4 ± 28.6 |

Indeed, acid **6**, devoid of the hydroxamate moiety, showed only a modest inhibition (<15%) at 10 μM.

In spite of the prominent relevance of class I HDAC and HDAC6 isoforms, the role of individual HDAC enzymes as well as the action of specific HDACis in neurodegenerative diseases remains far from clear.[10] Thus, to preliminary address selectivity of the submicromolar inhibitors **8** and **9**, we profiled them in single dose duplicate mode at a concentration of 10 μM against HDACs 1−11 (Figure 4). Trichostatin A (TSA) was used as reference compound.

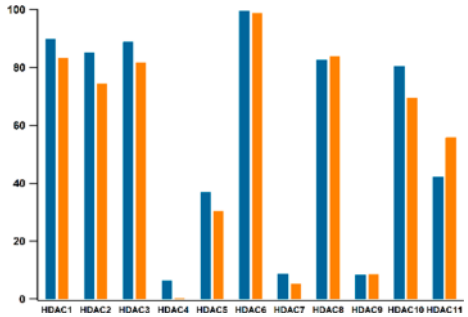



**Figure 4.** Percentages of inhibition of HDACs 1−11 by derivatives **8** (blue) and **9** (orange) at 10 μM.

From these data, we confirmed that the newly synthesized derivatives **8** and **9** display a class I HDAC/HDAC6 selectivity profile, very similar to **1**. Once again, the close resemblance among **8**, **9**, and **1** accounts for a similar HDAC selectivity.

**BBB Permeation Studies.** For AD-directed HDACis, the capability to cross the blood−brain barrier (BBB) is a fundamental prerequisite. Nevertheless, recent studies have revealed that several HDACis, potentially useful to study/treat neurodegenerative diseases, show limited BBB permeation.[24] For the prediction of **8** and **9** to passively penetrate the BBB, a Parallel Artificial Membrane Permeability Assay (PAMPA) was used. Data obtained for **8** and **9**, together with precursors **2a** and **3a**, were correlated to standard drugs, where CNS bioavailability is known. The results shown in Table S1 clearly demonstrate that **8** and **9** are predicted to cross the BBB by passive diffusion as their *Pe* values are above those of the standard AD drugs (tacrine, donepezil, and rivastigmine). Moreover, the modifications performed improved the CNS drug-like properties of natural **3a**, for which passive brain bioavailability is uncertain. Notably, **2a**'s BBB penetration estimation was not determined due to its low solubility in the assay media.

**Neurotoxicity Assays.** Compound **1** is an approved drug for the treatment of cutaneous T cell lymphoma, but intuitively, the use of HDACis for nononcology indications requires more stringent safety profiles.[25] Thus, neurotoxicity of **1**, **8**, and **9**, in comparison with precursors **2a** and **3a**, was evaluated on primary cultures of cerebellar granule neurons (CGNs), as a useful in vitro model to study neuronal death.[26] CGN viability was assessed after 24 h treatment at three



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different concentrations (5, 25, and 50 $\mu$M) using the MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) assay (Figure 5).

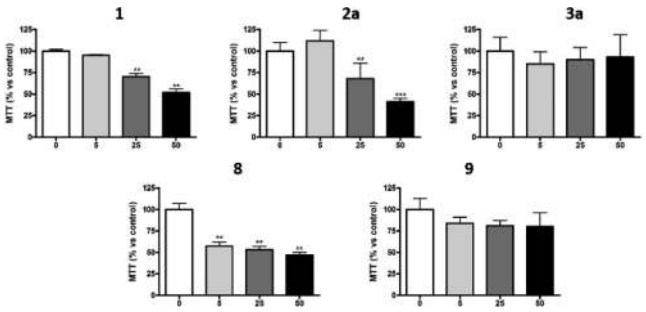


**Figure 5.** Neurotoxicity of **1**, **2a**, **3a**, **8**, and **9** on primary rat CGNs after 24 h treatment. Results are expressed as percentage of controls and are the mean ± SE of at least three different experiments, each run in triplicate. $^{**}p < 0.01$ $^{***}p < 0.001$ compared to control conditions.

It is evident that **1** displays signs of neurotoxicity at the higher tested concentrations (CGNs viability 70% at 25 $\mu$M and 52% at 50 $\mu$M). Compound **8** affects neuronal viability even at 5 $\mu$M concentration (CGN viability $\leq$ 50%). A more suitable profile is showed by **9** at all tested concentrations: CGN viability >80% even at 50 $\mu$M. Regarding the corresponding precursors, **3a** shows a more promising safety profile compared to **2a**, with no evident signs of toxicity at the tested concentrations.

