

HETEROCYCLES, Vol. 105, No. 1, 2022, pp. 202 - 243. © 2022 The Japan Institute of Heterocyclic Chemistry  
Received, 5th February, 2022, Accepted, 28th March, 2022, Published online, 5th April, 2022  
DOI: 10.3987/REV-22-SR(R)6

## **8-HYDROXYQUINOLINES: A PROMISING PHARMACOPHORE POTENTIALLY DEVELOPED AS DISEASE-MODIFYING AGENTS FOR NEURODEGENERATIVE DISEASES: A REVIEW<sup>#</sup>**

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<sup>#</sup>Special issue in an honor of Prof. Somsak Ruchirawat on 80th Birthday

**Abstract** – 8-Hydroxyquinoline (8HQ) is an attractive heterocyclic scaffold with well-known metal chelating property, broad-ranging pharmacological activities, and preferable drug-likeness, thus, it had gained a continual attention in areas of drug development, especially, drug repurposing. Alzheimer's disease (AD) is one of globally health concern in an era of aging society and its management is considered challenging as effective disease-modifying drugs are still clinically unavailable. Loss of metal ion homeostasis is one of key factors contributing to pathogenesis and progression of AD in which its imbalance could trigger many related key factors and harmful events, especially, oxidative neuronal damages. Hence, restoration of homeostasis and distribution of brain's metal ions served to be a promising strategy for development of disease-modifying agents. In this review, essential key points relating to AD pathogenesis, roles of metal ions in AD, and pioneer 8HQ-based compounds are introduced. A series of recently reported 8HQ-based neuroprotective compounds (i.e., derivatives, hybrids, conjugates, and metal complexes) focusing on compounds acting as metal chelators are reviewed. Related 8HQ-based neuroprotective compounds with other mechanisms of actions are also discussed. Additionally, summary of key contents is included to provide an

overview of current development situations. Taken together, this article would be beneficial and inspiring for the related future drug design and development to tackling an increasing prevalence of neurodegenerations in the global aging society.

## INTRODUCTION

8-Hydroxyquinoline (8HQ, Figure 1) has been recognized as an attractive heterocyclic pharmacophore in drug development displaying a diverse range of biological activities and preferable drug-like properties.<sup>1</sup> Notably, its metal-chelating property is noted to be one of key characteristics behind the mechanisms of action.<sup>2</sup> Recently, research publications relating to potential therapeutic applications of 8HQ-based compounds and their repurposing potentials for various therapeutic purposes have been continuously reported by our group<sup>3-6,7-10</sup> as well as others.<sup>11-13</sup>

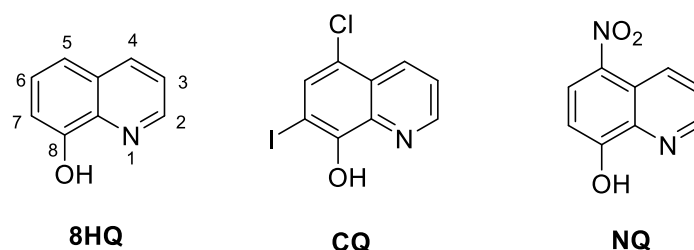
Alzheimer's disease (AD) is one of the most common causes of dementia globally and its prevalence is predicted to be continuously increased.<sup>14</sup> AD is clinically characterized by progressive losses of memory, cognitive functions, and behavioral changes.<sup>15</sup> Onset of symptoms is sporadic and mostly triggered by aging.<sup>15</sup> Currently, only symptomatic drugs are available for clinically management (i.e., cognitive enhancing and psychotropic agents) and there are still some gaps to be fulfilled for improving treatment outcome.<sup>16</sup> The better way to delay and improve prognosis of the progressive neurodegeneration is disease-modifying agents which are defined as drugs that can alter biological process and protect the neuronal cell death.<sup>17</sup> However, the development of disease-modifying drugs is still in its extensive research pipeline.<sup>18</sup> Therefore, a research area on discovery of promising compounds for potential use as disease-modifying drugs has gained extensive interest for years. Most common widely explored research areas were driven towards the discovery of compounds that restore metal imbalance in the brain, reduce production and aggregation of  $\beta$ -amyloid protein, and protect against oxidative neuronal cell death.<sup>18</sup>

In the recent years, many novel 8HQ-based compounds (i.e., derivatives, hybrids, conjugates, and metal complexes) have been continuously designed and reported for their anti-neurodegeneration potentials. Additionally, some of them are ongoing the clinical trial phases. The global trend towards aging society along with continual active attention in 8HQ-based drug development had inspired us to conduct this review article to depict the recent overview landscape of 8HQ-based compounds as potential neuroprotective agents, emphasizing on compounds acting on restoration of metal homeostasis, along with their mechanism of actions which would be beneficial for the future related research in design and development of more effective drugs for AD management.

## 8-HYDROXYQUINOLINE (8HQ)

8HQ is a quinoline-based bioactive scaffold originated in plants (i.e., *Asteraceae*<sup>19</sup> and *Euphorbiaceae*<sup>20</sup>

families) as well as from the synthetic methods.<sup>2</sup> Among all hydroxyquinoline derivatives, 8HQ has gained considerable attention due to its promising metal coordinating ability and pharmacokinetic profiles.<sup>2</sup> 8HQ is widely used for many agricultural and industrial (i.e., paper, textile, wood, analytical, separation, and chelation purposes).<sup>21</sup> Some stories indicating that 8HQ derivatives are in spotlighted for drug development has been demonstrated by continual exploring for therapeutic and repurposing potentials of clioquinol (CQ, Figure 1). CQ, a halogenated 8HQ derivative, was originally used during 1950s-1970s to treat traveler's diarrhea, however, it was withdrawn in 1960s due to its reported neurotoxicity.<sup>22</sup> However, this compound still be an attractive one for drug design and drug repurposing as regard to its small size, high lipophilicity, and metal chelating properties.<sup>2</sup> CQ has been widely explored for its repurposing potentials (i.e., anticancer,<sup>7,23</sup> antibacterial,<sup>5</sup> and antifungal<sup>24</sup>) as well as a scaffold for design of hybrid compounds with neuroprotective activity.<sup>25,26</sup> Similar investigations were also demonstrated for a nitro-8HQ derivative, nitroxoline (NQ, Figure 1).<sup>4,5,7,9,27</sup> Until now, there are several novel and repurposed 8HQ-based compounds reported for potential therapeutic applications (including as antioxidant,<sup>6,28</sup> anticancer,<sup>7,10,11,23,29</sup> antimicrobial,<sup>3-5,30</sup> antiviral,<sup>31</sup> antimycobacterial,<sup>32</sup> antifungal,<sup>24,33</sup> and neuroprotective<sup>8,9,26,34,35</sup> agents.

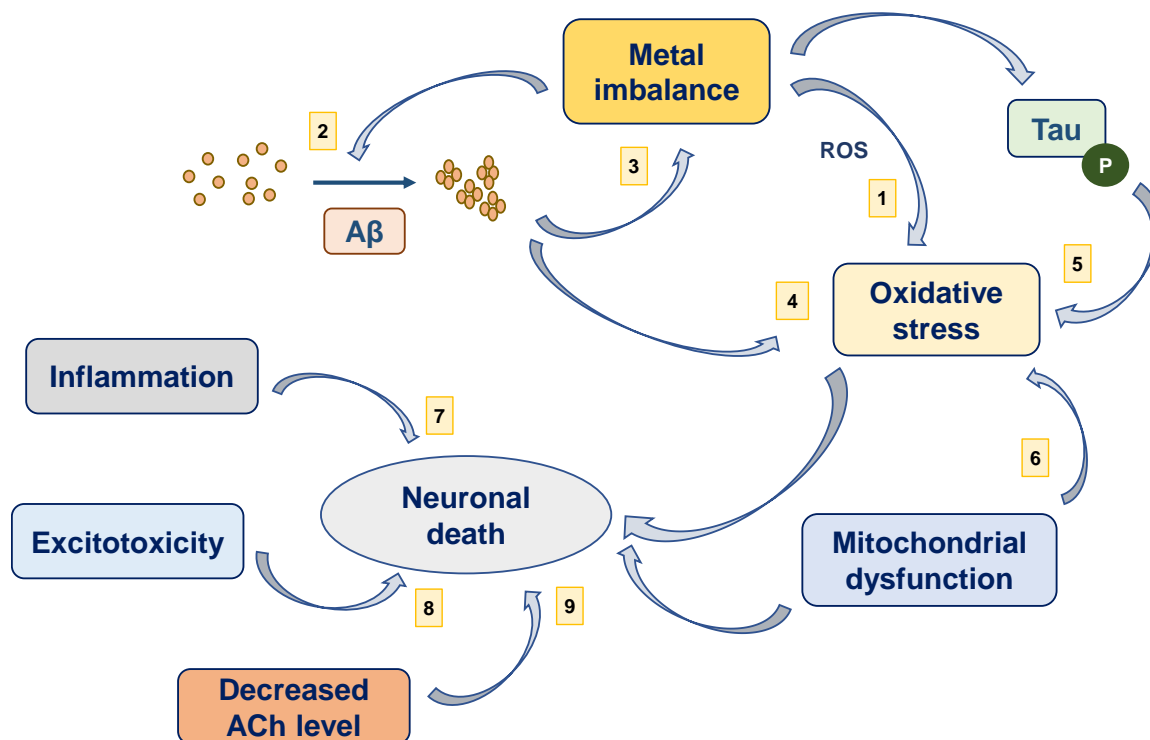


**Figure 1.** Chemical structures of 8HQ and its derivatives

## ALZHEIMER'S DISEASE (AD)

### Pathogenesis of AD

AD is a multifactorial disease in which multiple factors play key roles in its pathogenesis and progression. The disease itself displays as a collective series of pathological events that leads to neuronal cell death and losses of memory and cognitive functions. The proposed hypotheses included abnormal proteins (i.e., accumulations, aggregations, and formation of toxic forms of  $\beta$ -amyloid ( $A\beta$ ) and tau proteins), oxidative stress, neuroinflammation, alteration of acetylcholine (ACh) level, mitochondrial dysfunction, as well as loss of metal ion homeostasis.<sup>15,16,18,36</sup> It should be noted that most of factors are related to one another, in which oxidative stress is considered a key linker of many destructive events (Figure 2). Notably, the imbalance of metal ions plays part in driving many sequelae that worsen the disease's conditions due to its close linkage to oxidative stress (Figure 2).

