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REVIEW ARTICLE

Curcumin, Resveratrol and Cannabidiol as Natural Key Prototypes in Drug Design for Neuroprotective Agents

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Abstract: Nowadays, neurodegenerative diseases (NDs), such as Parkinson's disease (PD), Alzheimer's disease (AD), Huntington's disease (HD), and amyotrophic lateral sclerosis (ALS), represent a great challenge in different scientific fields, such as neuropharmacology, medicinal chemistry, molecular biology and medicine, as all these pathologies remain incurable, with high socio-economic impacts and high costs for governmental health services. Due to their severity and multifactorial pathophysiological complexity, the available approved drugs for clinic have not yet shown adequate effectiveness and exhibited very restricted options in the therapeutic arsenal; this highlights the need for continued drug discovery efforts in the academia and industry. In this context, natural products, such as curcumin (**1**), resveratrol (**2**) and cannabidiol (CBD, **3**) have been recognized as important sources, with promising chemical entities, prototype models and starting materials for medicinal organic chemistry, as their molecular architecture, multifunctional properties and single chemical diversity could facilitate the discovery, optimization and development of innovative drug candidates with improved pharmacodynamics and pharmacokinetics compared to the known drugs and, perhaps, provide a chance for discovering novel effective drugs to combat NDs. In this review, we report the most recent efforts of medicinal chemists worldwide devoted to the exploration of curcumin (**1**), resveratrol (**2**) and cannabidiol (CBD, **3**) as starting materials or privileged scaffolds in the design of multi-target directed ligands (MTDLs) with potential therapeutic properties against NDs, which have been published in the scientific literature during the last 10 years of research and are available in PubMed, SCOPUS and Web of Science databases.

Keywords: Neuroprotection, neurodegenerative diseases, curcumin, resveratrol, cannabidiol, rational drug design, molecular hybridization.

1. INTRODUCTION

Neurodegenerative diseases (NDs) are one of the biggest challenges for the current research in the fields of medicinal chemistry, physiology, molecular biology and medicinal practices [1-4]. NDs are a group of incurable, progressive and disabling severe neurological pathologies, which include Alzheimer's disease (AD), Parkinson's disease (PD, Huntington's disease (HD) and amyotrophic lateral sclerosis (ALS) as the most common prevalent forms. In 2017, 50 million people were estimated to be suffering from some type of ND, and considering the increase in the rate of elderly population worldwide, the number of individuals with dementia could reach 131.5 million by 2050 [5]. Currently, AD, PD, ALS and HD are all recognized as chronic neuroinflammatory diseases, characterized by a complex mosaic of concomitant interconnected imbalances in physiological and biochemical levels in brain functionalities [6-9]. Considering that ageing is a natural process, the higher susceptibility of certain individuals to develop some kind of dementia reveals an individual neuronal cell's vulnerability. This concept explains why all regions of the peripheral (PNS) and central nervous systems (CNS) are affected by ageing, with a normal time-dependent decline in memory, motor coordination and sensory, but in NDs, only specific neurons and brain regions become degenerated [8, 10]. In fact, it is well established that the probability of a person to develop some kind of dementia dramatically increases with time, especially for AD and PD over the age of 65.

Besides ageing, all these NDs are also related to genetic, epigenetic and environmental factors that determine changes in the neuronal physiology due to abnormal protein

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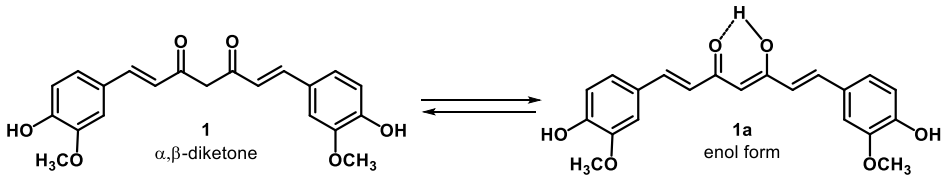

Fig. (1). Keto-enol equilibrium of curcumin in the physiological environment.

processing, oxidative stress (OS), neuroinflammation, mitochondrial dysfunction, and lower energy supply [9-15]. Recently, some studies have pointed out transcellular hormesis mediated by reactive oxygen species (ROS) as an important player in response to OS, leading to stimulation of angiogenesis in the brain [16, 17]. However, considering that specific molecular mechanisms underlying mitochondrial production of ROS remain poorly understood, emerging evidence suggests an important role of certain transcriptional regulators [18, 19]. In the last decades, a number of neurobiological evidences demonstrate how specific neurons in specific brain regions are more capable of responding to ageing compared to other cells in the body. In this way, the most recent findings indicate that different populations of neuronal cells, in different individuals, are distinctively vulnerable to the effects of overproduction of reactive radical species related to an increased OS, with energy supply perturbation, agglomeration and deposition of damaged proteins [8, 10].

In addition to abnormal protein processing, which is a hallmark of AD, PD and HD, related to Aβ, α-synuclein and huntingtin, respectively, neuroinflammation, neuronal vulnerability and OS seem to be common pathological factors related to the onset and severity of all these NDs. Despite that a multitude of physiological changes are nowadays recognized as the determinant of the complex pathogenesis of NDs, the current therapeutic arsenal is restricted to drugs with selective mechanisms of action, modulating specifically single molecular targets, such as acetylcholinesterase (AChE) inhibitors for AD and dopamine supply for PD; this could be a reasonable explanation for the lack of efficacy in the clinical management of such NDs [20-23]. In this regard, new strategies of drug design that focus on multifunctional ligands capable of activating or increasing mechanisms related to neuroprotection, increasing neurogenesis and/or modulating oxidative or inflammatory neuronal damage, are expected to offer additional benefits and a real potential for more efficient disease-modifying drugs in comparison to the current therapeutics used for NDs. For such a goal, many research groups in the academic sector and in the pharma industry have explored a number of bioactive natural products as molecular prototypes for the design of novel molecular hybrid scaffolds with selective affinity for multiple targets, preferably in different biochemical cascades [23-30].

In this scenario, curcumin (**1,** Fig. **1**), resveratrol (**2,** Fig. **2**) and cannabidiol (**3**, Fig. **3**) have grabbed special attention, due to their antioxidant, anti-inflammatory, metal-chelation and other neuroprotective properties, to be used as molecular prototypes in the design and development of drug candidates expected to represent radical innovation in the development of a more efficient therapy for NDs.

2. CURCUMIN, RESVERATROL AND CANNABIDIOL: BIOLOGICAL AND CHEMICAL ASPECTS

2.1. Curcumin

Curcumin (**1**), a natural α,β-unsaturated diketone, isolated from the rhizomes of *Curcuma longa*, is a common Indian medicinal plant, which has been widely investigated in clinic due to its different biological activities [31, 32]. Literature data demonstrate neuroprotective, antioxidant and anti-inflammatory properties of curcumin, and its ability to modulate different signaling pathways involved in the development and severity of NDs [33-36]. However, curcumin could be easily metabolized and shows low bioavailability due to its diketone structure [37]. In the physiological environment, compound **1** exists under a keto-enol equilibrium (Fig. **1**), being stabilized by an intramolecular hydrogen interaction when in its enol form (**1a**), whereas its ketone form involves intermolecular H-interaction acceptor sites at the carbonyl oxygen atoms [36].

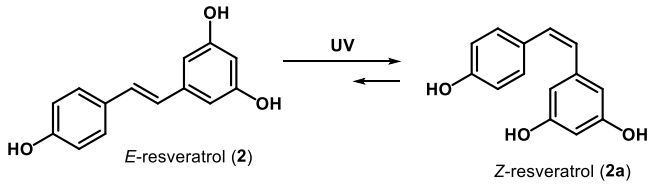

Fig. (2). Structure of resveratrol (2) and formation of the *Z* isomer (2a) by the action of UV light.

Literature suggests that the ferulic acid-like scaffold of curcumin and its derivatives, with two 3-methoxy-4-hydroxy aromatic subunits connected by an α,β-unsaturated diketone system **1** (Fig. **3**), is of particular importance for its biological and chemical properties [38]. In addition to the high antioxidant property of **1**, attributed to the presence of the 3-methoxy-4-hydroxy substituted benzene ring pattern [39], many studies involving cellular and animal models have shown that the diketone and 3,4-substituted aromatic ring features play an important in metal chelation and the consequent inhibition of ROS formation and nuclear factor Kappa B (NF-κB) [38]. On the other hand, computational and biological findings suggest that the α,β-unsaturated diketone moiety, a chalcone-like subunit, is a pharmacophore site for the inductive activity of Nuclear factor erythroid 2-related factor 2 (Nrf2), which translocates to the nucleus to combine with one of the small Maf proteins (MAFF, MAFG, MAFK) and bind to the antioxidant response element (ARE) in order to promote the transcription of antioxidant genes and, in turn, the production of glutathione (GSH) and other antioxidant endogen substances. This ability for Nrf2 activation is attributed to the presence of a Michael acceptor site at the un-

saturated β-carbon, which could be a phosphorylation site or an electrophilic site for a nucleophilic attack by a cysteine residue from keap1 protein (Fig. **3**) [40].

Curcumin (**1**) has been described in the literature as a compound capable to act on different molecular targets and, in turn, modulate diverse aspects of NDs pathogenesis [41], including some specific targets related to OS. In general, the most severe stages of NDs are associated with an exacerbated OS condition, and many studies have proven **1** to be capable of triggering a potent antioxidant effect in *Drosophila*, suggesting a probable mediation by Nrf2 activation [42]. In spite of the antioxidant effect, curcumin has been reported for its metal chelation ability, especially for copper and iron species normally found in high concentrations in degenerated neurons [38], and anti-neuroinflammatory properties in LTA-stimulated BV-2 microglial cells through inhibition of NF-κβ and p38 MAPK activation [43]. In addition to the beneficial effects on these three common molecular targets related to almost all NDs, curcumin has also shown to act on some specific pathogenic targets of AD and PD. In the case of AD, **1** showed to inhibit the formation of Aβ protein tangles and to suppress genetic markers responsible for the synthesis of AchE [33, 35, 44]. A study involving both nanoencapsuled and free curcumin preparations showed strong evidences of *in vivo* neuroprotection. The injection of $A\beta_{1-42}$ increased the release of pro-inflammatory cytokines and decreased levels of brain-derived neurotrophic factor (BDNF) and other neurotrophins, which are released by glial cells and assist in neuronal survival. On the other hand, treatment with curcumin rescued BDNF levels in the hippocampus, which may be related to memory improvement. In addition, activation of the BDNF pathway is thought to be related to the decrease in Akt (also known as protein kinase β) phosphorylation and inhibition of GSK-3β, which culminates in decreasing the hyperphosphorylation of tau protein [45]. In PD, curcumin showed to prevent Lewy bodies formation by the inhibition of gene expression, which activates the production of α-synuclein as well as its aggregation, and also facilitates an increase in dopamine levels due to a neuroprotective effect on dopaminergic neurons exposed to OS [27, 46, 47]. Conversely, curcumin has limited application in the clinic due to its low absorption rate and tissue distribution, rapid metabolization and, in turn, low half-life [48, 49]. When taken orally, the absorption of **1** is very slow as a result of poor gastrointestinal absorption and a first-passage metabolism effect, leading to a drastic decrease in its concentration in blood and limited therapeutical uses [50, 51].