**HDAC Cellular Assays.** To confirm the HDAC biochemical results at a neural cellular level, Western blotting experiments to detect histone H3 acetylation were performed with **1**, **8**, and **9**. As HDACis were reported to prevent the lipopolysaccharide (LPS)-induced decrease of acetylated histones H3 in microglia (but had no effect on the basal HDAC activity),[27] LPS-treated N9 microglial cells were incubated for 24 h with three different concentrations (5, 10, and 25 $\mu$M) of the tested compounds. In accordance with the HDAC enzymatic profiles, **8** and **9** are able to induce H3 acetylation in a similar fashion to **1** (Figure 6).

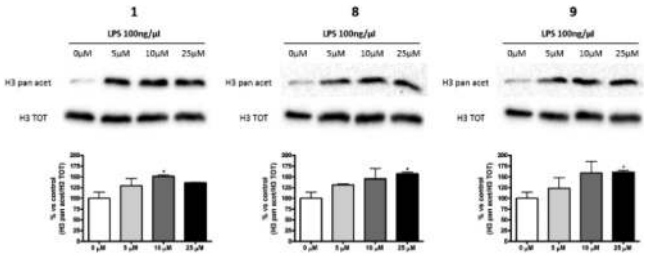


**Figure 6.** Western blots of acetyl-H3, and total H3 after treatment of N9 cells with **1**, **8**, and **9**. Results are expressed as percentage of controls and are the mean ± SE of three different experiments. $^{*}p < 0.05$ compared to control conditions.

**Immunomodulation Assays.** In neurology, HDACis have a long history of clinical use as mood stabilizers and antiepileptics. More recently, **1** and other HDACis have attracted attention for AD primarily on the basis of their promising antineuroinflammatory profile.[28] Microglia, as the immune cells of the brain, are pivotal mediators of neuroinflammatory processes. Microglial activation in the CNS is heterogeneous, categorized into two opposite phenotypes: M1 and M2. M1 microglia, activated by LPS or IFN-$\gamma$, have pro-inflammatory, neurotoxic properties, inducing the proliferation of lymphocyte. Alternatively activated M2 microglia are able to repair small damage, have an anti-inflammatory phenotype, contributing to trophic support of neurons and to degradation of toxic aggregates, and increase the neuroprotective functions thanks to anti-inflammatory interleukins and growth factors production. M1 activation is associated with the expression of pro-inflammatory molecules, like inducible nitric oxide synthase (iNOS). The M2 activation state is associated with the production of anti-inflammatory cytokines and specific markers of phagocytosis, such as mannose receptor type C 1 (MRC1).[29] On this basis, immunomodulation strategies aiming to attenuate M1 microglial activation or to trigger an M1/M2 microglial shift may contribute to counteract, at least partially, cognitive impairment in AD and other neurodegenerative diseases.[30] To this end, we tested whether our compounds could affect iNOS, triggering MRC1 profile expression upon inflammatory stimuli with LPS (100 ng/mL) at 5 and 25 $\mu$M concentrations. As reported in Figure 7,

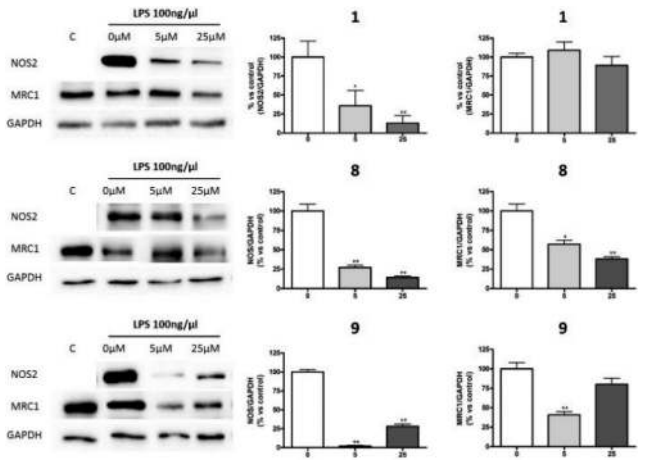


**Figure 7.** Immunomodulatory effects of **1**, **8**, and **9** in microglial cells evaluated through Western blot analysis of iNOS and MRC1 expression. GAPDH was used as loading control. Densitometric results are expressed as percentage of LPS only and are the mean ± SE of three independent experiments. $^{*}p < 0.05$, $^{**}p < 0.01$ compared to LPS condition.