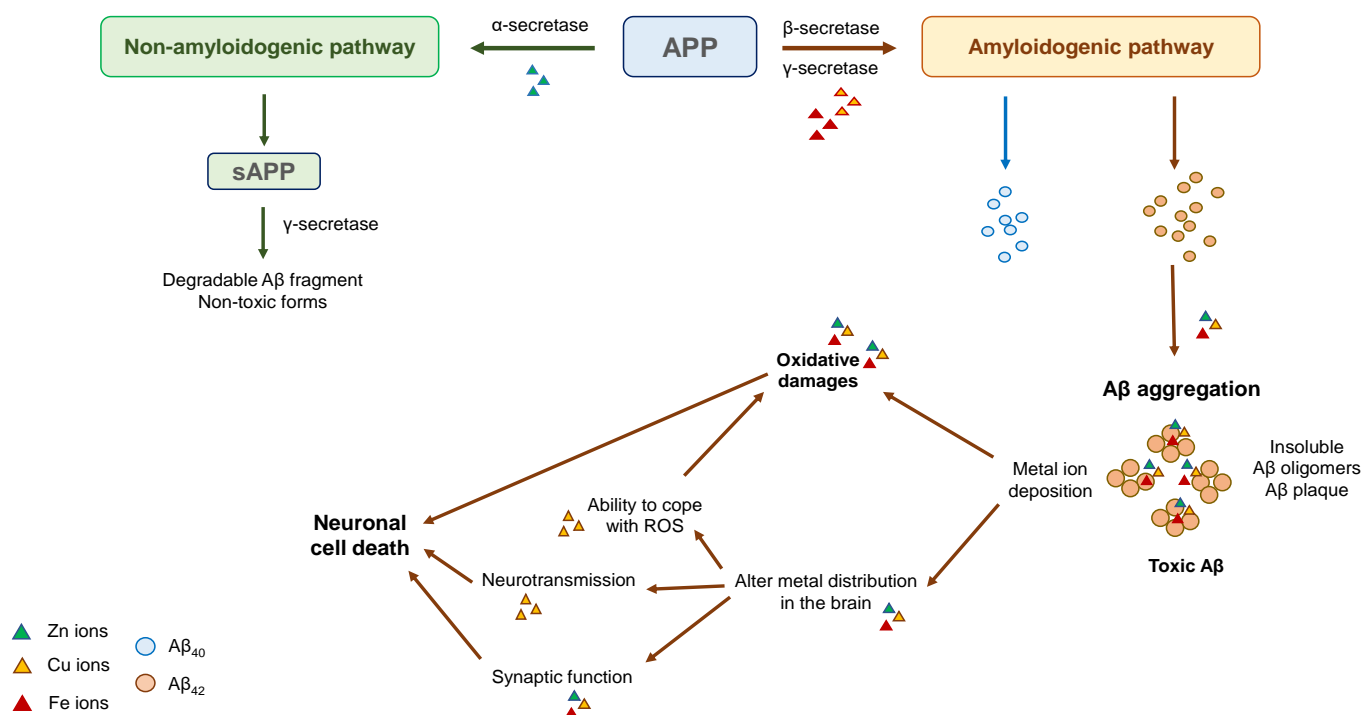


**Figure 2.** Summarized influencing factors contributing to pathogenesis and progression of AD. Relatively high levels of metal ions are found in AD's brain, in which the conditions themselves produce high reactive oxygen species (ROS) leading to oxidative stress (process 1). High levels of metal ions could induce the productions and aggregations of A $\beta$  (process 2). Metal ions also likely to accumulate in the aggregated forms of A $\beta$  which in turn affect the distribution of metal ions in the brain (process 3). Due to the redox reactive nature of the metal ions, the A $\beta$  plaque becomes to be oxidative-related neurotoxic (process 4). Metal imbalance also promotes phosphorylation of tau protein (a protein normally functions to maintain stability and to promote assembly of microtubules). The phosphorylated tau generates high ROS products and involves in chronic neurodegeneration (process 5). Mitochondrial dysfunction also leads to high ROS production and oxidative stress condition (process 6). Oxidative stress induces oxidative damages to the neuronal cells, and along with other factors (i.e., neuroinflammation, excitotoxicity, and ACh deprivation), leading to neuronal cell death (process 7-9).

### Roles of transition metal ions in AD

Transition metal ions play essential roles in pathogenesis of AD. Loss of metal ion homeostasis such as Fe, Cu, and Zn was noted to related with cognitive and memory loss in the AD.<sup>15,37</sup> This could lead to an inappropriate distribution of metal ions in other brain areas resulting in an impairment of metal physiological functions as well as many deprived consequences (i.e., aggravating the deposition and formation of toxic A $\beta$  and tau proteins, activating redox reaction and oxidative damages, and impairing synaptic functions).<sup>15</sup> Among all transition metal ions, iron (Fe), copper (Cu) and zinc (Zn) are widely

recognized for their roles in pathogenesis and progression of the AD.<sup>38</sup> In this article, the discussion is emphasized on their 3 main aspects including i) effects on production and/or aggregation of the abnormal proteins (i.e., A $\beta$  and tau) and their toxic forms (i.e., A $\beta$  plaque and tau neurofibrillary tangles, NFTs), ii) effects on the reactive oxygen species (ROS) production and oxidative damages, and iii) effects on synaptic functions as summarized in Figure 3.



**Figure 3.** Summarized roles of transition metal ions in A $\beta$  production and aggregation. Metal ions drive amyloid precursor protein (APP) processing toward the amyloidogenic direction (*via* an activation of  $\beta$ -secretase and  $\gamma$ -secretase activities by Cu and Fe ions as well as an inhibition of  $\alpha$ -secretase activity by Zn ion), thereby, increases productions of A $\beta$ . Metal ions enhance aggregation of A $\beta$  leading to the formations of aggregated toxic forms of A $\beta$ , oxidative damages and improper distribution of metal ions in other brain areas leading to the impairments of other physiologic functions of the brain (i.e., synaptic function, neurotransmission) and neuronal cell death.

### Iron (Fe)

Iron (Fe) is the most abundant ion found in human body. It is commonly existed in the protein-bound forms (i.e., hemoglobin, myoglobin, heme-enzymes, non-heme proteins/compounds). Fe functions for synthesis of oxygen transport proteins and enzymes involved in oxidative metabolism as well as many cellular functions.<sup>39</sup> In the AD, high level of Fe was presented and noted for its destructive effects.<sup>40</sup>

High level of Fe drives the processing of the APP protein toward the amyloidogenic direction *via* an

activation of the  $\gamma$ -secretase and  $\beta$ -secretase activities,<sup>15</sup> while it inhibits the processing toward non-amyloidogenic pathway *via* blocking the  $\alpha$ -secretase activity.<sup>41</sup> This phenomenon leads to an increase of production/deposition of A $\beta$ .<sup>42</sup> Moreover, Fe induces an aggregation of A $\beta$  leading to the formation of toxic plaque.<sup>43</sup> Similarly, Fe promotes a hyperphosphorylation of tau and activates the formation of toxic neurofibrillary tangles (NFTs).<sup>44</sup>

From oxidative-induced damages aspect, Fe ion can directly bind to A $\beta$  at N-terminal, thus, leading to high accumulation of Fe in the A $\beta$  plaque.<sup>45,46</sup> The precipitated Fe could induce the transformation of non-toxic A $\beta$  forms to toxic A $\beta$  oligomers,<sup>46</sup> which subsequently causes the generation of ROS *via* the Fenton reaction, especially, the hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>), leading to excessive ROS, oxidative-induced neuronal apoptosis, as well as direct oxidative damages to nearby cellular components.<sup>45,47</sup> Additionally, it was reported that high level of Fe could induce the neuronal cell death *via* ferroptosis process which is the ROS-independent way.<sup>48</sup> Increased amount of produced H<sub>2</sub>O<sub>2</sub> in glial cells also leads to an increase of monoamine oxidase (MAO) activity. MAO is an enzyme functions for degradation of many amine-based neurotransmitters in which its increased activity could in turn leads to an increase of H<sub>2</sub>O<sub>2</sub> and oxidative-induced neuronal damages.<sup>49</sup>

Fe also plays roles in synaptic functions.<sup>50</sup> High level of Fe induces an overactivation of synaptic activity, which could lead to cytotoxic effects to the neuronal cells. This event was observed for the brain of early-stage AD patients.<sup>51</sup> Long-term investigation in mice also indicated that high Fe level in the brain could impair memory and cognitive functions.<sup>52</sup>

### **Copper (Cu)**

Copper (Cu) is the three most abundant metal ions found in human body and functions for many essential biological processes.<sup>53</sup> Cu plays key roles by incorporating as a cofactor of enzymes (i.e., antioxidant enzyme superoxide dismutase (SOD) and mitochondrial cytochrome c oxidase) as well as in synaptic functions.<sup>53</sup>

Similar with the Fe ion, high level of Cu ion leads to an increased production of the A $\beta$ <sup>54</sup> as well as a hyperphosphorylation of tau.<sup>55</sup> Cu ion can directly interact with Cu<sup>2+</sup>-binding domain of the APP leading to an activation of  $\beta$ -secretase enzyme.<sup>54</sup> Cu ion also plays role in A $\beta$  aggregation as it binds with the A $\beta$  and activates the formation of toxic A $\beta$  oligomers.<sup>56</sup> Due to its high binding affinity, the Cu ion is highly accumulated in the A $\beta$  plaque while lowly distributed or deficiency in the other neuronal tissues.<sup>57</sup> The first event leads to a production of hydrogen peroxide and peroxy radicals leading to oxidative neurotoxicity<sup>58</sup> as well as induces oligomerization of the A $\beta$ .<sup>59</sup> In contrast, the latter event causes a mis-localization of Cu ion in other brain areas resulting in an impaired functions of many Cu-related proteins and enzymes.<sup>57</sup> Moreover, it was observed that the binding of Cu to A $\beta$  could increase the cell permeability of this toxic

protein (*via* stabilizing its interaction with lipid bilayer) and promote its penetration into the neurons.<sup>56</sup> Cu is a cofactor of an essential antioxidant enzyme, Cu/Zn-superoxide dismutase 1 (SOD1), plays key role in radical scavenging and anti-inflammatory functions.<sup>60</sup> Decreased expression of SOD1 was observed in the AD patients which indicates the impaired capacity of the brain to cope with the excessive ROS.<sup>61</sup> This may be due to the highly accumulation of Cu ion within the A $\beta$  plaque that consequently leads to deprived amount of Cu ions in other required brain areas. Highly presence of brain Cu ion also causes a decreased level of glutathione (GSH), which is a substrate needed for radical scavenging, leading to an increased level of ROS and oxidative-induced cytotoxic effects.<sup>62</sup> Moreover, the Cu<sup>2+</sup>-binding sites are presented in both APP and A $\beta$ , in which the Cu ion can directly bind and induce redox reaction and production of the ROS that is harmful to the bound-proteins themselves as well as the surrounding cellular components.<sup>62</sup> Cu ion plays role in synaptic functions and neurotransmission.<sup>63</sup> Cu is released in the synaptic cleft in which the released Cu ion has high binding affinity to interact with the receptors of many neurotransmitters including glutamate and GABA.<sup>64</sup> The binding of Cu ion to these receptors alters the degree of excitability/inhibitory actions of the neurotransmissions, which could be contributed to many clinical cognitive/behavioral impairments. Therefore, it is no doubt that loss of the Cu homeostasis in the brain could lead to many deleterious effects including oxidative damages, neuroinflammation, and worsen prognosis of the AD.