2.2. Resveratrol

Resveratrol (**2**) is a natural phenolic compound, isolated for the first time in 1939 by Takaoka and co-workers from the roots of *Hellebore* species. It is a very abundant metabolite in red wine, red grapes and blueberries, but it is also present in peanut, pine, and other seeds and fruits. In the literature, there are a number of studies and strong evidences that support the cytoprotective activity of **2** in the heart, metabolic disorders and NDs [52]. During the last years, many other biological properties of **2** and its derivatives have been reported, including anti-inflammatory, antioxidant and anti-protein aggregation [53, 54]. The singular biological properties of **2** have been mainly attributed to the *E* configuration at the exocyclic unsaturation and the presence of a hydroxyl group attached to the 4' position of one of the aromatic rings (Fig. **3**). In fact, the resonance hybrids of resveratrol are responsible for a better stabilization of an oxygen radical formed at the 4'-position than at the 3 or 5 positions in the other benzene ring (Fig. **3**). In addition, compound **2** could suffer isomerization under UV light action, but the *Z* isomer (**2a**) lacks most of the biological properties observed for **2** [55-58].

Recently, resveratrol has been described as a very versatile molecule in the treatment of NDs, being capable to act in different pathophysiological aspects [59, 60]. In the 90's, one of the first reported biological effects of **2** was related to its potent antioxidant activity, associated with the inhibition of the monoamine oxidase A (MAO-A) and metal chelation, especially for iron [61, 62]. During the last decade, a deep knowledge has been accumulated regarding the antioxidant and other biological properties of **2**, including improvement in the mitochondria-dependent redox function of neuronal cells by inducing the production of mitochondrial antioxidant enzymes [54, 63]. To date, the known beneficial effects of polyphenols on brain functions are thought to be linked to increased blood flow in the brain [64]. Even though a large amount of data evidences the positive effects of polyphenols on brain and vascular function, the mechanisms of action underlying their beneficial effects appear to be complex and are not yet fully understood [65, 66]. In fact, polyphenols have been found to exert neuroprotective effects in NDs [67], which is strongly evidenced by experimental results supporting their effects on the increased neuronal survival in PC121 cells [67]. In particular, it has been shown that resveratrol increases the release of BDNF and GDNF in cultures of dopaminergic neurons enriched with astroglia in a concentration and time-dependent mode [68]. Neurotrophins play an important role in neuronal development, maintenance, repair, and survival, being of great importance for the development of therapeutic strategies for DNs, since BDNF levels tend to decrease with ageing [67]. In relation to proteotoxicity, despite resveratrol not being capable to prevent the formation of insoluble protein aggregates, it induces the solubilization of Aβ aggregates in neurons. In addition, compound **2** was found capable of promoting protein clearance by selective activation of proteasome related to degradation of Aβ peptide [69]. Recent studies evidence that resveratrol could act synergistically with small concentrations of L-dopa in *in vivo* PD models. Experiments with transgenic mice revealed that, besides anti-inflammatory and neuroprotective effects, the co-administration of resveratrol and L-dopa (5 mg/Kg) resulted in an equivalent response of a single dose of 8mg/Kg of L-dopa [70].

However, in spite of its promising biological and pharmacological results, resveratrol shows low *in vivo* bioavailability, limiting the access to target tissues. Despite its quick absorption, only 30% of the orally administered dose reaches the blood circulation, as most of the dose is metabolized by conjugation with sulfates and glucuronic acid or is metabolized by gut microbiota and is promptly excreted [71, 72].

2.3. Cannabidiol (CBD)

Currently, the endocannabinoid system (ECS), which is constituted by the specific cannabinoid receptors 1 (CB1) and 2 (CB2), has been reported to play an important role in

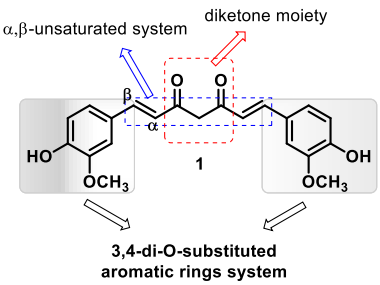

Fig. (3). Functional and pharmacophoric sites of curcumin (1).

the modulation of different targets related to the pathogenesis of several neurodegenerative and neuro-inflammatory illnesses [73-77]. The activation of these cannabinoid receptors involves a variety of enzymes, transporters and other proteins related to the synthesis, mobilization and uptake of many endogenous micromolecules [78-80]. Depending on the brain region in which the endocannabinoids (*e.g.*, AEA or arachidonoylglycerol (AG)) are produced, different physiological effects are generated, including body temperature and appetite regulation (hypothalamus), reduction of pain threshold (cortex) and modulation of cognitive processes (basal ganglia), with all these events being mediated by the action of agonists and antagonists on CB1 and CB2 receptors [96, 97]. Besides, ECS is a neuromodulatory system, being responsible for a retrograde release of neurotransmitters, neuronal excitotoxicity control, and regulation of neuronal plasticity [83]. Thus, ECS is involved in the regulation of fundamental processes in the CNS and PNS [84], such as oxidative process [85], and is thought to be involved in the pathogenesis of NDs associated with oxidative damage and neuroinflammation, indicating a close relationship between an imbalance in ECS and PD and AD [86].

Cannabidiol (CBD, **3**, Fig. **4**) is a non-psychotomimetic phytocannabinoid, produced as one of the main secondary metabolites in *C. sativa* [87, 88]. Depending on cultivation conditions, CBD could reach up to 40% of crude plant extract [76, 89], when it occurs as only the (-)-cannabidiol isomer [88]. The concentrations of the main constituent tetrahydrocannabinol (THC, **4**, Fig. **4**) and **3** in *Cannabis* can vary substantially depending on the plant variety, clone plants, weather, soil type, pathogens and other environmental and management factors [90].

Differently from THC (**4**), CBD (**3**) is not a psychotropic agent [91], which could be explained by conformational differences between both compounds leading to different interaction modes with cannabinoid receptors [92]. CBD shows a low affinity for CB1 and CB2, acting as a negative non-competitive allosteric modulator of CB1 [80, 92, 93]. In addition, CBD is capable of reducing the efficacy and potency of THC (**4**), blocking its psychotic effects and reducing anxiety caused by high doses of **4**, without significant adverse effects [93-95]. Thus, compound **3** does not cause the known tetrad cannabinoid effects [88, 96], responsible for the psychotomimetic, anxiolytic and dependency properties of THC, and shows an excellent profile of security and tolerance in the treatment of diverse illnesses related to CNS [77, 91]. In fact, CBD has shown an affinity of 74,47% for CB2 in comparison to CB1 [97], and has been characterized as an inverse agonist [98], which could contribute to its anti-inflammatory effects [86, 99, 100] besides its anxiolytic and anti-psychotic properties [89, 101]. On the other hand, some other studies have evidenced CBD as a negative allosteric modulator, *i.e.*, it could reduce the affinity or efficacy of an orthosteric ligand [102]. As a liposoluble substance, CBD shows low oral bioavailability (13-19%), but it quickly overcomes the blood-brain barrier (BBB) when used as an injectable [100, 103, 104].

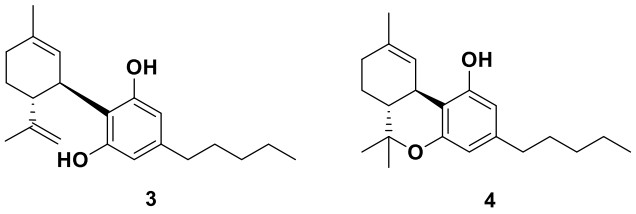

Fig. (4). Chemical structures of cannabidiol (CBD, **3**) and THC (**4**), the main bioactive phytocannabinoids from *Cannabis sativa*.

The mechanism of action of CBD (**3**) remains unclear [105], and one hypothesis is that CBD (**3**) does not have specific receptors [106, 107] but it is capable of modulating concomitantly more than one receptor, and exerts an agonist effect on transient receptor potential ion channels (TRPV1, TRPV2, TRPA1 e TRPM8) [108, 109], which forces some authors to describe CBD (**3**) as a potential multitarget drug candidate [110, 111]. Stimulation of TRPV1 by CBD, leading to inhibition of serotonin reuptake and anandamide (AEA) hydrolysis [106, 112], in addition to the allosteric modulation of serotoninergic receptor (5-HT_{1A}), could be also a plausive explanation related to the antipsychotic [113], antidepressive and anxiolytic effects observed in animal models [114]. These findings strongly suggest CBD (**3**) to play an important role in the neurobiology of depression and in emotional regulation and, in turn, could be an interesting molecular model for the design of new antidepressive drugs [115]. In other studies, CBD has also been shown to be capable of inhibiting glutamate release, suggesting potential anticonvulsant and neuroprotective effects [72, 73]. On the other hand, compound **3** has been studied for its contribution to anti-inflammatory mechanisms related to the decrease in inflammatory gene expression due to activation of peroxisome proliferator-activated receptors gamma (PPARγ), which are nuclear hormone receptors associated with inflammation, cellular proliferation and differentiation, with increased levels in some pathologies, such as AD [53, 63, 64, 72, 73]. The activation of adenosine receptor (A_{2A}) also leads to a decrease in inflammatory response, reducing immune cells' proliferation, production of pro-inflammatory

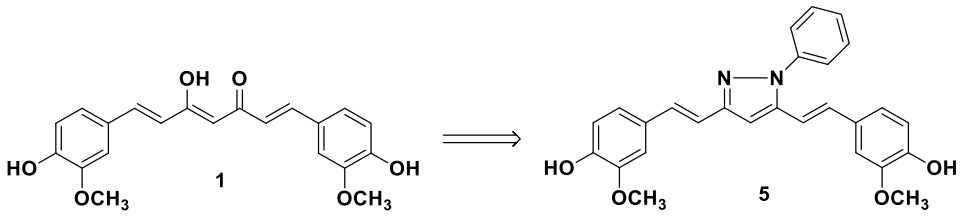

Fig. (5). Chemical structure of curcumin-based pyrazole derivative **5** with remarkable anti-inflammatory properties.

cytokines and cytotoxicity [116], in addition to the inhibition of synaptic reuptake of noradrenalin, GABA, adenosine and dopamine, and stimulation of glycine receptors, α3 and α1 [117, 118]. Recent studies show that the activation of each receptor is dependent on the CBD concentration, resulting in blockade/inhibition or increased activity of certain receptors, suggesting that the dose is a crucial factor in the activity and potential clinical use. These findings could explain, at least in part, the different CBD effects due to the possibility of a multiple target-based mechanism of action [61, 75].

CBD (**3**) also exhibits higher antioxidant activity compared to α-tocopherol and ascorbic acid, and neuroprotective effects that increase cell viability and synaptic plasticity [72, 38]. Recent data from the literature highlight other beneficial effects of CBD, including anticonvulsant, antiemetic, anxiolytic, antidepressive and anticancer properties, with low toxicity and high tolerability in humans and other animal species [119-123]. These wide range of biological effects of **3** reinforce its potential importance in the development of novel alternatives for the treatment of neurological and neuroinflammatory disorders, such as epilepsy, schizophrenia, oxidative lesions, and anxiety [39, 49, 61, 62, 76-78].