**1**, **8**, and **9** all suppressed the microglial production of proinflammatory marker iNOS. Importantly, at 5 $\mu$M, **8** and **9** were even more effective than reference compound **1**, by almost completely abolishing iNOS expression. These results highlight the potential of both **8** and **9** to effectively modulate glial cell-induced inflammation, and to be able, in principle, to revert the pro-inflammatory phenotype. Then, we examined the capability of **1**, **8**, and **9**, to promote M2 microglial phagocytosis, by evaluating MRC1 profile expression (Figure 7). Positively, **1** does not affect MRC1 expression levels at the two tested concentrations, whereas **9** shows a positive outcome only at 25 $\mu$M. Conversely, **8** displays a dose-dependent negative effect. These findings suggest that the M1/M2 immunomodulatory profile might not be directly linked to the HDAC inhibitory activity, as indicated by the strong induction of histone H3 acetylation in microglial cells (Figure 6). Indeed, the transcriptional machinery responsible for



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regulating the gene networks accounting for the two activation states is complex and still not elucidated.

**Neuroprotective Assays.** In spite of the well-recognized potential of HDAC inhibition against neurodegeneration, increasing recent evidence suggest that inhibition of single isoforms can result in both neuroprotective and neurodegenerative effects.[31] Although not yet elucidated, this might depend on context-specific and tissue/cell-specific effects. Taking this into account, we tested whether **1**, **8**, and **9** can protect CGNs from low serum- and $K^+$-induced neuronal death (Figure 8). Tacrine (1,2,3,4-tetrahydroacridin-9-amine),

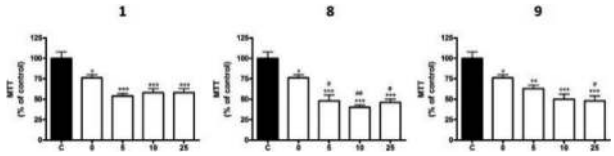


**Figure 8.** Neuroprotective effects of **1**, **8**, and **9** on serum and $K^+$ deprivation-induced neurotoxicity in CGNs. $^*p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$ compared to control conditions; $^{\#}p < 0.05$, $^{\#\#}p < 0.01$ compared to serum and $K^+$ deprivation conditions.

the first FDA-approved AD drug, was used as reference compound (Figure S2). Unfortunately, under these experimental conditions, all three HDACis were not able to restore neuronal viability, with 6 h pretreatment followed by 24 h cotreatment, although their effect is not so detrimental in terms of reduction of viability. To note, **1** and **9** display a similar profile.

## CONCLUSIONS

In conclusion, we were successful to discover **8** and **9** as the first HDACis derived from the inexpensive CNSL raw material. Although clinical translation of HDACis in AD remains elusive, in our hands, they (particularly **9**) displayed a therapeutic potential similar to that of AD investigational drug **1**. At the same time, they might have an improved potential in terms of sustainability and less toxicity in some cases. As a starting material for the synthesis of new drugs, CNSL presents clear advantages from economical and ethical perspectives, compared to both synthetic and natural chemicals:[32] (1) abundant volumes are available in those countries (Brazil and India), which still are and will be main actors in the AD global scenario; (2) it is an inedible raw material not depleting natural resources; (3) it is a food waste-product amenable to waste valorization. All these considerations point to the use of food waste-products as an enlightening perspective toward more accessible and sustainable drugs to the global AD community patients.

## ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsmedchemlett.9b00071.

Figures S1 and S2, Table S1, experimental details for chemistry and biological assays, spectral copies of $^1H$ NMR and $^{13}C$ NMR of compounds **8** and **9** (PDF)

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### Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

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### Notes

The authors declare no competing financial interest.

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## ABBREVIATIONS

AD, Alzheimer's disease; ADDF, Alzheimer's Drug Discovery Foundation; APOE$\varepsilon$4, apolipoprotein E $\varepsilon$4; APP, amyloid precursor protein; BBB, blood−brain barrier; CGNs, cerebellar granule neurons; CNSL, cashew nut shell liquid; HDACi, histone deacetylases inhibitor; HDACs, histone deacetylases; iNOS, inducible nitric oxide synthase; LPS, lipopolysaccharide; MRC1, mannose receptor type C 1; PAMPA, Parallel Artificial Membrane Permeability Assay; TSA, trichostatin A

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