### **Zinc (Zn)**

Zinc (Zn) is the second most abundant trace element found in human body. Zn mostly existed in protein-bound form and functions for growth and development, structural maintenance, and enzymatic activities.<sup>15,65</sup> The unbound mobile form is noted for its importance in synaptic functions and modulation of neurotransmission.<sup>66</sup> Loss of Zn homeostasis could lead to memory and learning impairments, while an excessive Zn causes the oxidative stress mediated *via* mitochondrial dysfunction.<sup>67</sup> Roles of Zn in pathogenesis and progression of the AD are still controversial, however, its detrimental effects were widely noted.<sup>38</sup>

In the presence of Zn, inhibition of  $\alpha$ -secretase cleavage was observed leading to an increase of A $\beta$  production.<sup>68</sup> The presence of Zn enhances an aggregation of A $\beta$  as it shows good binding affinity to A $\beta$ ,<sup>69</sup> in which this bound form elicited decreased solubility and become non-degradable against proteolytic enzymes.<sup>70</sup> The formation of the bound complexes renders the accumulation of Zn in the plaque and deprives the availability of free Zn in the synaptic cleft, especially at glutamatergic nerve terminals,<sup>66</sup> which could lead to impair synaptic functions, loss of memory and cognitive deficits.<sup>71</sup> Moreover, Zn both directly binds to tau or modulates its hyperphosphorylation *via* kinases leading to an enhancement of tau aggregation and fibrillation.<sup>72</sup> The presence of Zn was also noted to associate with tau-related

neurotoxicity.<sup>73</sup>

Although Zn is considered a redox inert ion, its excessive availability plays part in oxidative-induced neuronal cell death.<sup>15</sup> Excessive release of Zn at synapse could activate redox reaction and ROS production *via* an activation of nicotinamide adenine dinucleotide phosphate (NADPH)-oxidation.<sup>74</sup> Zn ion is noted as an inhibitor of many enzymes required for metabolic functions. Additionally, mitochondrial respiratory chain is highly sensitive to Zn<sup>2+</sup>. As regards, excessive intracellular Zn could alter multiple cellular metabolic processes, enhance oxidative stress,<sup>75</sup> and induce neuronal death.<sup>74</sup>

Zn plays important roles in synaptic functions and is recognized as a potent allosteric inhibitor of glutamate receptors such as N-methyl D-aspartate (NMDA) receptors. Glutamate is an excitatory neurotransmitter in which an inhibition of its action leads to overexcitation of the neurons and neurotoxicity.<sup>76</sup>

### **CURRENT STAGE OF DRUG DEVELOPMENT FOR AD MANAGEMENT**

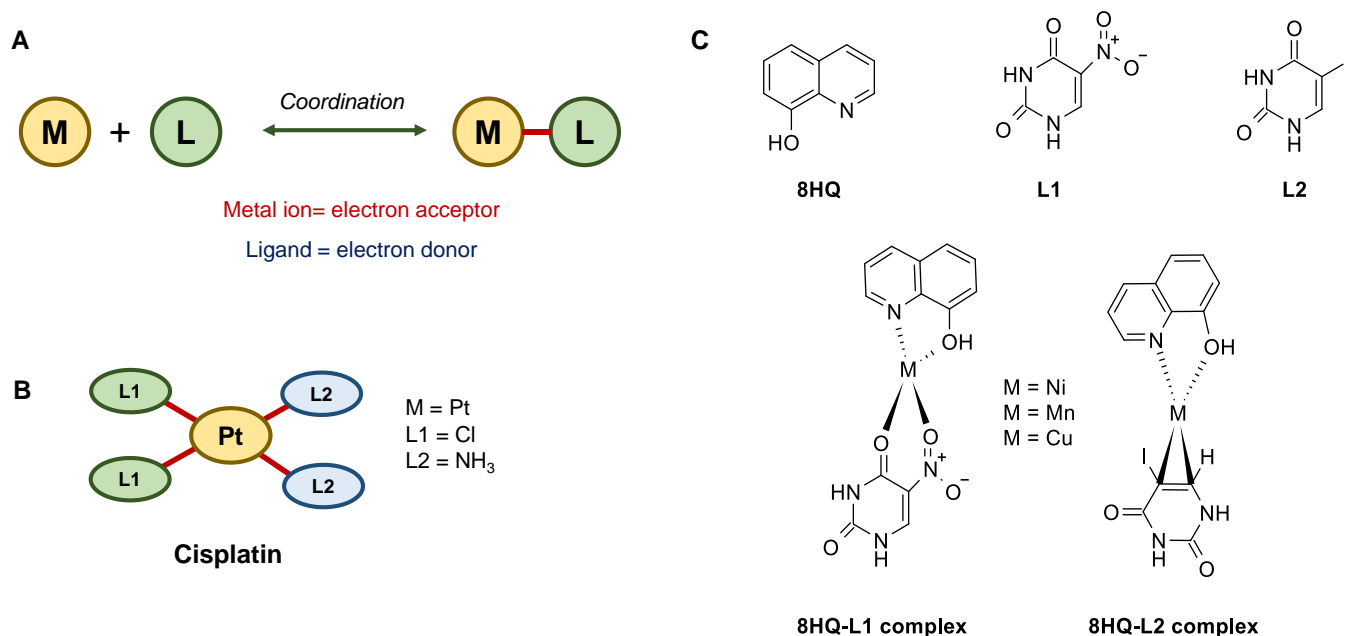
Current approved drugs available for AD treatment are drugs that target the resolving of symptoms (i.e., cognitive and memory impairments, behavioral and psychological changes) without any modifications on biological processes involved in pathogenesis and progression of the diseases.<sup>49,77</sup> These drugs are classified as symptomatic drugs (i.e., cognitive enhancing and neuropsychiatric improving agents).<sup>16</sup> Cognitive enhancing drugs are drugs that alter levels or modulate actions of the related neurotransmitters (i.e., cholinesterase inhibitors, glutamatergic agents, serotonin agents, gamma-aminobutyric acid (GABA) allosteric modulators, cannabinoids, and neuropeptides).<sup>16</sup>

Disease-modifying drugs are capable of delaying progression of the AD. This includes the modulations of A $\beta$  deposition and aggregation, modulations of tau protein deposition, modulation of inflammation, protection against oxidative damages, alterations of metal ions levels and distributions, and modulation of vascular-related factors.<sup>78</sup> History of the development of disease-modifying agents originated by targeting a reduction of A $\beta$  production *via* inhibiting activities of the related secretases enzymes<sup>79</sup> as well as an enhancement of A $\beta$  removal by immunization.<sup>80</sup> Unfortunately, the first strategy was failed in the clinical trials due to its considerable toxicity.<sup>79</sup>

Research on this area has been continuously conducted toward discovery of multitarget agents with multiple actions<sup>81,82</sup> in relevantly suit with the multifactorial nature of the diseases. One of the most interesting areas is the development of compounds targeting the restoration of the loss of brain metal homeostasis.<sup>15,38,49,83</sup> In this regard, the developed compounds require some set of key properties for accessing the brain to elicit chelating action such as an ability to pass across the blood brain barrier (BBB), moderate binding affinity to key metal ions (i.e., iron, zinc, copper), as well as non-toxic nature.<sup>38</sup> It should be noted that ideal metal chelators should be able to chelate both free metal ion and metal deposited in the A $\beta$  plaque, but not the ions in other metalloproteins/enzymes which function for other essential physiological processes.<sup>49</sup>

## 8HQ AS A PROMISING SCAFFOLD FOR ANTI-NEURODEGENERATIVE AGENTS

Among classes of pharmacophores in the development pipeline, 8HQ-based compounds have gained the most considerable focus for restoring metal homeostasis potential due to their chelating properties. The chelation is achieved by the formation of coordination bond between ligands (L) and metal ions (M) to form metal complex (M-L, Figure 4A). The ligands can be the same or different types of compounds. One example of well-known metal complex drug is an anticancer drug namely cisplatin, a tetra-dentate mixed ligand metal complex with the centered platinum is complexed with two different types of ligands (i.e., Cl groups on one side and two NH<sub>3</sub> groups on another, Figure 4B). A set of six 8HQ-uracil mixed ligand metal complexes reported by our research group as aromatase inhibitors are given as examples, in which 3 types of central metal ions (i.e., Ni, Mn, and Cu) along with 8HQ and two uracil derivatives (L1 and L2) were used for the designed and synthesis of the complexes (Figure 4C).<sup>10</sup>



**Figure 4. A:** An example illustration explaining the coordination bond formation to form metal complex. A metal ion (M) serves as an electron acceptor located in the center of the metal complex (M-L) molecule, while the ligands (L) serve as surrounding electron donors. **B:** Cisplatin is an anticancer drug which is a mixed ligand platinum complex. **C:** 8HQ-mixed ligand metal complexes reported as aromatase inhibitors by our research group.<sup>10</sup>

Moreover, 8HQ metal complexes were developed to improve pharmacokinetics as well as to deliver active ligands to reach target site in the CNS.<sup>2</sup> Additionally, 8HQ is considered a promising scaffold for development of multitarget and multifunctional neuroprotective agents due to its outstanding characteristics that makes it capable of displaying multiple actions. Current publications demonstrated that 8HQ-based

compounds are attractive to be developed as both symptomatic anti-AD agents (i.e., acting as acetylcholinesterase (AChE) inhibitors and NMDA receptor modulators) and disease-modifying agents (i.e., acting as antioxidant and anti-A $\beta$  production/aggregation *via* metal-related mechanisms). In this regard, 8HQ pharmacophore was noted as a core scaffold for the design of hybrids or conjugates to provide multitargets/multifunctional compounds to combat multifactorial nature of the AD.<sup>1</sup>

In this article, the search was performed to select a collection of reported 8HQ-based compounds (mainly focused on the pioneer compounds and recent published works during 2016-2021) as potential therapeutic agents for management of the AD. Herein, we provide subsections based on chelating actions of the recently reported 8HQ-compounds towards the metal ions (i.e., Cu chelators, Fe chelators, Zn ionophores). The reported compounds with other mechanism of actions to benefit the AD treatment were also provided (as summarized in Table 1).

**Table 1.** Summary of compounds and their actions

Compound	Chelator	Effects	Reference
<b>Pioneer compounds</b>			
8HQ	Multiple ions (Non-selective)	<ul style="list-style-type: none"> <li>• Neuroprotective</li> </ul>	8, 84
CQ	Multiple ions (More selective to Cu and Zn)	<ul style="list-style-type: none"> <li>• Decrease Cu-induced and Fe-induced A<math>\beta</math> aggregation</li> <li>• Neuroprotective</li> <li>• Improvement of memory deficit in AD and PD mice models</li> <li>• Clinical trial phase II: Reduce accumulations of A<math>\beta</math> in AD patients</li> </ul>	85-89
PBT2	Cu chelator	<ul style="list-style-type: none"> <li>• Sequestrate Cu<sup>2+</sup> from A<math>\beta</math> plaque and inhibit A<math>\beta</math> aggregation and oligomerization</li> <li>• Neuroprotective</li> </ul>	90-93

		<ul style="list-style-type: none"> <li>• Phase 2 trials (safe but not significantly reduce A<math>\beta</math> concentration in mild AD patients)</li> <li>• Decrease phosphorylation and aggregation of tau protein</li> </ul>	
VK-28	Fe chelator	<ul style="list-style-type: none"> <li>• Neuroprotective</li> </ul>	94-96
M30	Fe chelator	<ul style="list-style-type: none"> <li>• Neuroprotective</li> <li>• Regulates APP and decrease amyloid production</li> <li>• Non-selective MAO inhibitor</li> <li>• Neurorestorative: impacts neuronal differentiation, induces neurite outgrowth and re-establish synaptic connection loss in the injured neuronal cells</li> </ul>	97-99, 100, 101
HLA-20	Fe chelator	<ul style="list-style-type: none"> <li>• Neuroprotective</li> <li>• Lower APP expression and A<math>\beta</math> production</li> <li>• Inhibit metal-induced A<math>\beta</math> aggregation (Fe, Cu, and Zn)</li> <li>• Selective MAO-B inhibitor</li> </ul>	102-104
<b>Cu chelators</b>			
CQ-Se (1)	Cu chelator	<ul style="list-style-type: none"> <li>• Antioxidant / H<sub>2</sub>O<sub>2</sub> scavenging activity</li> <li>• Inhibit Cu<sup>2+</sup>-induced A<math>\beta</math> aggregation and disassembling of the formed A<math>\beta</math> aggregates</li> <li>• Better activity than CQ</li> </ul>	105
Bis-8HQ (2)	Cu chelator	<ul style="list-style-type: none"> <li>• Chelate Cu from Cu-A<math>\beta</math> complex, both in the absence and presence of Zn<sup>2+</sup></li> <li>• Higher selectivity to Cu<sup>2+</sup> &gt; Zn<sup>2+</sup></li> </ul>	13