3. CURCUMIN DERIVATIVES AND ANALOGUES

The structure of curcumin (**1**) was used as a prototype model by Akaishi and Abe in the development of a pyrazole derivative (**5,** Fig. **5**), designed as a potential ligand able to trigger a microglia-mediated inflammatory response in AD. Microglia are immune cells in CNS, responsible for homeostasis regulation by releasing many pro-inflammatory cytokines and mediators. Microglia could be activated by lipopolysaccharide (LPS) *in vitro* and *in vivo*, leading to an increase in inducible NO synthase (iNOS) expression and, in turn, in the production of NOs, which is related to the development of many NDs [124, 125]. Compound **5** was evaluated for its ability to suppress the LPS-induced nitric oxide (NO) production and expression of iNOS, showing a better activity then curcumin at 10 μM. In addition, compound **5** also showed a hydroxyl radical (OH·) scavenging activity comparable to that of curcumin [126].

Also focused on the search for innovative drug candidates, Bisceglia and co-workers developed a small set of curcumin analogues (**6a**, **6b**, **7a** and **7b**, Fig. **6**) aiming to address multiple factors affecting AD, including the inhibition of Aβ oligomerization, antioxidant and anti-inflammatory activities, since the formation of Aβ aggregates in the brain is one of the AD hallmarks, leading to microglia and astrocyte activation, thereby contributing to neuroinflammation and OS. For such, a prenyloxy function was introduced as a substituent in one or both curcumin aryl subunits. In addition, structure simplification was carried out on the central keto-enolic linker in compounds **6a** and **6b**, modified for a conjugated dienone functionality in **7a** and **7b** derivatives. Biological evaluation revealed derivative **6a** as the most promising ligand, showing greater effectiveness in reducing the formation of Aβ aggregates and suppression of pro-inflammatory cytokines, with low toxicity. In addition, compound **6a** showed significant antioxidant activity by induction of Nrf2 nuclear translocation [127].

Memoquin (**8**, Fig. **7**) is a quinone-bearing polyamine with multifunctional properties; it is under preclinical investigation as an anti-AD drug candidate [128]. Considering the singular pharmacologic profile of **8**, Bolognesi and co-workers designed a new set of memoquin analogues as potential optimized multitarget-directed ligands (MTDLs). In their goal, the authors planned diverse modifications in the original memoquin scaffold, keeping intact the 2,5-diaminobenzoquinone subunit for ensuring the capacity of modulating protein-protein interactions. Biological evaluation revealed that the curcumin-memoquin hybrid **9** (Fig. **3**) did not affect cell viability and showed the best protective effect against $A\beta_{1\text{-}42}$-induced neurotoxicity in neuroblastoma human SH-SY5Y cells, inhibiting approximately 80% of neuronal damage at 10 μM, similarly to the parent prototype **8**. Furthermore, compound **9** showed a significant selective cholinesterase inhibition with IC_{50} values of 0.198 and 8.24 μM for AChE and butyrylcholinesterase (BuChE), respectively [128]. It is important to note that inhibition of AChE and BuChE (from animal sources or recombinant from human serum) is the most common method in the literature for the evaluation of new bioactive compounds against AD. These enzymes are responsible for the degradation of ACh into the synaptic cleft and, during the progress of the disease, its concentration is reduced, leading to a cholinergic deficit [129, 130].

Considering the multifactoriality associated with AD pathophysiology, Chojnacki and co-workers designed a new series of multifunctional compounds merging the structures of curcumin (**1**) and diosgenin (**10,** Fig. **8**), which have been linked by different triazole-amide spacers. Among all compounds tested in cellular models, derivatives **11** and **12** stood out as the most promising ligands, showing significant inhibition of Aβ-induced cellular death and OS using MC65 cell cultures, that is an AD model involving both OS and Aβ-induced damage. Additionally, compounds **11** and **12** showed strong neuroprotective ability, rescuing cellular viability up to > 80% with EC_{50} values of 231.7 and 111.7 nM, respectively, and attenuating ROS levels. Furthermore, both compounds showed inhibitory effects on the process involving direct interaction with Aβ oligomerization with IC_{50} values of 4.79 and 10.85 μM, respectively [131].

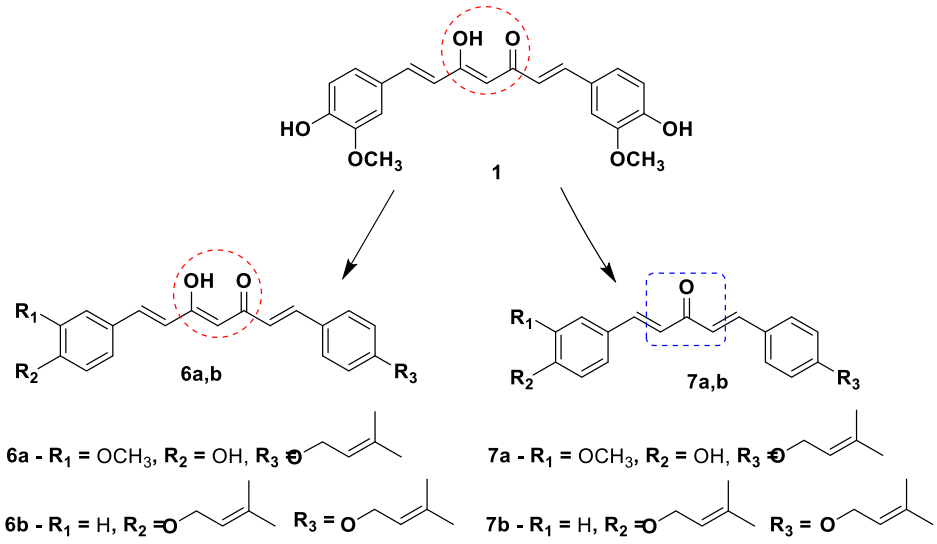

Fig. (6). Chemical structures of curcumin-prenyloxy analogues **6a**, **6b**, **7a** and **7b** with anti-Aβ-aggregation and anti-inflammatory properties.

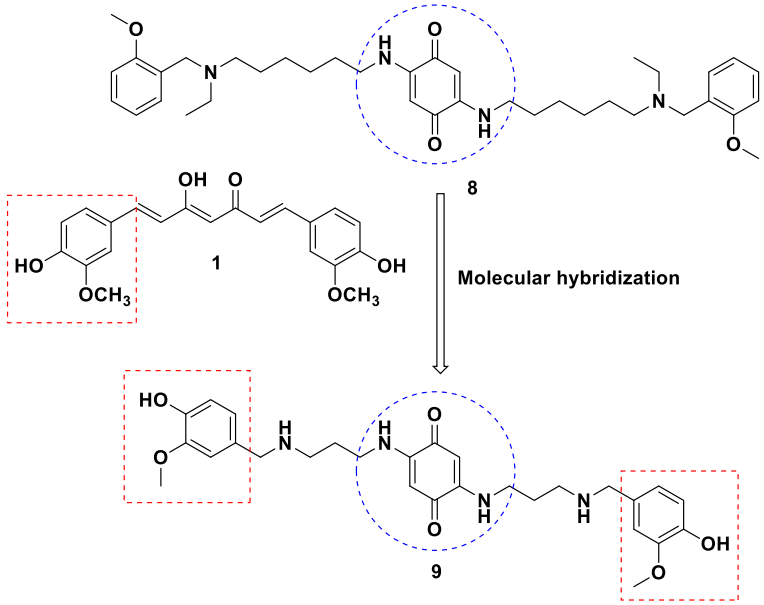

Fig. (7). Chemical structure of the memoquin-curcumin hybrid derivative **9** with promising multifunctional properties against AD.

Melatonin (**13,** Fig. **9**) is a well-known bioactive compound capable of modulating an immune response and several other physiologic functions, with free radical scavenging ability. Taking these properties into account, Chojnacki and co-workers used **13** and curcumin (**1**) as scaffold models in the design of a novel set of hybrid compounds suitable to act as antioxidant and neuroprotective agents. Structurally, the new hybrid compounds were planned by keeping phenolic group and β-diketone moiety from prototype **1** and 5-methoxy and acetamide functionalities from **13**, combined by an amide linkage. *In vitro* pharmacological screening using MC65 cells highlighted compound **14** for its potent nanomolar neuroprotective and antioxidant activities, with EC_{50} value of 27.60 nM and IC_{50} value of 68 nM, respectively. The authors speculate that these strong biological effects might be due to its interference in interactions of Aβ oligomers within the mitochondria of MC65 cell. Furthermore, compound **14** was able to permeate BBB and deliver a sufficient amount of the ligand in brain tissue after oral administration [132].

In another work, Di Martino and co-workers synthesized a small library of curcumin analogues, introducing different moieties on the side aryl portions of the main scaffold of **1**. By this approach, the authors aimed to obtain novel curcumin-based derivatives capable of inhibiting β-secretase (BACE-1) and glycogen synthase kinase-3β (GSK-3β), acting on the Aβ and tau protein cascades. Biological evaluation led to the identification of **15** and **16** (Fig. **10**) as the most promising compounds, showing them to be well-balanced low-micromolar inhibitors of both enzymes with IC_{50} values of 0.97 μM and 2.28 μM for BACE-1 and IC_{50} values of 0.90 μM and 2.78 μM for GSK-3β, respectively. Furthermore, both compounds showed antioxidant effects due to induction of NADPH: quinone oxidoreductase 1 (NQO1) and good BBB permeability evidenced by PAMPA assay,

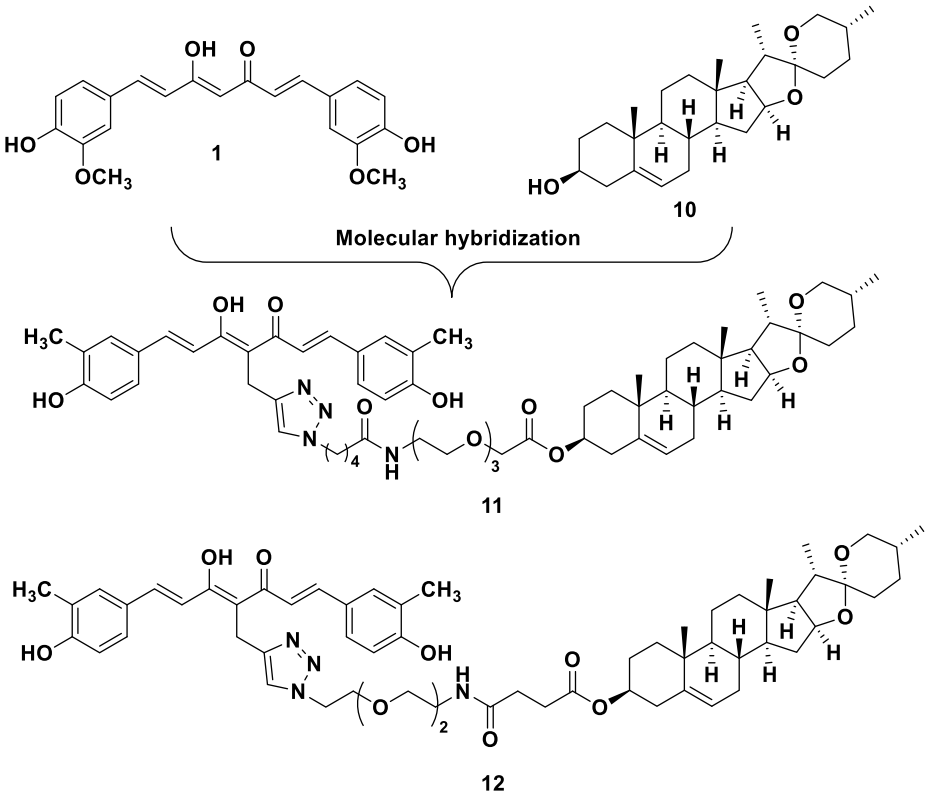

Fig. (8). Multifunctional bioactive curcumin-diosgenin hybrid compounds **11** and **12** with remarkable neuroprotective properties.

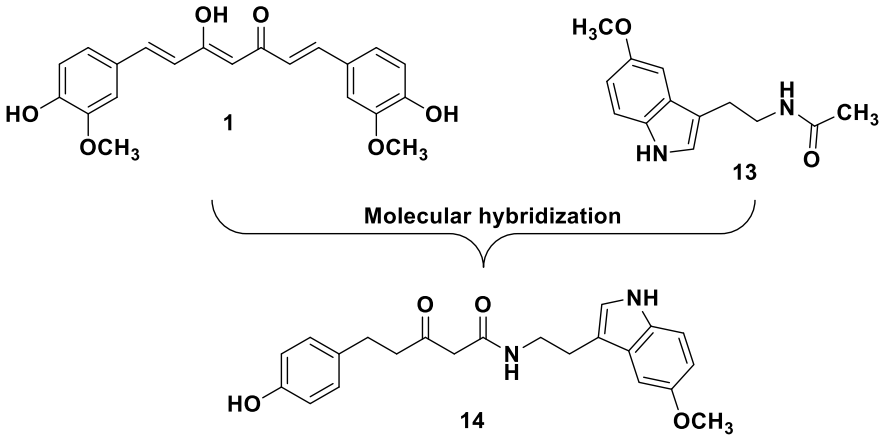

Fig. (9). Design of curcumin-melatonin hybrid amide **14** with nanomolar potency for neuroprotection in MC65 cells.

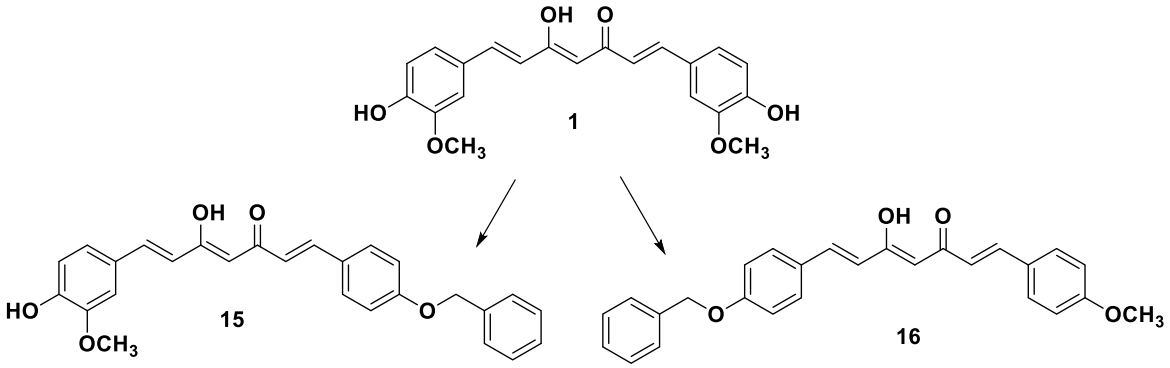

Fig. (10). Design of curcumin analogues **15** and **16** with BACE-1 and GSK-3β inhibitory properties.

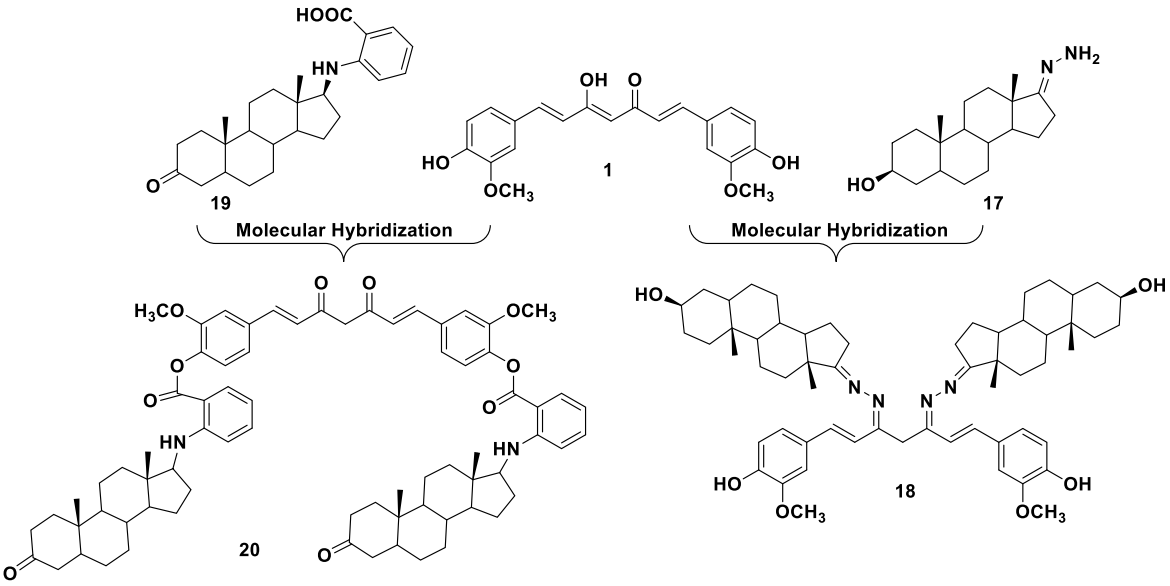

Fig. (11). Design of steroidal-curcumin hybrid derivatives with antioxidant and anti-apoptotic properties.

with compound **15** showing additional moderate ROS scavenging activity at 10 μM [133].

The combination of steroidal fragments ranging from prototypes **17** and **19** to the structure of curcumin (**1**) was adopted by Elmegeed and co-workers as a designing approach to generate a series of novel steroidal-curcumin derivatives **18** and **20** (Fig. **11**) with potential multifunctional profile of action. In addition, a series of hybrid phenylpyrazole-curcumin sulfonamides were planned by using pyrazole-curcumin derivative **21** and the sulfonamide **22** (Fig. **12**) as bioactive prototypes. Biological evaluation revealed compounds **18, 20** and **23** as the most promising ligands, being capable for *in vivo* inhibition of AChE in AD-induced rats. Compounds **20** and **23** were responsible for a moderate decrease of 15.19 and 17.45% in AChE activity, respectively. Additionally, all three compounds **18, 20** and **23** showed a significant increase in glutathione (GSH) level (58.62%; 86.20% and 75.86%, respectively) and in brain BCL2 level (32.85%, 87.5% and 76.42%), besides decreasing 8-OHG levels (21.18%, 40.83% and 31.74%, respectively). Administration of compounds **20** and **23** also resulted in a significant decrease in caspase-3 levels (19.19 and 16.16%, respectively) in the brain and, particularly, compound **20** was able to increase urinary paraoxonase activity by 38.12% and decrease brain P53 levels, demonstrating to be a potential drug candidate for further investigation against NDs [134].

Exploring the biological properties of glutamic acid, Harish and co-workers designed a set of curcumin ester derivatives, aiming to target OS related to NDs, such as AD and PD. In this work, three new glutamic acid-curcumin hybrids were evaluated for protection against GSH depletion mediated by OS, leading to identification of compound **24** (Fig. **13**) as the most promising ligand. Biological evaluation was based on the BSO-N27 model, along with N27 cell line and BSO (buthionine sulfoximine), to mimic PD-related GSH depletion. In this model, compound **24** showed an increasing effect of ~ 64% in the total GSH level, with 83% pre-treatment restoration at 0.5 μM and 136% on post-treatment at 0.5 μM, compared to control group (BSO alone at 1.5 μM). Furthermore, **24** reduced lipid peroxidation up to 50% on pre-treatment and 90% on post-treatment [135].

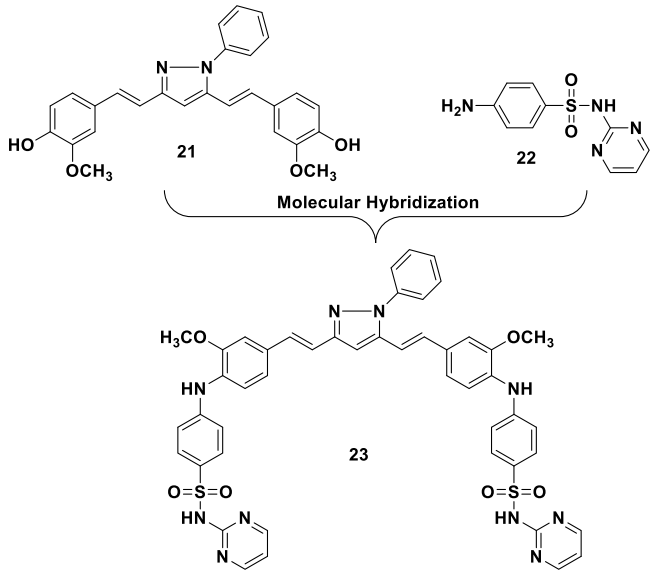

Fig. (12). Design of phenylpyrazole-curcumin sulfonamide derivatives with antioxidant and anti-apoptotic properties.

Shi and co-workers investigated the neuroprotective effects of two mono-ketone curcumin analogues **25a** and **25b** (Fig. **14**) on oxygen–glucose deprivation and re-oxygenation (OGD/R)-induced injury in cortical neurons, which are widely accepted *in vitro* models for ischemic reperfusion. Their results evidenced that derivative **25b** increased resistance of cortical neurons to OGD/R by decreasing autophagy and cell apoptosis. Notably, this effect was blocked by the mTOR inhibitor rapamycin, which is suggestive that the neuroprotective effect arises from an mTOR-dependent mechanism. Moreover, compound **25a**, which shows a very similar structure to **25b** , was able to promote neurogenesis in mouse hippocampal dentate gyrus region after intraperitoneal administration, suggesting an adequate BBB permeability [136].

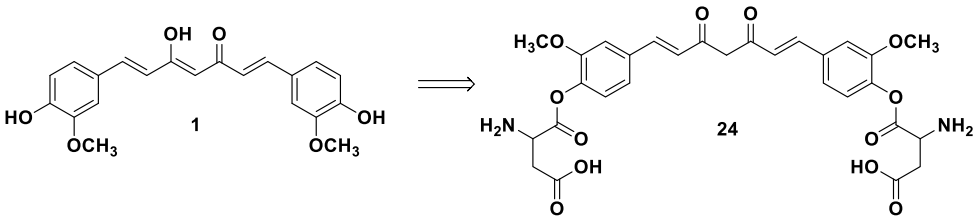

Fig. (13). Chemical structure of the new glutamic acid-curcumin hybrid **24** with remarkable effect on GSH increasing levels under OS conditions.