		<ul style="list-style-type: none"> <li>• Preferable stability and drug-like properties</li> </ul>	
Quinoline-triazole (3)	Cu chelator	<ul style="list-style-type: none"> <li>• Inhibit self- and Cu<sup>2+</sup>-induced A<math>\beta</math> aggregation <i>via</i> interacting with the A<math>\beta</math> peptides (hydrophobic region and glutamic acid residue)</li> </ul>	106
8HQ-indole (4)	Cu chelator	<ul style="list-style-type: none"> <li>• Decrease overall cerebral A<math>\beta</math> deposition in mice model</li> <li>• Improve cognitive deficits in mice model</li> <li>• Antioxidant and neuroprotective</li> <li>• Neurorestorative effect (enhance neuronal differentiation)</li> <li>• Display preferable <i>in vivo</i> pharmacokinetic profile</li> </ul>	35
NQ-selective BuChE inhibitor (5)	Cu chelator	<ul style="list-style-type: none"> <li>• Potent BuChE inhibitor</li> <li>• Inhibit self-induced A<math>\beta</math> aggregation</li> <li>• Selective Cu<sup>2+</sup> chelator</li> <li>• Weak antioxidant</li> </ul>	107
8HQ-cinnamic acid (6)	Cu chelator	<ul style="list-style-type: none"> <li>• Inhibit self-induced A<math>\beta</math> aggregation</li> <li>• Inhibit Cu<sup>2+</sup>/Zn<sup>2+</sup>-induced A<math>\beta</math> aggregation</li> <li>• Antioxidant</li> <li>• Neuroprotective</li> </ul>	34
8HQ-resveratrol (7)	Cu chelator	<ul style="list-style-type: none"> <li>• Inhibit self- and Cu<sup>2+</sup>-induced A<math>\beta</math> aggregation</li> <li>• Antioxidant</li> <li>• Neuroprotective</li> </ul>	50
8HQ-boric acid (8)	Prochelator	<ul style="list-style-type: none"> <li>• Prodrug to be activated by oxidative condition with high H<sub>2</sub>O<sub>2</sub></li> </ul>	108

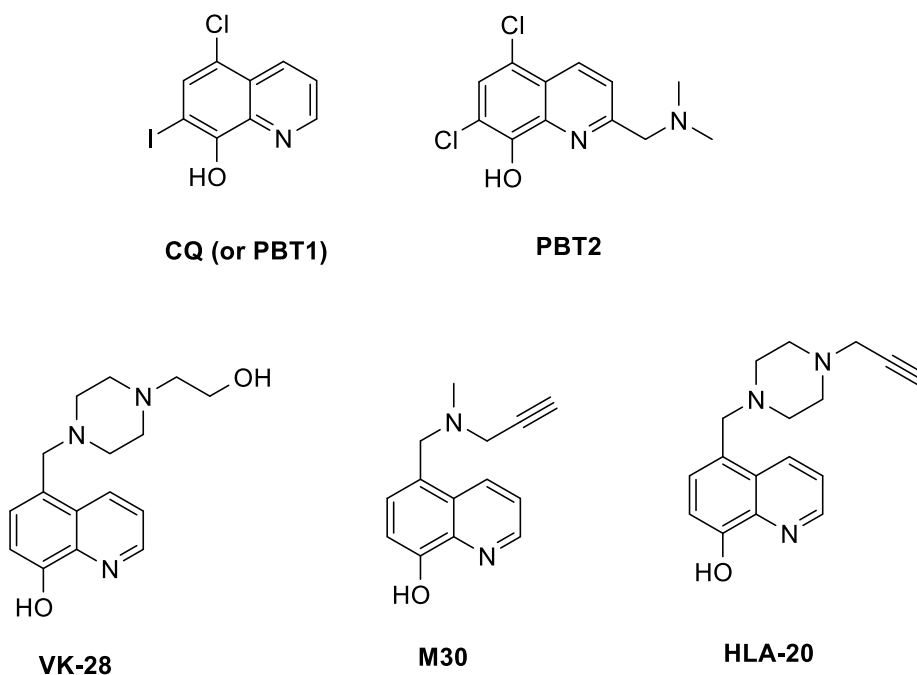
		<ul style="list-style-type: none"> <li>• After activation, release active ligand 8HQ acting as Cu<sup>2+</sup>, Zn<sup>2+</sup> and Fe<sup>2+</sup> chelators</li> </ul>	
CQ-roflumilast hybrids ( <b>9</b> )	Cu chelator	<ul style="list-style-type: none"> <li>• Antioxidant</li> <li>• Neuroprotection</li> <li>• Inhibit Cu<sup>2+</sup>-induced A<math>\beta</math> aggregation</li> <li>• PDE4 inhibition</li> </ul>	26
8HQ-piperidine ( <b>13</b> )	Cu chelator	<ul style="list-style-type: none"> <li>• Antioxidant</li> <li>• AChE and BuChE inhibitors</li> </ul>	109
8HQ-tacrine ( <b>14</b> )	Cu chelator	<ul style="list-style-type: none"> <li>• Metal chelation</li> <li>• Antioxidant</li> <li>• AChE and BuChE inhibitors</li> </ul>	110
CQ- PF-04447943 ( <b>15</b> )	Cu chelator	<ul style="list-style-type: none"> <li>• Selective PDE9 inhibitor</li> <li>• Inhibit Cu<sup>2+</sup>-induced A<math>\beta</math> aggregation</li> <li>• Antioxidant</li> </ul>	111
CQ-moracin M ( <b>16</b> )	Cu chelator	<ul style="list-style-type: none"> <li>• PDE4D2 inhibitor</li> <li>• Inhibit A<math>\beta</math> aggregation</li> <li>• Antioxidant</li> <li>• Anti-neuroinflammation</li> </ul>	25
<b>Fe chelators and Zn ionophores</b>			
<b>17 and 18</b>	Fe chelator	<ul style="list-style-type: none"> <li>• Neuroprotective</li> </ul>	112
<b>19</b>	Prochelator of HLA-20	<ul style="list-style-type: none"> <li>• Prochelator is converted to active chelator (HLA-20) after binding with AChE</li> </ul>	113
<b>20-25</b>	Zn ionophore	<ul style="list-style-type: none"> <li>• Halogenated derivatives of CQ and PBT2 with improved ionophore properties (Cu and Zn)</li> <li>• Inhibit Zn-induced A<math>\beta</math> aggregation and oligomerization</li> </ul>	114

<b>Chelators of multiple ions</b>			
8HQ-arylhydrazone (26)	Multiple ions chelator	<ul style="list-style-type: none"> <li>• Inhibit aggregation of A<math>\beta</math> and <math>\alpha</math>-synuclein</li> </ul>	115-117
8HQ-propargylamine-donepezil (27)	Multiple ions chelator	<ul style="list-style-type: none"> <li>• Antioxidant</li> <li>• Cholinesterase inhibitor</li> <li>• MAO inhibitor</li> </ul>	118
Bis-8HQ compound (28)	Multiple ions chelator	<ul style="list-style-type: none"> <li>• Inhibit Cu-, Zn-, and Fe-induced A<math>\beta</math> aggregation</li> <li>• Antioxidant</li> </ul>	119
CQ-donepezil hybrids (29-31)	Multiple ions chelator	<ul style="list-style-type: none"> <li>• Antioxidant</li> <li>• Inhibit A<math>\beta</math> aggregation</li> <li>• Selective BuChE inhibitor</li> </ul>	120
8HQ-biotin (32-33)	Multiple ions chelator	<ul style="list-style-type: none"> <li>• Antioxidant</li> </ul>	121
8HQ-glutathione (34)	Multiple ions chelator	<ul style="list-style-type: none"> <li>• Antioxidant</li> <li>• Neuroprotective</li> </ul>	122
8HQ-lipoic acid (35)	Multiple ions chelator	<ul style="list-style-type: none"> <li>• Antioxidant</li> <li>• Neuroprotective</li> </ul>	123
8HQ-L-alanine (36)	Multiple ions chelator	<ul style="list-style-type: none"> <li>• Antioxidant</li> <li>• Neuroprotective</li> </ul>	124
8HQ-neuropeptide (37)	Multiple ions chelator	<ul style="list-style-type: none"> <li>• Antioxidant</li> <li>• Neuroprotective</li> </ul>	125
<b>Compounds with other mechanisms of action (beside chelation)</b>			
8HQ-indole (38-40)	Direct binding to metal ion binding site of A $\beta$	<ul style="list-style-type: none"> <li>• Inhibit self-induced and metal induced A<math>\beta</math> aggregations</li> </ul>	126

Donepezil-propargylamine-8HQ hybrid ( <b>41</b> )	Direct interaction with enzymes	<ul style="list-style-type: none"> <li>• Cholinesterase inhibitors (AChE and BuChE)</li> <li>• MAO inhibitors (MAO-A and MAO-B)</li> </ul>	127
8HQ-ebesen ( <b>42</b> )	Antioxidant as well as metal chelation	<ul style="list-style-type: none"> <li>• Inhibit self-induced and metal induced A<math>\beta</math> aggregations</li> <li>• Disassembling the preformed aggregated A<math>\beta</math></li> </ul>	128
DMAMQ ( <b>43</b> )	Activation of ROS signaling pathway	<ul style="list-style-type: none"> <li>• Facilitate neural stem cell growth</li> <li>• Enhance neural stem cell proliferation and neurite growth (<i>via</i> an increase of intracellular ROS)</li> </ul>	129
Q134 ( <b>44</b> )	Modulate hypoxic-inducing factor (HIF) system	<ul style="list-style-type: none"> <li>• Acting as HIF1A protein stabilizer</li> <li>• Cytoprotective effect</li> <li>• Promote neuronal cell survival</li> </ul>	130

### Pioneer compounds

Binding affinity of the hydroxyquinoline (HQ) compounds towards transition metal ions was ranked as  $Mn^{2+} < Co^{2+} < Ni^{2+} < Cu^{2+} > Zn^{2+}$ .<sup>131</sup> 8HQ (Figure 1) possesses a beneficial antioxidant effect for neuroprotection which was noted to elicit *via* scavenging activity against ROS (especially hydrogen peroxide, H<sub>2</sub>O<sub>2</sub>) as well as metal ion coordination such as Fe ion.<sup>84</sup> Although 8HQ is well-recognized for its promising metal chelating ability,<sup>2</sup> its low selectivity toward each metal ion has been concerned.<sup>132</sup> It was also noted that 8HQ forming complex with Fe ion could display both antioxidant (protective) and prooxidant (cytotoxic) roles.<sup>133</sup> Accordingly, newer derivatives such CQ and PBT2, with more selectivity against metal ions (i.e., Cu<sup>2+</sup> and Zn<sup>2+</sup>) played roles in AD was developed as a first pioneer compound. However, most of the first-generation chelators are non-selective chelators which are capable of chelating various types of ions but with different binding affinity. Herein, 8HQ and its derivatives firstly developed as chelators for AD management are discussed and summarized in Figure 5.



**Figure 5.** Pioneer 8HQ-based chelators developed as anti-neurodegenerative agents

### ***CQ and PBT2 (Cu, Zn, and Fe chelators)***

CQ, 5-chloro-7-iodo-8HQ also known as PBT1 (Figure 5) has moderate binding affinity toward multiple metal ions (i.e., Cu, Zn, and Fe). The CQ was found to remove metal ions from the A $\beta$  peptides, inhibit metal-induced A $\beta$  aggregation, disaggregate the A $\beta$  plaque, inhibit ROS production *in vitro*.<sup>82,86,87,134,135</sup> It was suggested to be owing to the chelating ability of CQ to form complex with the metal ions (i.e., Cu, Zn, and Fe).<sup>136</sup> Moreover, preclinical studies and clinical trials showed that CQ exhibits promising inhibition of A $\beta$  aggregation, reversal of metal-induced neurotoxicity and improvement of memory deficit in AD and PD mice models.<sup>86-88</sup> Clinical trials phase II also demonstrated that CQ is beneficial to reduce accumulations of A $\beta$  in AD patients.<sup>89</sup> However, some disadvantages of CQ have been noted including neurotoxicity,<sup>137,138</sup> potential inductions of metal ions (i.e., Cu, Zn, and Fe<sup>138,139</sup>) deficiencies, undesirable ability to completely stop progression of A $\beta$  aggregation,<sup>49</sup> as well as difficulty of large-scale synthesis.<sup>87</sup> Despite its limitations, attention has been continuously drawn to CQ as a promising prototype for developing anti-amyloid agents.

As regard, a second-generation chelator PBT2 (5,7-dichloro-2-[(dimethylamino)methyl]-8HQ) was developed. The PBT2 is a CQ derivative designed for improving ease of synthesis as well as for avoiding iodine-induced toxicity. PBT2 possesses a tertiary amine in the molecule for improving the solubility that could contribute to improved efficacy.<sup>92</sup> The PBT2 can form (bi- or tri-dentate) complex with Cu<sup>2+</sup> and demonstrated good brain penetration and good ability to sequester Cu<sup>2+</sup> from A $\beta$  plaque.<sup>90,140</sup> This more structural flexibility is related to an ability of the compound to form tri-dentate complex with Cu<sup>2+</sup> ion

which could contribute to its superior ionophoric activity beyond that of the CQ.<sup>87</sup> More promising anti-AD effect of the PBT2 also may be due to its potential to form bi-/tri-dentate complex with many possible Cu<sup>2+</sup>-binding ligand such as phenolic oxygen, tertiary amine nitrogen, and pyridine nitrogen.<sup>87,140</sup> *In vivo* study showed that oral administration of PBT2 decreased A $\beta$  aggregation and oligomerization in AD mice models.<sup>87</sup> Clinical trial phase IIa demonstrated beneficial effect on AD patients.<sup>91</sup> Besides A $\beta$ , PBT2 was reported to decrease phosphorylation and aggregation of tau protein which proposed to be beneficial for other neurodegenerative disease such as Parkinson's disease (PD) and Huntington's disease (HD).<sup>93</sup> Clinical trials showed that PBT2 effectively decrease toxic oligomers *via* removing excessive Cu ions and restore Cu imbalance in HD patients.<sup>93,141</sup>

Possible effects of CQ and PBT2 were proposed to be *via* their abilities to act as metal chelators and/or metal ionophores (ion carrier across membrane). Chelating ability of these compounds to form metal-HQ complex can i) affect APP processing and A $\beta$  production, ii) inhibit metal-induced A $\beta$  aggregation and/or oligomerization, iii) remove metal ions from A $\beta$  plaque, therefore, inhibit ROS production and oxidative-induced neuronal damages, iv) promote degradation of metal-dependent A $\beta$  oligomers/aggregates<sup>142</sup> (Figure 3). However, both compounds are failed in clinical phase IIb of AD trial due to an ineffectiveness to reduce A $\beta$  plaque in mild stage AD patients.<sup>49,135</sup>

#### **VK-28, M30, and HLA-20 (Fe chelators)**

VK-28, a piperazine derivative of 8HQ (Figure 5), is a potent Fe chelator with neuroprotective effect.<sup>143</sup> VK-28 has comparable Fe binding affinity to that of desferrioxamine (a drug of choice used for treatment of iron overload) which indicates its therapeutic potential for disease with Fe imbalance.<sup>143</sup> VK-28 also displayed potent antimicrobial activity which noted to be due to its potent chelating and good membrane penetrating properties.<sup>94</sup> It was suggested that the piperazine ring is a crucial moiety responsible for membrane permeability of the compound across microbial cell membrane.<sup>94</sup> Accordingly, VK-28 can pass across blood-brain-barrier (BBB) and displays good neuroprotective effect against oxidative-induced neuronal damages (i.e., Fe-induced lipid peroxidation and 6-hydroxydopamine (6-OHDA) induced neurotoxicity).<sup>95,96</sup>

High level of Fe and Fe-induced oxidative neuronal death were noted in many neurodegenerative diseases.<sup>49</sup> The ROS production *via* the Fenton reaction is also associated with an increase of MAO activity. Good example was noted for characteristic of PD, in which high Fe level in nigral area was found along with increased MAO-B activity as well as decreased glutathione level.<sup>96</sup> Therefore, most of the compounds acting as Fe chelators were rationally designed to obtain an additional MAO inhibitory effect. Rasagiline is an anti-PD drug acts as MAO-B inhibitor, in which a propargyl amine moiety presence in its molecule was noted as a crucial part for its potent MAO-B inhibitory and neuroprotective effects.<sup>102</sup> This was also

indicated by the lack of MAO inhibitory action for the VK-28 due to the absence of this moiety in its molecule.<sup>96,144</sup> Accordingly, the rational design of multifunctional compounds is based on an incorporation of a propargyl amine moiety into 8HQ scaffold. The pioneer compounds in this class are M30 and HLA-20 (Figure 5).

M30 is a multifunctional 8HQ-propargyl hybrid compound with potent Fe<sup>3+</sup> chelating, antioxidant, neuroprotective, and MAO inhibitory activities.<sup>97,98</sup> M30 possesses desirable brain and membrane permeabilities<sup>98,144,145</sup> and demonstrates beneficial neuroprotection in various PD and AD models.<sup>98,100,144,145</sup> However, the selectivity toward subtype of MAO was raised for this compound. M30 selectively inhibits MAO activity in the brain, however, it is a suicidal inhibitor that inhibits both MAO-A and MAO-B.<sup>98</sup>

HLA-20 (Figure 5) was designed as propargyl analog of VK-28 to obtain selectivity toward MAO-B inhibition.<sup>102</sup> Similar with M30, the compound exhibit strong Fe chelating, potent radical scavenging, neuroprotective and MAO-B inhibitory effects as well as good membrane penetration.<sup>103</sup> Both M30 and HLA-20 exhibited neuroprotective and neurorestorative effects in many *in vitro* and *in vivo* models of neurodegenerations such as AD and PD.<sup>99</sup> Fe chelating ability could restore brain Fe homeostasis which in turn regulates the APP processing and A $\beta$  production as well as protects against oxidative damages. Inhibition of MAO could enhance the availabilities of many related neurotransmitters (i.e., dopamine, norepinephrine, and serotonin) which are therapeutic benefits.<sup>101,146</sup> Moreover, M30 is a potent up-regulator of hypoxia induce factor (HIF). As a result of Fe chelation, decreased level of Fe mimics hypoxia condition that upregulates the HIF leading to an increase of neurotropic factors and activation of neuronal differentiation.<sup>146</sup>

In overview, the developed prototypes are mainly discovered and designed based on metal chelating property of the compounds in which most of them are still act as single-acting and/or non-selective compounds. To combat multifactorial nature of neurodegenerative diseases, the strategy of hybridization of multiple crucial pharmacophores/functional groups has been used to obtain multifunctional/multitarget compounds. The newer generation of 8HQ-based potential anti-neurodegenerative compounds are discussed in the next section.

### ***8HQ-based compounds as Cu chelators***

Newer generations of Cu chelators were developed and are summarized in Figure 6. Most of the developed compounds have common properties such as antioxidant, inhibitory effect against Cu<sup>2+</sup>-induced A $\beta$  aggregation, and neuroprotection. The discussion provides herein will be started with the reported 8HQ derivatives targeting A $\beta$  (compounds **1-12**) followed by others without anti-A $\beta$  effects (compounds **13-16**).



Design and development of bis- or tris- derivatives is also noted as another area of worthy investigation to find potential compounds with improved bioactivities. Recently, Oliveri reported a novel bis-8HQ ligand (compound **2**) with promising *in vitro* anti-A $\beta$  activity and good drug-like properties.<sup>13</sup> The study demonstrated that the compound **2** was able to chelate Cu<sup>2+</sup> accumulated in the A $\beta$  plaque (both in the absence and presence of Zn<sup>2+</sup>) which could address the loss of Cu homeostasis in the AD-mimic condition with the presence of excessive Zn<sup>2+</sup>, which may be due to the higher selectivity of the compound toward Cu<sup>2+</sup>. This indicated that the compound **2** is promising for protection against ROS-induced damages in the Zn-rich AD brain.<sup>13</sup>

Triazole is an attractive scaffold for discovery of anticancer agents as well as others.<sup>148</sup> Quinoline-triazole compound (MC-AB4, **3**) was designed and reported to inhibit both self- and Cu<sup>2+</sup>-induced A $\beta$  aggregation.<sup>106</sup> *In silico* finding revealed that the compound **3** interacted with the hydrophobic region and glutamic acid residue of A $\beta$  peptides to prevent their aggregations. *In vitro* findings also demonstrated that binding affinity of the compound **3** was stronger in the condition with excessive Cu<sup>2+</sup> when compared with that of the absent Cu<sup>2+</sup>. This suggested that the compound **3** has preferable potential for the AD condition with excessive Cu ion deposited in A $\beta$  plaque.

Indole pharmacophore was recognized as one of privileged structures in drug discovery.<sup>149</sup> Compound **4** was reported as the most promising compounds from a series of newly synthesized 8HQ-indole derivatives.<sup>35</sup> Oral administration of compound **4** showed several neuroprotective-related activities in the APP/PS1 AD mice, which includes improving cognitive deficits, decreasing overall cerebral  $\beta$ -amyloid deposition, inhibiting A $\beta$  aggregation, displaying intracellular antioxidant, redistributing the metal ions, as well as exhibiting the neurorestorative effect *via* an enhancement of neuronal differentiation. Additionally, compound **4** displayed preferable *in vivo* pharmacokinetic profiles i.e., good metabolic stability, brain penetration ability, as well as drug-like properties.

Besides halogenated-8HQ compounds, nitro derivative such as NQ had gain interest as one of moiety in discovery of multitarget drug design. A series of NQ-based multifunctional chelators were designed by merging the NQ and selective butyrylcholinesterase (BuChE) inhibitor.<sup>107</sup> Compound **5** was noted as the most potent compound acting as a BuChE inhibitor (IC<sub>50</sub> value = 215 nM) and selective Cu<sup>2+</sup> chelator, as well as capable of inhibiting self-induced A $\beta$  aggregation. However, the compound possessed weak antioxidant activity. Molecular docking also indicated that, beside the main interaction at active site of the BuChE, the NQ moiety of the compound **5** could fit well with the acyl-binding pocket of the enzyme to form an additional interaction which may contribute to its high potency of inhibition.