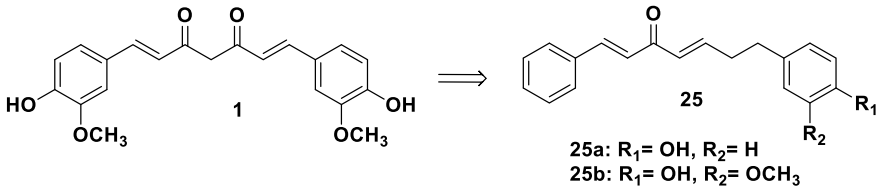

Fig. (14). Chemical structures of the mono-ketone curcumin analogues **25a** and **25b**.

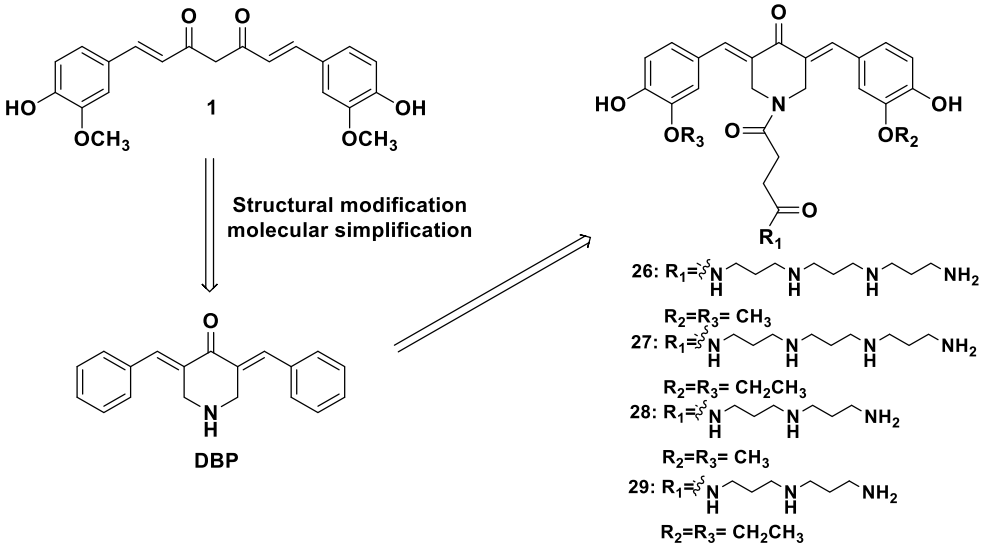

Fig. (15). Design strategy for polyamine-like DBP derivatives **26-29** with remarkable antioxidant properties.

Taking the structure of curcumin (1) as a model of antioxidant, anti-inflammatory, neuroprotective and radical scavenger chemical entity, Simoni and co-workers explored a cascade of structural modifications leading to simplified 3,5-dibenzylidenepiperidin-4-one (DBP) scaffolds, with significant potential antioxidant properties and less pharmacokinetic restrictions compared to **1**. Aiming to target mitochondrial dysfunction related to NDs, the authors designed a series of polyamine-based derivatives conjugated to *N*-spermine and nor-spermidine substituted DBPs (**26-29**, Fig. **15**). These compounds were firstly evaluated in bovine heart mitochondria and then in human fibroblasts, once mitochondria have been known as central sites and primary targets for ROS production. Biological investigation, to assess their antioxidant and antiproliferative effects, revealed that compounds **26-29** significantly decreased ROS production by 38-45%, similarly to the reference compound **1** (at 10 μM) in fibroblasts, without exerting considerable cytotoxic effects on the studied healthy cell lines. These findings highlight these innovative compounds as useful pharmacological tools for developing valid neuroprotective agents [137].

Aiming at the development of innovative compounds capable of modulating Aβ-induced OS as a hallmark in AD, Xu and colleagues designed and synthesized two new monocarbonyl curcumin analogues (**30a** and **30b,** Fig. **16**). *In vitro* evaluation confirmed both the compounds to be effective against Aβ-induced oxidative damage under different treatments in PC12 cells. Further investigation of the possible mechanism of action provided evidences that **30a** and **30b** could exert neuroprotective effects at low doses by activating Kelch-like ECH-associated protein 1 (Keap1)/Nuclear factor erythoid-2-related factor 2 (Nrf2) signaling pathway and upregulating the expression of heme oxidase 1 (HO-1) and other antioxidant enzymes, such as superoxide dismutase (SOD) and catalase. Moreover, compounds **30a** and **30b** showed protective activity on PC12 cells against $A\beta_{25-35}$-induced oxidative damage at a very low dose, both in preventive and restoring ways, suggesting a possible pharmacological basis of their clinical use for the prevention and treatment of AD [138].

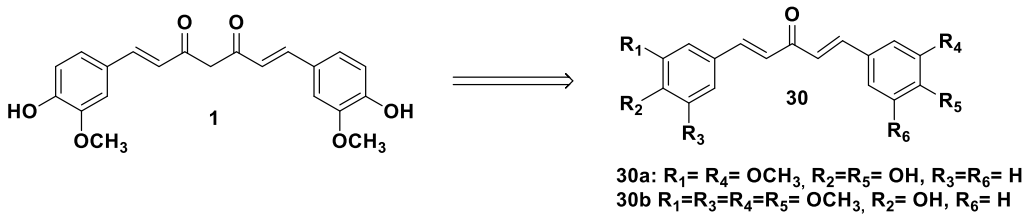

Fig. (16). Chemical structures of compounds **30a** and **30b**, two curcumin analogues with antioxidant properties via activation of the Keap1/Nrf2 pathway.

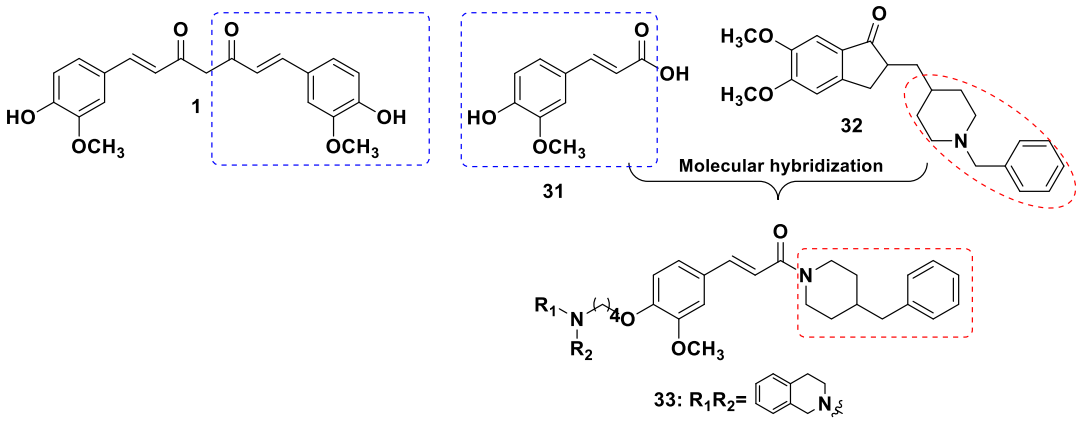

Fig. (17). Design strategy for donepezil-ferulic acid-*O*-alkylamine hybrid compound **33**, with potential clinical use against NDs.

Considering that ferulic acid (**31**) could be explored as a mimic fragment of curcumin (**1**), Sang and co-workers designed a new series of ferulic acid-*O*-alkylamines as MTDLs with antioxidant properties potentially useful in the treatment of NDs. For such a goal, *N*-benzylpiperidine fragment from donepezil (**32**) was combined with ferulic acid scaffold, and substituted by a variety of alkylamine groups to generate the desired series of donepezil-ferulic acid-*O*-alkylamine hybrids. *In vitro* evaluation led to the identification of compound **33** (Fig. **17**) as the most promising multifunctional derivative, showing noteworthy inhibitory effects on self-induced $A\beta_{1-42}$ aggregation (50.8%), with additional ability to disaggregate self-induced $A\beta_{1-42}$ aggregation (38.7%). Moreover, compound **33** showed moderate antioxidant activity (0.55 eq. of Trolox), good neuroprotective effect against H_2O_2-induced PC12 cell injury (76.7% at 10 μM), and low toxicity on PC12 cells (85.8% at 100 μM). These results were highlighted by the authors, suggesting that further study is required of compound **33** for the development of new drugs against NDs, such as AD and PD [139].

In another approach, Xiao and co-workers designed a series of chalcone-rivastigmine hybrids as MTDL candidates, expecting that chalcone moiety could effectively mimic curcumin pharmacophore, exhibiting antioxidant activity and inhibiting MAO isoforms, and that carbamate fragment from rivastigmine (**34**) could ensure anti-cholinesterase activity. Monoamine oxidases (MAOs) are important enzymes in the nervous system physiology, being responsible for the regulation and metabolization of biogenic amines through oxidative deamination. Particularly, MAO-B led to an increase in dopamine metabolism, despite a high production of H_2O_2, contributing to neuronal damage. Biological evaluation with respect to cholinesterase inhibition, antioxidant and metal chelating effects, as well as inhibitory effects on Aβ aggregation and MAO, resulted in the selection of compound **35** (Fig. **18**) as the most promising multi-target bioactive ligand. Compound **35** showed the best selective inhibitory activity of AChE with IC_{50} value of 4.91 μM, with excellent antioxidant (2.83 Trolox eq.) and inhibitory effects on self-induced $A\beta_{1-42}$ aggregation (89.5%) and Cu^{2+}-induced $A\beta_{1-42}$ aggregation (79.7%) activities. In addition, compound **35** displayed selective inhibition of MAO-B (IC_{50}= 0.29 μM), besides metal chelation ability and adequate BBB permeability. Taking into account all these biological properties, compound **35** was considered a potential disease modifying drug candidate for AD [140].

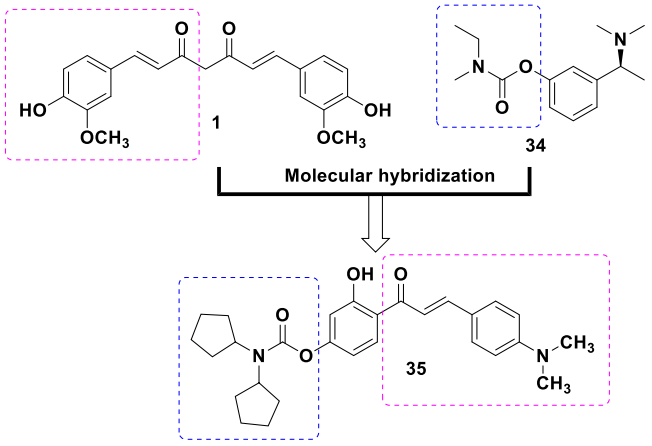

Fig. (18). Design strategy for chalcone-rivastigmine hybrid **35** with remarkable potential multifunctional properties against AD.

Wan and co-workers developed a series of curcumin analogues with the potential to mitigate Aβ pathology in the AD brain. *In vivo* and *in vitro* results disclosed the diazo-boron

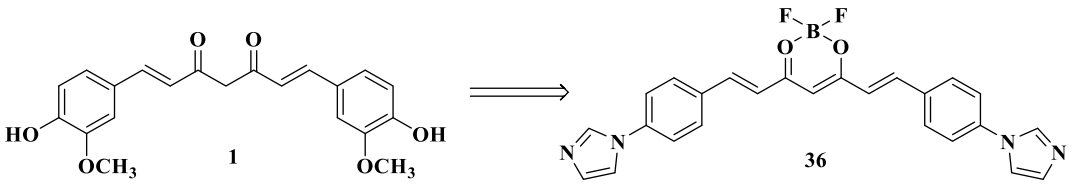

Fig. (19). Chemical structure of curcumin (**1**) and its analogue **36** with a remarkable effect of reducing Aβ levels in *in vitro* and *in vivo* models.