Natural-derived bioactive compounds had gain interest as important sources for discovery of various drugs, including anti-neurodegeneration.<sup>150,151</sup> Herein, 8HQ hybrids with natural-derived compounds such as cinnamic acid, resveratrol, and boric acid are discussed. Cinnamic acid is a natural compound found in

various plants and spices.<sup>152</sup> Piperazine is a moiety found in many approved drugs and is widely used as a linker for designing of novel compounds.<sup>153</sup> A series of 8HQ-cinnamic acid with piperazine linker were developed as multifunctional compounds.<sup>34</sup> The promising one is compound **6**, which exhibited inhibitory effect against both self-aggregation ( $IC_{50} = 5.64 \mu\text{M}$ ) and  $\text{Cu}^{2+}/\text{Zn}^{2+}$ -induced  $\text{A}\beta$  aggregation (% inhibition:  $\text{Cu}^{2+}$ -induced = 88.9%,  $\text{Zn}^{2+}$ -induced = 73.3). Additionally, compound **6** displayed antioxidant and neuroprotective effects against  $\text{H}_2\text{O}_2$ -induced neurotoxicity in the PC12 cells, showing good brain permeability (*in vitro*) as well as non-toxicity (dose 2000 mg/kg *in vivo*).

Resveratrol is well-known as a potent antioxidant compound with neuroprotective effect.<sup>154</sup> 8HQ-resveratrol hybrid (compound **7**) was reported as a multifunctional compound with anti- $\text{A}\beta$  aggregation, metal chelator, and antioxidant effects.<sup>50</sup> The compound could inhibit both self-induced and  $\text{Cu}^{2+}$ -induced  $\text{A}\beta$  aggregations. Additionally, it induces the disassembling of well-structured  $\text{A}\beta$  fibrils that were formed as a result of self- and  $\text{Cu}^{2+}$ -induced aggregations. Neuroprotective effect of the compound **7** was also noted to be *via* its metal chelating ability that could prevent the production of  $\text{H}_2\text{O}_2$  generated by a redox cycling of the  $\text{Cu}^{2+}$  as well as its antioxidant property. Compound **7** also showed preferable brain penetration and acute non-toxic effect was observed *in vivo* at dose 2000 mg/kg.

The complexity of brain's metallobiology has been arosed as a challenging issue in development of desirable metal-targeting compounds. The ideal compounds should be capable of conserving their abilities to combat  $\text{A}\beta$  burden and neuroprotection while displaying minimum altered effects on metal distribution and physiological functions in the brain. As regard, the design of prochelator (as prodrug) has gained interest to provide a selective effect of the chelation at a desirable site of action. 8HQ-boric acid hybrid was reported as a prochelator (compound **8**).<sup>108</sup> The compound **8** was designed to be activated by oxidative condition with the presence of high  $\text{H}_2\text{O}_2$ . After being activated, the compound will release the 8HQ (as an active chelator ) to elicit the Cu chelation at highly Cu-deposited  $\text{A}\beta$  target site. This is suggested to be beneficial for managing the  $\text{A}\beta$  burden without affecting metal distribution in the brain.

Phosphodiesterase (PDE) is an enzyme which hydrolyzes the intracellular cyclic adenosine monophosphate (cAMP).<sup>155</sup> PDE4 is a subtype of PDE family which functions for the process of memory consolidation and long-term potentiation.<sup>156</sup> The elevation of cerebral cAMP level by inhibiting the PDE activity has been noted as a strategy to benefit neurodegenerative diseases.<sup>156,157</sup> CQ was also used as a pharmacophore to develop a series of hybrid compounds with an available PDE4 inhibitor namely roflumilast.<sup>26</sup> Among all, compound **9** elicited the most promising multifunctional *in vitro* effects such as antioxidant (comparable to that of the parent compound **CQ**), neuroprotective, anti- $\text{A}\beta$  aggregation, and PDE4 inhibitory ( $IC_{50} = 0.399 \mu\text{M}$ ) activities as well as blood-brain-barrier penetration. The compound **9** showed more potent inhibition against  $\text{Cu}^{2+}$ -induced  $\text{A}\beta$  aggregation than that of the **CQ**. Molecular docking also demonstrated that the compound could fit well in the enzyme cavity in similar manner with the parent drug roflumilast. *In vivo*

investigations also demonstrated that the compound **9** effectively improve cognitive and memory in the oral-administered AD mice. The compound is potentially metabolic stable and safe as none of acute toxicity was observed at the dose up to 2000 mg/kg.

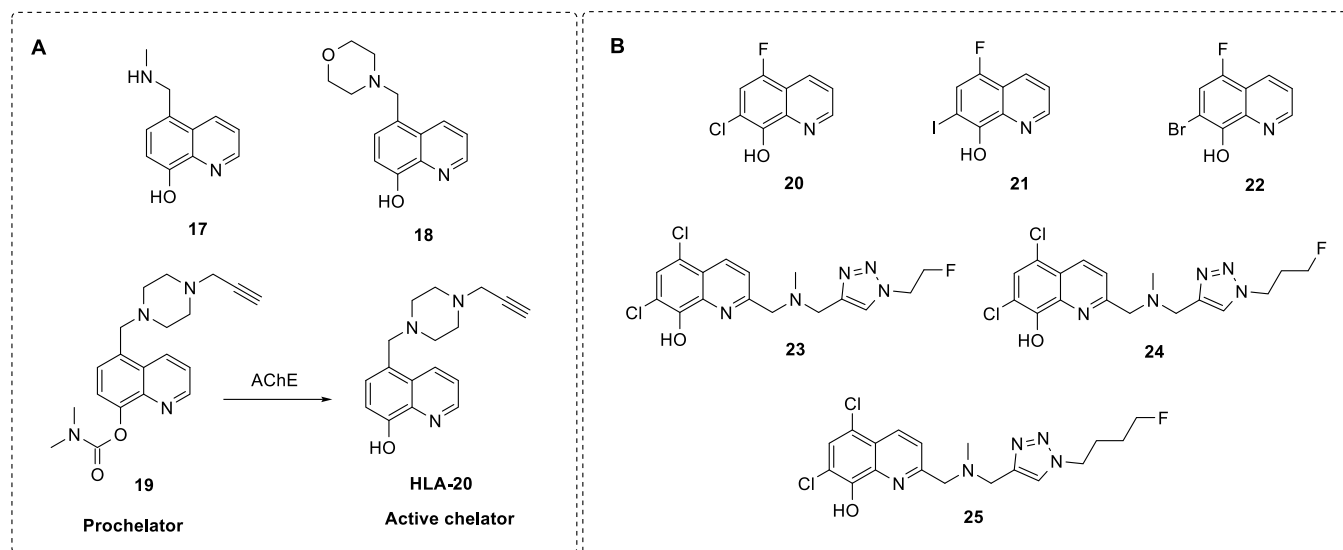
In addition to 8HQ, related quinoline-based derivatives such as 8-aminoquinoline (8AQ)-carbazole as well as some CQ-inspired compounds were reported for beneficial neuroprotection. 8AQ-carbazole dimer (PZ001, compound **10**) was developed as antioxidant, neuroprotective, and anti-A $\beta$  compound with low toxicity.<sup>158</sup> CQ also inspires the design of compounds with multiple actions, in which the crucial moiety for metal chelation of the CQ was incorporated with the well-known antioxidant, resveratrol, to obtain compounds **11** and **12**.<sup>159</sup> Both compounds inhibit self- and Cu<sup>2+</sup>-induced A $\beta$  aggregations as well as acting as MAO and AChE inhibitors, potent Cu chelator, and antioxidant agents.

Some multifunctional Cu chelators without anti-A $\beta$  effect were reported (compounds **13-16**). 8HQ-piperidine compound (**13**) showed good metal chelating property, antioxidant activity (DPPH IC<sub>50</sub> = 544  $\mu$ M) and inhibitory effects against both human AChE (% inhibition = 75.8%) and BuChE (IC<sub>50</sub> = 11.11 nM).<sup>109</sup> Compound with similar AChE inhibitory effect such as 8HQ-tacrine **14** (AChE inhibitor) hybrid was developed. The compound **14** displayed more potent inhibition (IC<sub>50</sub> in nanomolar range) against both AChE and BuChE when compared to that of the parent tacrine as well as selective Cu<sup>2+</sup> chelating and radical scavenging activities. Additionally, *in vitro* finding suggest its possibility to pass across blood-brain-barrier.<sup>110</sup> Besides targeting AChE, development of CQ-PDE inhibitor hybrid compounds as multifunctional PDE inhibitors were reported (compounds **15** and **16**). An inhibition of PDE9 has been noted as one of strategies in AD treatment and many PDE9 inhibitors are ongoing studied in clinical trial phase II.<sup>160</sup> Compound **15** is a hybrid of CQ and PDE9 inhibitor, namely PF-04447943 reported as an inhibitor of many PDE subtypes, but with great selectivity and potent toward PDE9 inhibition (IC<sub>50</sub> = 34 nM). The compound **15** effectively inhibited Cu<sup>2+</sup>-induced A $\beta$  aggregation and disassembled the preformed Cu<sup>2+</sup>-induced A $\beta$  fibrils, with greater potency than the parent compound CQ. It also displayed good metal chelating and antioxidant properties as well as brain permeability.<sup>111</sup> Similarly, compound **16** (a moracin M containing compound) was reported as PDE4D2 inhibitor (IC<sub>50</sub> = 0.32  $\mu$ M), antioxidant, anti-A $\beta$  aggregation as well as antineuroinflammatory agent.<sup>25</sup>

### **8HQ-based compounds as Fe chelators and Zn ionophores**

Some newly designed Fe chelators were reported for protection against neurodegeneration (Figure 7). 8HQ derivatives substituted with 5-methylamino (**17**) and 5-morpholinomethyl (**18**) groups were designed and reported for their neuroprotective potentials in both cellular and *in vivo* models of PD.<sup>112</sup> Both compounds effectively rescued dopaminergic neuronal cell line (SHSY-5Y) from oxidative-induced damage *via* acting as Fe chelators to decrease the levels of Fe in mitochondrial and cytoplasmic pools, thereby, suppressed

ROS production.<sup>112</sup> Additionally, compound **19** (HLA-20A) was developed as a site-activated multifunctional chelators of the parent chelator, HLA-20.<sup>113</sup> The compound **19** was designed as a prochelator (inactive) by incorporating the crucial structure (a carbamate group) of two cholinesterase inhibitors (i.e., rivastigmine and donepezil). The prochelator **19** was then converted into the active chelator, HLA-20, after its activation by binding with the AChE at target site. This is suggested to be more selective strategy that could minimize an alteration of the brain metal ion homeostasis.

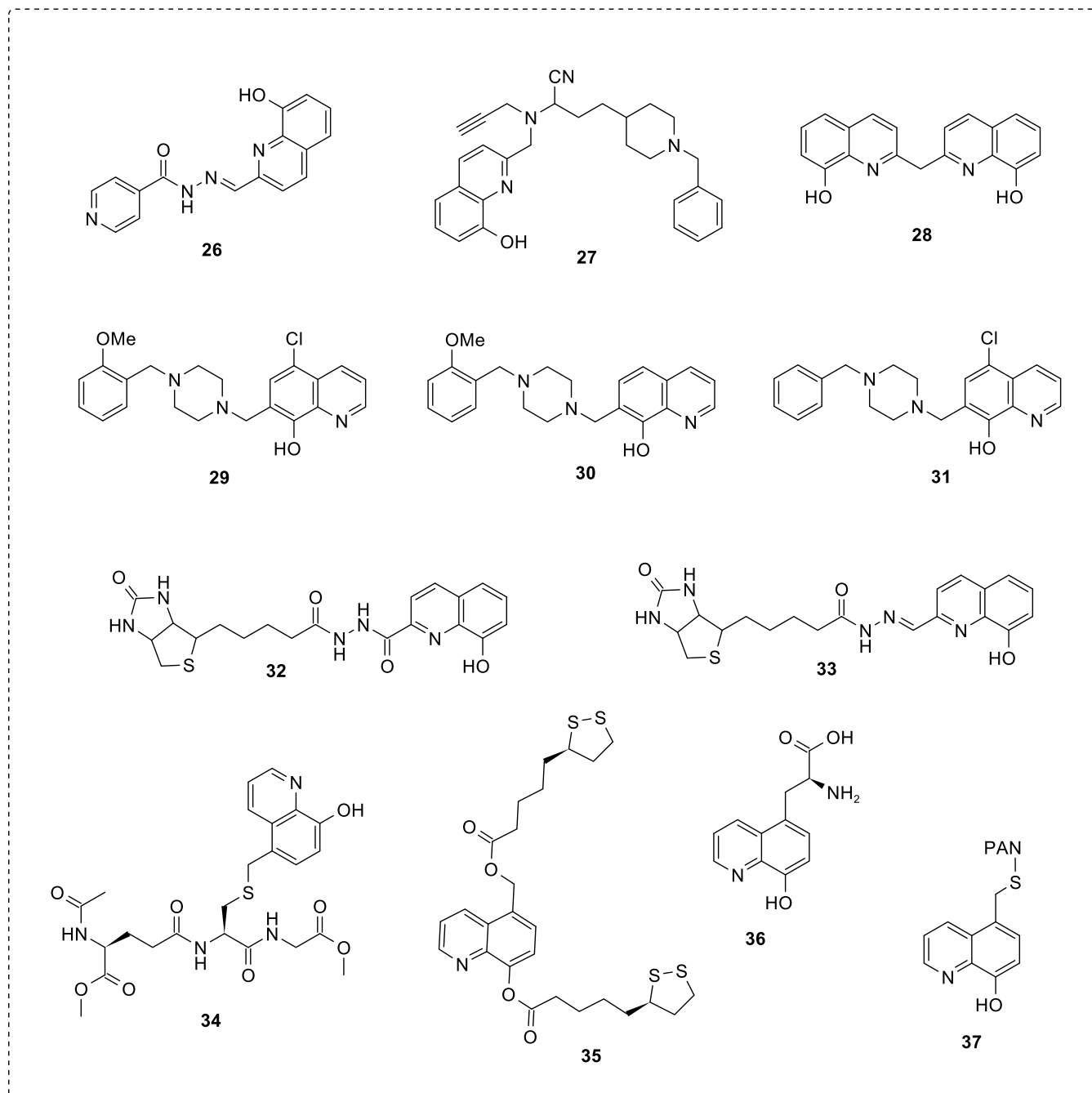


**Figure 7.** 8HQ-based iron chelators (A) and Zn ionophores (B) as anti-neurodegenerative agents

Unlike metal chelators that decrease and remove metal ions from the body, metal ionophores are compounds that transport the ions across the membrane leading to an increased levels of intracellular metal ions.<sup>161</sup> Therefore, ionophores are well-known for metal ions redistributing abilities in many related diseases.<sup>161,162</sup> A series of novel 8HQ-based Zn ionophores were reported as anti-amyloid agents (compounds **20-25**, Figure 7).<sup>114</sup> Halogenated derivatives of CQ (**20-22**) and PBT2 (**23-25**) were designed and displayed better ionophore property than those of the parents towards the uptake of Cu (> 6 folds) and Zn (> 2 folds) ions. These compounds also exhibited promising *in vitro* inhibitory effects against Zn-induced A $\beta$  aggregation and oligomerization (EC<sub>50</sub> values < ~5  $\mu$ M).

### 8HQ-based compounds as multiple ions chelators

Coping with neurodegenerative diseases is challenging due to their multifactorial natures, in which several metal ions play roles in pathogenesis and progression of the diseases.<sup>49</sup> Accordingly, some of the newly designed hybrids were reported as multiple chelators for combating the AD (Figure 8).



**Figure 8.** 8HQ-based multiple ions chelators developed for anti-neurodegeneration

Multiple ions chelators capable of chelating Cu/Zn/Fe ions were developed (compounds **26-31**). 8HQ-arylhyazone compound (**26**) was reported to sequester Cu and Zn from A $\beta$  peptides.<sup>117</sup> The compound also showed promising activities in both *in vitro* and *in vivo* models of the PD.<sup>115</sup> Compound **26** acted as a metal chelator to inhibit Cu- $\alpha$  synuclein interaction and prevented intracellular  $\alpha$  synuclein oligomerization. *In vivo* studies also demonstrated its desirable safety and brain permeability.<sup>115</sup> 8HQ-propargylamine-donepezil hybrid (compound **27**) was reported as multifunctional compounds with antioxidant, cholinesterase inhibitor (IC<sub>50</sub> values: AChE = 29 nM and BuChE = 39 nM), and MAO inhibitor (IC<sub>50</sub>

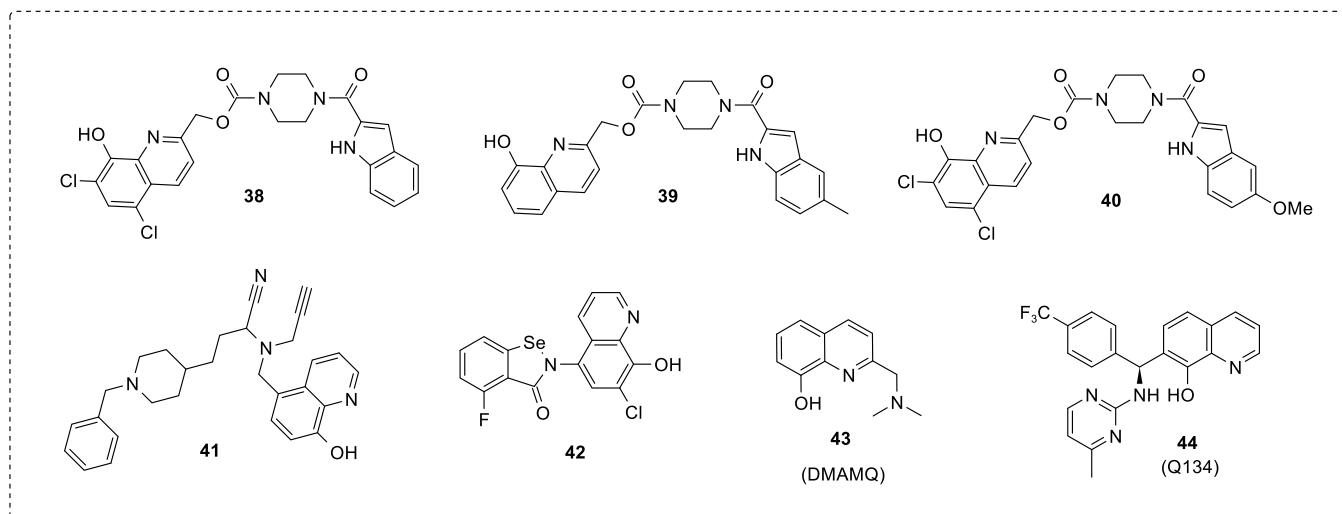
values: MAO-A = 10  $\mu$ M, MAO-B > 100  $\mu$ M).<sup>118</sup> Bis-8HQ compound (**28**) was reported to elicit promising improved properties when compared to the mono-8HQ.<sup>119</sup> The bis-8HQ performed better binding affinities to metal ions (i.e., Cu, Zn, and Fe) and exhibited better inhibitory effects for preventing metal ion-induced A $\beta$  aggregations as well as ROS production. However, it was found that 8HQ-trimer was less potent than the dimer in all aspects. CQ-donepezil hybrids (compounds **29-31**) were reported for their multiple therapeutic effects including Cu and Zn chelation, antioxidant, anti-A $\beta$  aggregation, and selective BuChE inhibition as well as preferable safety and high possibility to cross blood-brain-barrier.<sup>120</sup>

Many 8HQ-based bioconjugates with chelating ability toward multiple ions were designed (compounds **32-36**). 8HQ-biotin conjugates (**32-33**) and their metal (i.e., Mn<sup>2+</sup>, Co<sup>2+</sup>, Ni<sup>2+</sup>, Zn<sup>2+</sup>, and Cu<sup>2+</sup>) complexes were developed as antioxidant with improved gastrointestinal absorption ability.<sup>121</sup> 8HQ-glutathione conjugate (compound **34**) was reported for its neuroprotective potential.<sup>122</sup> The compound **34** can chelate Cu and Zn deposited in the A $\beta$  peptides and effectively protect the neuronal cells from oxidative-induced damage in the PD *in vitro* model. Pharmacokinetics *in vitro* study also suggested that the compound **34** performed good stability and brain penetrating ability. Similarly, 8HQ-lipoic acid (compound **35**) exhibited potent antioxidant activity and protective effect against oxidative-induced damages in both AD and PD *in vitro* dopaminergic cell line.<sup>123</sup>

System L is a system located within the endothelium of brain capillary, which is responsible for uptake of several amino acids and hydrophilic compounds/drugs into the brain.<sup>163</sup> An insertion of amino acids into bioactive molecule, therefore, could facilitate the selective targeting of the drug into the CNS. 8HQ-L-alanine (compound **36**) was developed as a selective brain-targeting antioxidant agent.<sup>164</sup> The compound was noted as a potent chelator of Fe as well as other metal ions (i.e., Cu and Zn). Although showing moderate affinity to Fe, the compound **36** is a potent antioxidant agent which was an effective inhibitor against Fe-induced lipid peroxidation (IC<sub>50</sub> = 12  $\mu$ M) comparable to that of the standard Fe chelator, desferal. The compound **36** also performed preferable neuroprotection in the PD *in vitro* model. It was suggested that the desirable selectivity of this compound was due to its water-soluble property, in which a specific carrier-mediated transporter is required for its uptake into the brain. In addition, 8HQ-neuropeptide conjugate (compound **37**) was designed as a peptidic chelator exhibiting radical scavenging and neuroprotective effects against oxidative-induced neuronal cell line and rat brain.<sup>125</sup>

### ***8HQ-based compounds exhibit beneficial effects against AD mainly via other mechanisms of action***

Besides taking actions *via* metal chelation, some 8HQ-based compounds were recently reported to benefit the AD *via* other mechanisms of action (Figure 9).



**Figure 9.** 8HQ-based compounds eliciting neuroprotective effects *via* other actions

A series of 8HQ-indole derivatives, containing piperazine linkage, were designed and reported as anti-A $\beta$  agents (compounds **38-40**).<sup>126</sup> These compounds inhibited both self-induced and metal induced A $\beta$  aggregations in the presence of Zn ion *in vitro*. Compound **40** was noted as the most promising one showing the most potent effects with 10-fold greater than that of the CQ. Molecular docking finding also suggested that the mode of action of these compounds could be *via* a competitive binding at the metal binding site of A $\beta$  (i.e., residue His13), and prevention of metal-A $\beta$  interaction.<sup>165</sup> Structure-activity relationship study also suggested the piperazine moiety as a crucial structural feature for the potent activity.<sup>126</sup>

Compound **41**, a donepezil-propargylamine-8HQ hybrid, was reported as a dual AChE/MAO inhibitor with metal chelating property.<sup>127</sup> The compound displayed inhibitory effects against subtypes of the enzymes (IC<sub>50</sub>: AChE = 1.8  $\mu$ M, BuChE = 1.6  $\mu$ M, MAO-A = 6.2  $\mu$ M, and MAO-B = 10.2  $\mu$ M) and showed lesser toxicity (at high dose) than the parent donepezil. The main action of the compound was suggested by molecular docking to be *via* direct interaction with the enzymes. For AChE, the compound **41** can interact with catalytic and peripheral sites simultaneously through its linker which suggested to promote the mix-type inhibitions toward subtypes of cholinesterase. For MAO, the quinoline moiety was noted as a crucial part for inhibition of both MAO subtypes, but with different site of binding. This quinoline moiety fitted in the substrate binding cavity for an inhibition of MAO-A, but occupied the entrance of active site cavity and prevented the binding of substrate of MAO-B. It was also revealed that the mode of inhibition toward MAO subtypes of the compound **41** is in an irreversible nature.