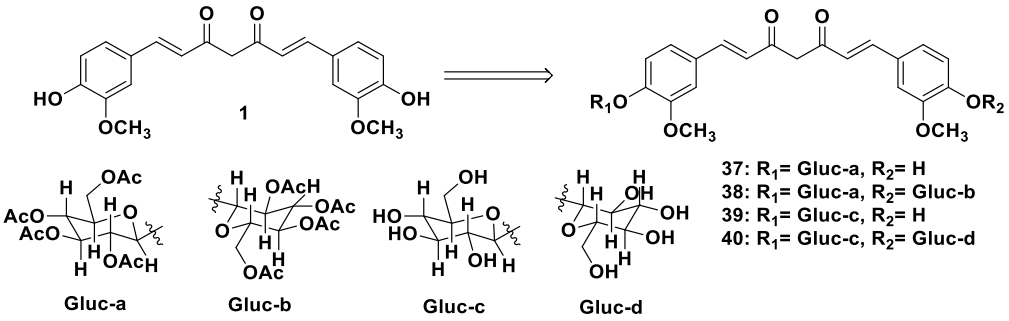

Fig. (20). Chemical structures of curcumin-glucoside derivatives **36-39**.

difluoride curcumin analogue **36** (Fig. **19**) to exhibit significant effects related to the reduction of Aβ neuropathology in AD transgenic mice (APP/PS1). In *in vitro* studies involving CHO cells, this compound was able to reduce Aβ (42:40) ratio and α- and β-processing of APP. Collectively, these data suggest that **36** may alter the activity of γ-secretase, favoring downregulation of toxic Aβ in cells. Moreover, compound **36**, similarly to curcumin, attenuated the maturation of APP in the secretory pathway, and interestingly, upregulated α-secretase processing of APP and inhibited β-secretase processing of APP by decreasing BACE-1 protein levels. According to all these molecular data, compound **36** has been proven to reduce Aβ levels following an innovative mechanism of action, strongly indicating its potential in the development of novel therapeutic agents to combat AD [141].

Gadad and co-workers synthesized a series of curcumin-glucoside derivatives **37-40** (Fig. **20**) that have been designed as novel synthetic ligands capable of inhibiting the formation of α-synuclein oligomers in PD conditions. Biological data suggest that the anti-fibrillogenic activities of derivatives **37-40** are much higher in potency than curcumin, particularly for the monoglucoside derivative **39**. In an *in vitro* model for α-synuclein fibrillization, compound **39** stabilized the monomer and prevented the oligomer formation and, in turn, the fibrils. Compared to the monomer of α-synuclein, **39** binds to the oligomer or to its partially folded intermediate and not to the monomer, suggesting that this glucoside analogue, unlike curcumin (**1**), also holds potent anti-amyloidogenic and anti-aggregating activities [142].

In a recent work, Liao and co-workers described the design, synthesis and pharmacological investigation of six new curcumin-pyrazole derivatives (**41a-f**, Fig. **21**) with potential properties of maintaining mitochondrial function and activating the Nrf2 antioxidant pathway. Firstly, all compounds were screened for their neuroprotective effect on sodium nitroprusside (SNP)-induced PC12 cell injury by testing cell viability and LDH release. Biological data highlighted compounds **41a-d** as capable of antagonizing SNP-mediated PC12 cell death and effectively reducing ROS levels, being more effective than curcumin and edaravone that have been used as controls. Additionally, compound **41c** showed to be the most active derivative with respect to the preservation of mitochondria function by inhibiting the mitochondrial membrane potential loss and enhancing nuclear translocation of Nrf2 in PC12 cell [143].

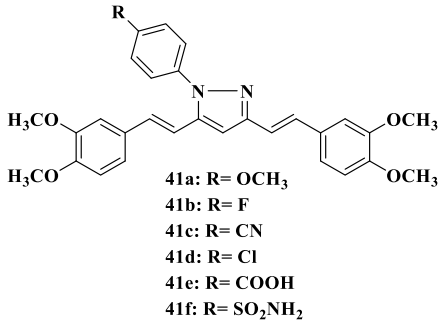

Fig. (21). Chemical structures of curcumin-pyrazole derivatives **41a-f** with potent antioxidant properties.

Considering the well-known contribution of the 3-methoxy-4-hydroxyphenyl subunit to the antioxidant properties of curcumin, Li and co-workers proposed a series of novel 2-methoxy-phenyl dimethyl-carbamate derivatives as potential site-activated MTDLs based on a curcumin-rivastigmine hybrid scaffold. Most of the target compounds exhibited good to excellent inhibition of AChE and BuChE in a sub-micromolar range, especially compound **42b** (Fig. **22**), which showed the strongest selective inhibition of AChE ($IC_{50=}$ 0.097 μM), being about 20-fold more potent than rivastigmine (**34**). In addition, compounds **42a-c** showed significant inhibitory activity against Aβ self-aggregation, similarly to curcumin, that is, an enhanced property in comparison to rivastigmine. Moreover, derivative **43**, which is the hydrolysis product of **42b**, showed potent

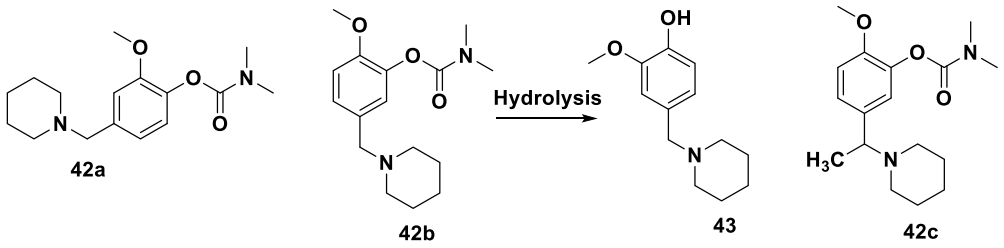

Fig. (22). Chemical structures of anti-amyloid aggregation compounds **42a-c** and derivative **43** with radical scavenging and metal-chelating properties.

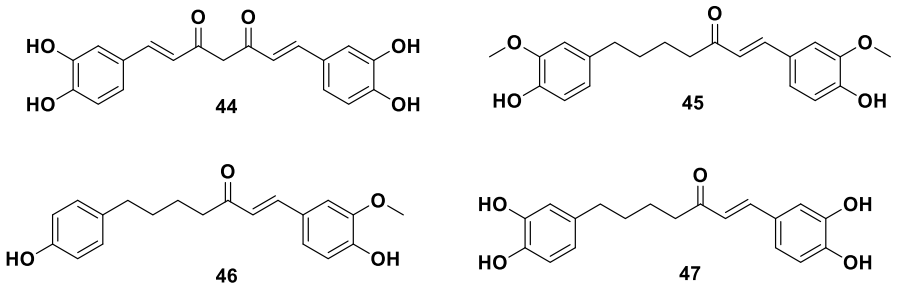

Fig. (23). Chemical structures of neuroprotective curcuminoids **44-47**.

$ABTS^{+}$ scavenging activity and moderate copper ion chelating ability *in vitro* [144].

In 2014, Jirásek and co-workers performed an investigation on the neuroprotective properties of natural and non-natural curcuminoids against glutamate-induced OS in mouse neuronal (HT-22) cells model, which is a valuable cell model for studies of glutamate-induced neuronal toxicity. In this work, a set of fourteen curcuminoids was synthesized, with varying substitution patterns at the aromatic portions and different functionalities in the seven-carbon aliphatic merge chain. All compounds were submitted to an *in vitro* screening for their protective activity against glutamate-induced neuronal cell death in a murine hippocampal cell line HT-22 model. Interestingly, the most active compounds, **45** and **46** (Fig. **23**), owned a ferulic acid-like subunit, suggesting its pharmacophore contribution to counteract glutamate-induced neurotoxicity. Moreover, both compounds showed significant neuroprotective activity in a concentration range of 1-25 μM, without significant toxic effects on HT-22 cells. In particular, the enone-derivative **45** exhibited a protective effect similar to its parent compound curcumin (**1**) with an increased cell viability of 47% at 5 μM and 62% at 10 μM, without exerting any cytotoxic effects. Furthermore, compound **47**, exhibiting a catechol-like feature, also present in caffeic acid, displayed a remarkable neuroprotective activity at the nontoxic concentration of 25 μM, in contrast to the bis-catechol-like derivative **44** that showed increased cytotoxic effects [145].

Novel synthetic chalcone-coumarin hybrids, involved in the licochalcone A (**48**, Fig. **24**) framework, were designed by Lee and co-workers as potential multi-target ligands for modulation of Aβ aggregation with antioxidant and neuroprotective properties. *In vitro* studies on Tet-On Aβ-GFP 293/SH-SY5Y cell models for AD led to identification of LM-031 (**49**, Fig. **24**) as the most potent chalcone-coumarin hybrid, inducing the inhibition of Aβ aggregation and ROS scavenging ability. In addition, due to a significant reduction in Aβ misfolding, compound **49** promoted neurite outgrowth and inhibited AChE in Tet-On Aβ-GFP 293/SH-SY5Y cells. Mechanistic studies evidenced a singular and multiple mode of action in upregulation of the HSPB1 chaperone, NRF2/NQO1/GCLC and CREB/ BDNF/BCL2 pathways. These findings suggest that this novel chalcone-coumarin hybrid small molecule **49** is capable of counteracting Aβ aggregation, exerting antioxidant and neuroprotective effects against Aβ toxicity by enhancing HSPB1 and the NRF2-related antioxidant pathways, as well as by activating the CREB-dependent survival and anti-apoptosis pathway in a singular mode of action [146].

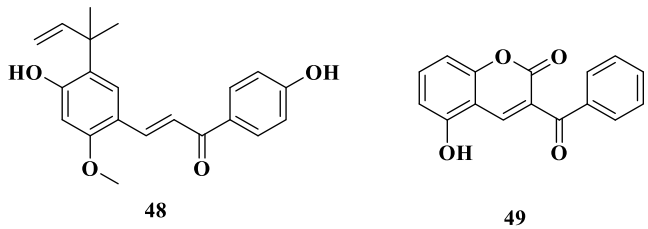

Fig. (24). Chemical structures of licochalcone A (**48**) and LM-031 (**49**) with remarkable neuroprotective and antioxidant properties in a multi-target mode of action.

The structures of ferulic and caffeic acids were used as molecular models by He and co-workers in the design of a series of dimeric ligands with multifunctional properties against AD. Biological data evidenced the enhanced inhibitory effect on $A\beta_{1-42}$ self-induced aggregation exerted by the combination of ferulic and caffeic acid features in the semi-rigid dimers. Moreover, compound **50** (Fig. **25**) also showed potent protective effects against glutamate-induced cell death without significant cell toxicity in mouse hippocampal neuronal HT22 cells, whereas **51** effectively scavenged diphenyl-1-picrylhydrazyl (DPPH) free radicals assay [147].

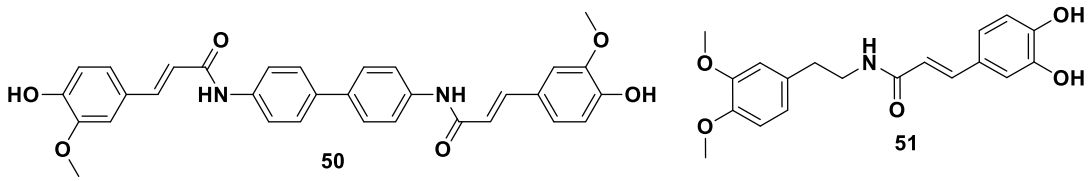

Fig. (25). Chemical structures of the caffeic and ferulic dimeric compounds **50** and **51** with enhanced anti-Aβ aggregation properties.

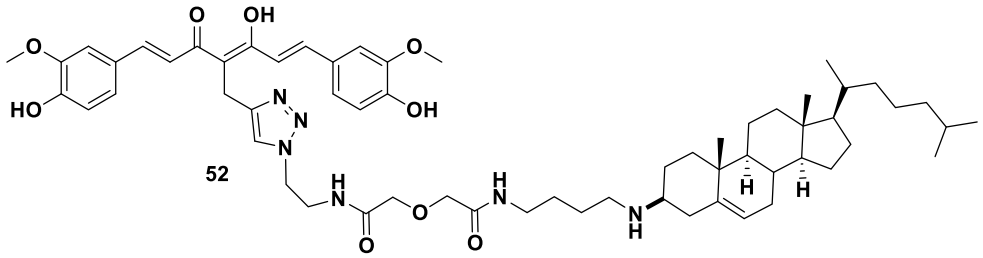

Fig. (26). Chemical structure of the novel bivalent ligand **52** with remarkable neuroprotective activity.

Searching for novel multifunctional drug candidate prototypes for therapeutic use in AD treatment, Liu and co-workers prepared a series of bivalent ligands with a curcumin-cholesterylamine combined scaffold. Based on earlier studies, the attachment position on curcumin subunit, as well as the spacer lengths of 17-21 atoms, were identified as essential features for optimal neuroprotection effects in human neuroblastoma MC65 cells. After optimization related to structure-activity relationship, the bivalent ligand **52** (Fig. **26**), with a spacer length of 17 atoms connected at the methylene carbon between the two carbonyl groups of the curcumin moiety, showed the most promising profile of multifunctional action. Compound **52** inhibited Aβ-oligomers formation with an EC_{50} value of 0.083 μM, induced antioxidant activity on MC65 cells, and demonstrated the ability to form complexes with biometals, such as Cu^{2+}, Fe^{3+}, and Zn^{2+}, without significant cytotoxic effects. Taking together, these results strongly support that this class of bivalent ligands and, particularly **52**, are multifunctional neuroprotective agents potentially suitable for further drug development against AD [148].

Molecular hybridization (MH) of **1** and tacrine (**53**, Fig. **27**) was explored by Liu and co-workers in the design of a novel series of multifunctional neuroprotective and AChE inhibitors. The rationale of this approach was based on the combination of tacrine structure and the 3-methoxy-4-hydroxy pharmacophore from curcumin (**1**), using a keto-alkylamide chain as a connection fragment. Among all compounds obtained from three different hybrid series, compound **54** showed the best neuroprotection profile in the MTT assay, showing higher potency than **1** when PC12 cells were exposed to H_2O_2-induced OS at 200 μM, without affecting cell viability at different concentrations [149].

In the search for innovative multifunctional ligands against AD, Pan and co-workers selected the structure of the multifunctional drug candidate memoquin (**8**) as a molecular model for fragment combination with 3-methoxy-4-hydroxy pharmacophore present in ferulic acid (**31**) and curcumin (**1**) for generating a novel series of cinnamoylamide hybrids. Biological evaluation based on several *in vitro* models (the ability to inhibit AChE (IC_{50}= 3.2 μM) and self-induced Aβ aggregation (30.8%)) for different pathophysiological aspects related to AD led to the selection of compound **55** (Fig. **28**) as the most promising multifunctional neuroprotective ligand. These findings were supported by the results obtained in human neuroblastoma SH-SY5Y cells assay, in which compound **55** showed to maintain the cell viability by 98.3% at 10 μM and reduce H_2O_2-induced injury in PC-12 cells. When exposed to H_2O_2, a significant reduction in PC-12 cells viability (47.6%) was observed, but at the same condition, compound **55** revealed a dose-dependent neuroprotective effect of 88.3 and 68.6% at the concentrations of 10 and 1 μM, respectively [150].

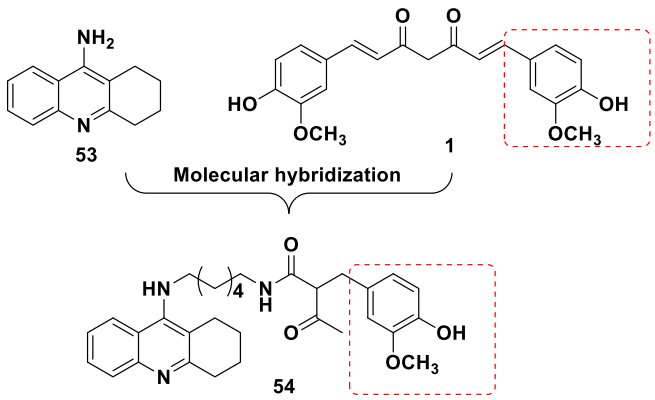

Fig. (27). Molecular hybridization of tacrine and curcumin fragments to generate the neuroprotective hybrid compound **54**.

Pandareesh and co-workers investigated a series of synthetic curcumin monoglycosides in order to obtain new neuroprotective compounds with optimized bioavailability and metabolic stability in relation to curcumin suitable for the treatment of PD. Preclinical studies evidenced a 10-fold greater solubility of monoglycoside derivatives in comparison to curcumin in N27 cells that possess all the physiological and biochemical properties of dopaminergic neurons and represent neuronal cells' loss during PD. The authors also reported that by inducing rotenone (ROT) toxicity in N27 cells, curcumin monoglycosides in general showed higher neuroprotective activities than curcumin (**1**), especially for

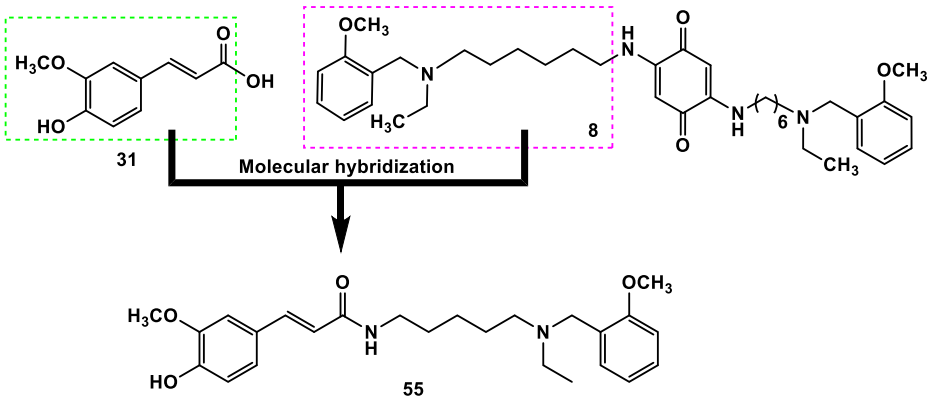

Fig. (28). Molecular hybridization of ferulic acid and memoquin to generate compound **55** with improved neuroprotective properties.

derivative **56** (Fig. **29**) that showed the most remarkable effect in mitigating ROT-induced apoptosis in N27 cells and in *in vivo Drosophila* model [151].

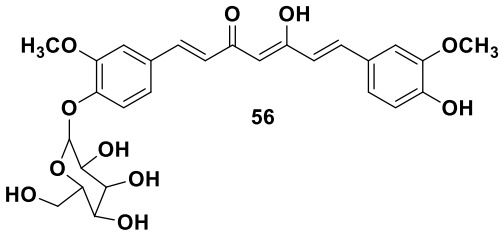

Fig. (29). Chemical structure of curcumin monoglycoside derivative **56** with effective *in vitro* and *in vivo* neuroprotective effects in ROT-induced damage in dopamine N27 cells and in *Drosophila* model.

Aza-analogues of curcumin (**1**) were designed and evaluated by Qneibi and co-workers in the search for novel antagonists of glutamatergic AMPA receptors with an adequate pharmacological profile for the treatment of NDs, including PD. Biophysical properties of AMPA receptors, specifically on the homomeric GluA2 and the heteromeric GluA2/A3 subunits, were used to characterize the antagonistic effect of the target aza-curcumin analogues. Biophysical parameters were based on the electrophysiology of a whole-cell patch clip, with and without the administration of seven curcumin derivatives into HEK293 cells. Experimental data evidenced that compounds **57-60** (Fig. **30**) showed up to 6-fold higher inhibition of all AMPA receptors. Particularly, the most potent AMPA-antagonists **57** and **58** exerted neuroprotective effects that seemed to be due to increased desensibilization and deactivation of AMPA receptors, since inhibition of activity and kinetics of these receptors caused a reduction in excitoxicity induced by glutamate [152].

Considering that extracellular Tau neurofibrils deposition is another AD hallmark and is reported in the literature as one of the first pathological events in the disease onset, Lo Cascio and colleagues investigated new curcumin derivatives as potential inhibitors of tau neurotoxicity. For such a goal, they used recombinant tau oligomers (TauO) to investigate the effect of compounds **61-66** (Fig. **31**) on the modulation of neuronal damage elicited by the aggregation of tau protein oligomers. These six derivatives were selected after a preliminary screening for cytotoxicity against the human neuroblastoma SH-SY5Y cell line, in which compounds **60** and **61** showed lesser inhibition of cell viability. Biochemical experiments using the anti-oligomeric tau antibody (T22), as well as generic tau antibodies, Tau 5 and Tau 13, revealed all compounds **61-66** to be able to interact with TauO, resulting in decreased oligomer levels. In addition, the ability of curcumin derivatives to rescue SH-SY5Y cells from toxicity induced by oligomeric tau protein was investigated. In the lactate dehydrogenase (LDH) assay, an expressive reduction in the release of LDH was observed in comparison to cells exposed only to oligomeric tau protein. Further, apoptosis assays were performed in SH-SY5Y cells culture, disclosing a significant cell retraction and death when comparing cells exposed only to TauO and cells exposed to TauO along with curcumin derivatives. Altogether, data from molecular biology studies suggest that the selected curcumin derivatives interacted and subsequently converted the toxic TauO into higher molecular weight aggregates, thereby modulating their toxicity. Additionally, toxicity of the **61-66**-induced aggregates was also evaluated by using primary cortical neurons from embryos of Htau mice, expressing non-mutant human tau, confirming the higher cell viability in neurons exposed to the curcumin derivatives. Finally, all these findings confirmed that derivatives **61-66** effectively modulated TauO aggregation pathways, converting them into a more aggregated non-toxic state in the human neuroblastoma SH-SY5Y cell line and primary cortical neuron cultures. Thus, these data provide new insights into tau aggregation and may become a basis for the discovery of new disease-modifying drugs for tauopathies, such as AD [153].