8HQ-ebesen (compound **42**) was reported with metal chelating, antioxidant, and anti-A $\beta$  aggregation properties.<sup>128</sup> The compound showed promising inhibitory effects against both self-induced and Cu-induced A $\beta$  aggregations as well as potentially disassembling the preformed aggregated A $\beta$ . Additionally, the compound **42** displayed superior properties for the ebesen-related properties such as H<sub>2</sub>O<sub>2</sub> scavenging and

glutathione peroxidase mimic activities. Preferable safety and pharmacokinetic properties of this compound were also observed from the *in vivo* model.

DMAMQ, 2-[(dimethylamino)methyl]-8-hydroxyquinoline (compound **43**), was reported as a potential neurorestorative compound. The treated adult murine neural stem cells (NSCs) showed an increase in neurite growth and proliferation along with an increase of intracellular ROS production.<sup>129</sup> The elevated intracellular ROS was suggested to be *via* an activation of the ROS signaling pathway mediated by nicotinamide adenine dinucleotide phosphate (NADPH) oxidase enzyme family as well as partly through the mimicking of ROS-initiated cell growth *via* an intrinsic ROS production by the compound **43** itself. However, the therapeutic concentration of the effect is narrow and needed to be further studied for suitable application in neurodegenerative diseases. Additionally, this proposed hypothesis is concurring with the mainstream strategy that suggests the reductions of ROS and metal ion-induced oxidative damages as beneficial effects.

Hypoxia is a condition noted as one of contributing factors in the pathogenesis of neurodegeneration (i.e., promoting A $\beta$  production and tau phosphorylation, inhibiting A $\beta$  clearance, and promoting neuronal cell death).<sup>166</sup> The hypoxia-inducible factors (HIFs) are transcription factors which modulate many protective cellular responses to cope with hypoxic condition. After translocated into the nucleus, the HIF1A could induce expressions of many hypoxic-related genes and these triggered genes produce responses which played roles in neuroprotection and neuronal cell survival.<sup>167</sup> The level of HIF1A protein is mainly maintained by its degradation and stabilization under normoxic/hypoxic conditions. Therefore, prevention of degradation and stabilization of these HIFs could be one of strategy for protecting the neuronal cells from hypoxic-induced damages.<sup>168</sup> Q134 (compound **44**) was reported for its cytoprotective effect *via* modulating HIF system by acting as a HIF1A protein stabilizer.<sup>130</sup> In this *in vitro* study, two enantiomers of Q134 (R and S) were studied and suggested that both enantiomers as well as its racemic showed comparable cytoprotective effect in a real time cytoprotection assay with IC<sub>50</sub> values in submolar ranges (Q134R = 180 nM, Q134S = 233 nM, racemic mixture = 198 nM).<sup>130</sup>

In overview, the recent reported compounds are mainly acted as Cu chelator, followed by Fe and Zn chelators, respectively. Most of the recent research focused on the development of multifunctional or multitarget compounds rather than the single-action ones. Additionally, there are some publications that demonstrated the interest on development of prochelators/prodrugs to improve the delivery into the target site and pharmacokinetic stability.

In addition to the newly synthesized compounds, our research groups had reported some different neuroprotection mechanisms of the known prototypes such as 8HQ, CQ, and NQ. Our group demonstrated that these three compounds elicit neuroprotective effect against high glucose-induced neurotoxicity in SH-SY5Y cells *via* calpain-dependent pathway with ranked potency as NQ > CQ > 8HQ.<sup>8</sup> Loss of calcium

homeostasis is noted as one of factors leading to neurodegeneration.<sup>169</sup> Calpain pathway is activated in the presence of intracellular calcium overload leading to the promotion of cell apoptosis. This study also demonstrated that the high glucose condition activated the calpain pathway by increasing expression of calpain and the pretreatment of 8HQ, NQ, and CQ showed the protection against neuronal apoptosis *via* decreasing the calpain expression.<sup>151</sup>

SIRT1 is a NAD<sup>+</sup>-dependent protein deacetylase recognized as one of therapeutic targets in neurodegeneration in which an enhancement of its expression could provide many beneficial effects for neuroprotection (i.e., decreasing ROS and oxidative damages and promoting cell survival). Activation of SIRT1 could also lead to increased expression of Forkhead transcription factors (FOXO), and subsequently promotes cellular antioxidant capacity as well as prevents cell apoptosis.<sup>170</sup> Another related work from our group had reported that NQ elicit neuroprotective effect against H<sub>2</sub>O<sub>2</sub>-induced neurotoxicity in SH-SY5Y cells *via* sirtuin 1 (SIRT1)-related mechanism.<sup>9</sup> It was found that NQ upregulated expressions of SIRT1 and FOXO3a, prevented apoptosis of the cells (*via* promoting the expression of antiapoptotic protein Bcl-2).<sup>9</sup>

## CONCLUSION

Metal ions play roles in processing and aggregation of A $\beta$  as well as oxidative damages of the neurons. As regard, many 8HQ-based compounds have been designed and investigated for their abilities to restore metal homeostasis in the brain to elicit aimed therapeutic actions (i.e., inhibiting production and aggregation of A $\beta$ , minimizing redox-induced oxidative neurotoxicity, and others as summarized in Table 2). From the recent review, it was revealed that most of the publications gain more attention toward the development of metal chelators (i.e., Cu, Zn, and Fe). However, it should be noted that clinical data and understanding about their possible effects caused by the alterations on redistributions of metal ions in the brain, toxicity from their pro-oxidant effects and excessive accumulation of ions in particular intracellular areas are still lacking. It was also noted that an area of developing 8HQ-metal complexes for anti-neurodegeneration is still in its infancy and has long journey to be explored. Several hybrid compounds also have drawn continual interest for discovering multifunctional and multitarget compounds to cope with multifactorial characters of the diseases. Drug delivery systems using the carriers (such as nanoparticles) were developed to enhance 8HQ-based neuroprotective compounds to reach the CNS target site and were reviewed elsewhere, which is beyond the scope of this article. In conclusion, this article demonstrates that 8HQ is an attractive pharmacophore for the development of disease-modifying agents for neurodegenerations. However, it should be noted that further studies are still necessary to gain more understanding on mechanisms of action, selectivity, drug profiles, and safety.

**Table 2.** Summarized 8HQ-based compounds as anti-neurodegenerative agents

	Amyloid targeting		Neuroprotective or Antioxidant	MAO inhibition	AChE or BuChE inhibition	Footnote
	A $\beta$ production	A $\beta$ aggregation				
8HQ	x	x	✓	x		
CQ	x	✓ b <sup>#,*</sup>	✓	x	x	
PBT2	x	✓ b <sup>#</sup>	✓	x	x	1
VK-28	x	x	✓	x	x	
M30	✓ b <sup>*</sup>	✓ b <sup>*</sup>	✓	✓	x	2
HLA-20	✓ b <sup>*</sup>	✓ b <sup>*</sup>	✓	✓	x	3
CQ-Se (1)	x	✓ b <sup>#</sup>	✓	x	x	4
Bis-8HQ (2)	x	✓ b <sup>#</sup>	x	x	x	
Quinoline- triazole (3)	x	✓ a,b <sup>#</sup>	x	x	x	5
8HQ-indole (4)	✓	✓	✓	x	x	6
NQ-selective BuChE inhibitor (5)	x	✓ a	✓	x	✓	7
8HQ-cinnamic acid (6)	x	✓ a,b <sup>#*</sup>	✓	x	x	
8HQ-resveratrol (7)	x	✓ a,b <sup>#</sup>	✓	x	x	8
8HQ-boric acid (8)	x	✓ b <sup>#</sup>	✓	x	x	
CQ-roflumilast hybrids (9)	x	✓ b <sup>#</sup>	✓	x	x	9
8HQ-piperidine (13)	x	x	✓	x	✓	
8HQ-tacrine (14)	x	x	✓	x	✓	
CQ- PF- 04447943 (15)	x	✓ b <sup>#</sup>	✓	x	x	10

CQ-moracin M (16)	x	✓ <sup>b#</sup>	✓	x	x	11
17 and 18	x	x	✓	x	x	
20 - 25	x	✓ <sup>b*</sup>	x	x	x	
8HQ- arylhydrazone (26)	x	✓ <sup>b</sup>	x	x	x	
8HQ- propargylamine- donepezil (27)	x	x	✓	✓	✓	
Bis-8HQ compound (28)	x	✓ <sup>b</sup>	✓	x	x	
CQ-donepezil hybrids (29-31)	x	✓ <sup>b</sup>	✓	x	✓	
8HQ-biotin (32- 33)	x	x	✓	x	x	12
8HQ-glutathione (34)	x	✓ <sup>b</sup>	✓	x	x	
8HQ-lipoic acid (35)	x	x	✓	x	x	13
8HQ-L-alanine (36)	x	x	✓	x	x	
8HQ- neuropeptide (37)	x	x	✓	x	x	
8HQ-indole (38- 40)	x	✓ <sup>a,b</sup>	x	x	x	
Donepezil- propargylamine- 8HQ hybrid (41)	x	x	x	✓	✓	
8HQ-epselen (42)	x	✓ <sup>a,b</sup>	✓	x	x	
DMAMQ (43)	x	x	x	x	x	14
Q134 (44)	x	x	x	x	x	15

\* = not be investigated / showed none of activity

-<sup>a</sup> Inhibit self-induced A $\beta$  aggregation, -<sup>b</sup> Inhibit metal ion-induced A $\beta$  aggregation

-<sup>b#</sup> Inhibit Cu-induced A $\beta$  aggregation, -<sup>b\*</sup> Inhibit Zn-induced A $\beta$  aggregation

**Footnote 1:** Decrease hyperphosphorylation and aggregation of tau protein.

**Footnote 2:** Non-selective MAO inhibitor / Neurorestorative (enhance neuronal differentiation)

**Footnote 3:** Selective MAO-B inhibitor

**Footnote 4:** Disassembling the preformed A $\beta$  aggregates

**Footnote 5:** Disassembling the preformed A $\beta$  aggregates action not *via* metal chelation, but *via* direct interaction with A $\beta$

**Footnote 6:** Decrease overall A $\beta$  deposition / Neurorestorative (enhance neuronal differentiation)

**Footnote 7:** Weak antioxidant

**Footnote 8:** Disassembling A $\beta$  fibrils formed by self- and Cu-induced aggregations

**Footnote 9:** PDE4 inhibitor

**Footnote 10:** PDE9 inhibitor

**Footnote 11:** PDE4D2 inhibitor / Anti-neuroinflammation

**Footnote 12:** Improve GI absorption

**Footnote 13:** Selective targeting to brain

**Footnote 14:** Selective targeting to brain promote neural stem cell proliferation and neurite growth

**Footnote 15:** Selective targeting to brain promote neural stem cell proliferation and neurite growth or cytoprotection via HIF system

## ACKNOWLEDGEMENTS

Veda Prachayasittikul (VP) is supported by Office of the Permanent Secretary, Ministry of Higher Education, Science, Research and Innovation, Research Grant for New Scholar (grant no. RGNS 64 – 167) and Mahidol University (Basic Research Fund: fiscal year 2022).

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