4. RESVERATROL DERIVATIVES AND ANALOGUES

In the search for novel inhibitors of human AChE (*h*AChE) and Aβ aggregation with antioxidant properties against AD, Xia and co-workers synthesized a family of 40 hybrid compounds with the general molecular features represented by compounds **67** and **68** (Fig. **32**), designed by MH between resveratrol (**2**) and tacrine (**53**) scaffolds. All compounds were initially screened for their inhibitory potencies on $A\beta_{1-42}$ self-aggregation by the Thioflavin T (ThT) fluorescence assay. Most of them exhibited moderate to strong inhibitory activities ranging from 41.1 to 104.2% (at 20 μM), especially compounds **67a-i** showed inhibitory effects higher than 91.3% in comparison to **2** (80.1%), curcumin (51.3%)

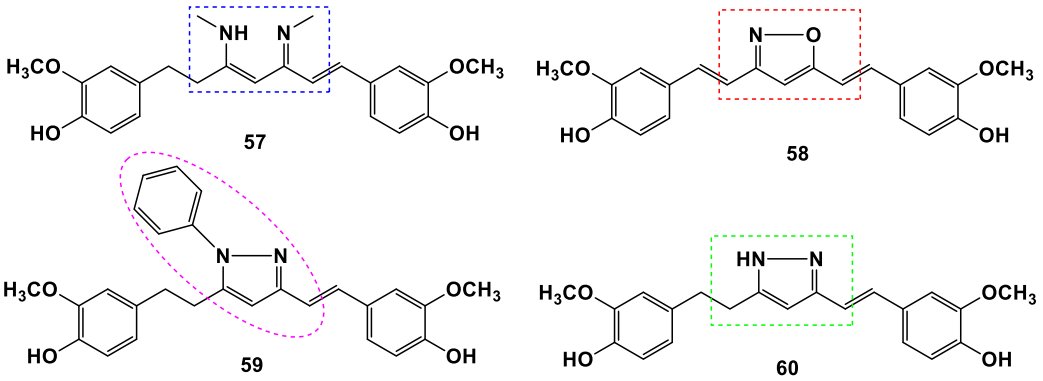

Fig. (30). Chemical structures of the aza-curcumin analogues **57-60** with remarkable antagonist effects on AMPA receptors.

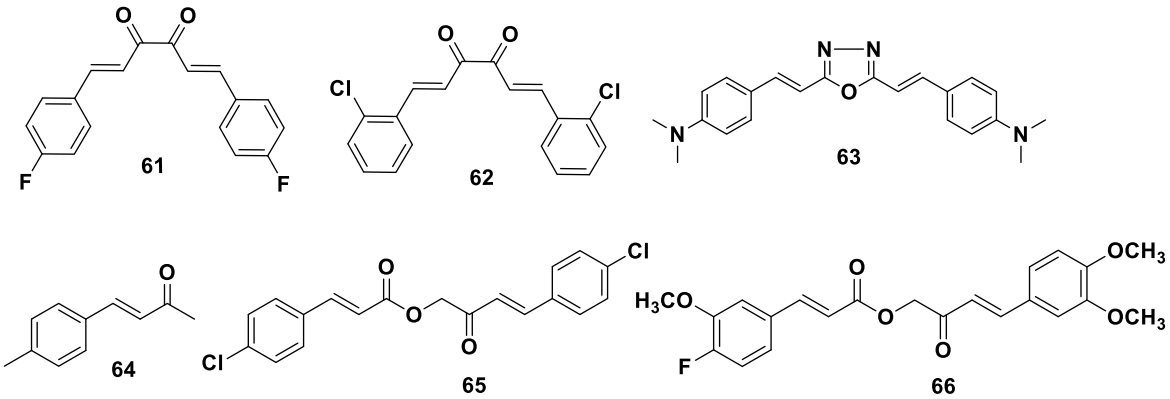

Fig. (31). Chemical structures of the novel curcumin derivatives **61-66** with remarkable effect on tau aggregates' formation and neurotoxicity.

and donepezil (33.7%) at the same concentration. In addition, the antioxidant activity was evaluated in the oxygen radical absorbance capacity (ORAC) assay using Trolox as the standard compound; compounds **67b-d** and **67f-h** showed 1.3-1.8-folds higher activity in comparison to Trolox at the concentration of 1 μM. Then, an investigation of the inhibitory activity of human AChE and BuChE revealed compounds **67b-e** as the most active. As BBB permeability is a key parameter in the development of drug candidates to target CNS, parallel artificial membrane permeability (PAMPA) assay was used as a selection criterion for the most promising ligands, revealing compounds **67b** and **67e** as exhibiting the best BBB permeability (5.2×10^{-6} and 6.0×10^{-6} $cm \cdot s^{-1}$, respectively). Altogether, these results highlight compound **67b** ($A\beta_{1-42}$ aggregation inhibition: 91.3%; ORAC: 1.8; IC_{50} for hAChE: 1.5 μM; IC_{50} for hBuChE: 1.1 μM) as a lead compound for further study, as it displayed significantly better antioxidant activity than **67e** (ORAC: 0.6). Binding experiments suggested **67b** as a non-competitive inhibitor of hAChE and that it could bind to the peripheral anionic site (PAS) of hAChE, as corroborated by computational studies. Additionally, considering that there is sufficient evidence that the PAS of AChE can bind to Aβ and promote the formation of amyloid fibrils, **67b** was evaluated for its inhibitory activity on hAChE-induced $A\beta_{1-42}$ aggregation, showing the best inhibitory effect (92.7% at 20 μM). Moreover, **67b** showed a significant neuroprotective effect against the glutamate-induced cytotoxicity in HT22 cells by preventing the ROS production and increasing the GSH level. Given all these biological data, compound **67b** could be considered as one of the most promising multifunctional ligands currently reported in the literature for further development as an innovative disease-modifying drug candidate for AD [154].

Yang and co-workers selected clioquinol (**69**, Fig. **33**), a well-known bioactive compound with significant metal chelating ability, and the synthetic quinoline derivative **70**, with inhibitory activity of MAO, as a structural prototype for the design of a hybrid series of resveratrol. Considering that resveratrol exhibits potent neuroprotective and antioxidant properties, also inducing the inhibition of Aβ deposits, the authors aimed to combine all these properties in one single molecule with a complete neuroprotective profile. Biological studies led to identification of compound **71** as a promising multi-target neuroprotective agent, capable of inhibiting 91.3% of $A\beta_{1-42}$ aggregation in ThT fluorescence assay (at 25 μM) and human MAO-B in fluorescence-based Amplex Red assay, with pargyline as the reference compound (IC_{50}= 1.73 μM). In addition, despite its subtle antioxidant activity in the DPPH assay (IC_{50}= 43.3 μM), compound **71** showed metal chelation ability for Cu^{2+}, Zn^{2+}, Fe^{2+} and Fe^{3+} and significant counteracting effects on ROS generation, H_2O_2-induced apoptosis, and 6-hydroxydopamine (6-OHDA)-induced cell injury. Moreover, compound **71** showed a significant *in vitro* anti-inflammatory activity and adequate BBB permeability, without significant toxicity on PC12 cell line. Altogether, these results highlight compound **71** as a lead candidate for drug development against NDs, especially for PD and AD [155].

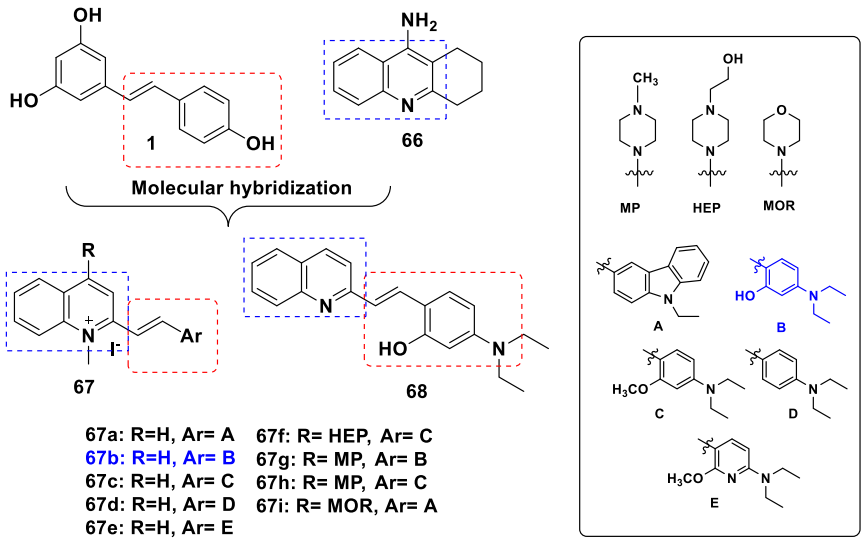

Fig. (32). Chemical structures of a new family of tacrine-resveratrol-based hybrid compounds **67a-i** and **68**, with multifunctional properties potentially useful for AD treatment.

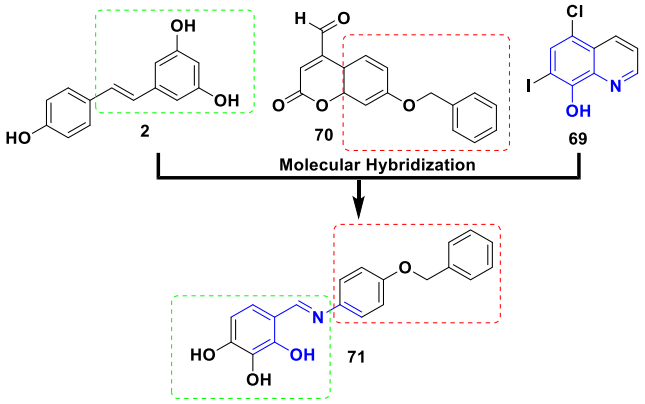

Fig. (33). Molecular hybridization of pharmacophore subunits of clioquinol (**69**), MAO-inhibitor **70** and resveratrol (**2**) to generate the hybrid derivative **71** with potent neuroprotective, MAO-B inhibition, metal chelating and anti-inflammatory properties.

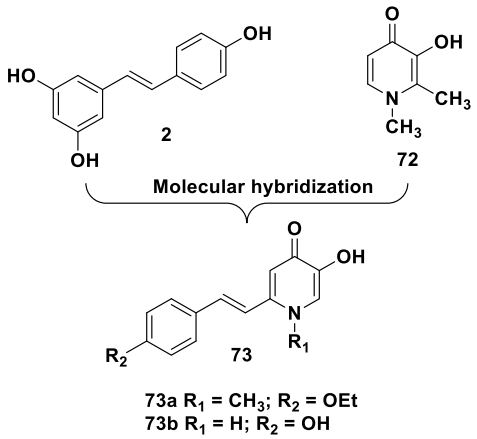

Fig. (34). Molecular design of a new series of deferiprone-resveratrol hybrid compounds, with **73a** and **73b** identified as the most promising multifunctional antioxidant, metal chelating and Aβ-aggregation inhibitors.

Deferiprone (**72**, Fig. **34**) is a metal chelating drug that is used to chelate iron in patients with iron-overload thalassemia. Considering the role of imbalance in biometals in the pathophysiology of certain NDs, such as AD, and its close relationship with OS and mitochondrial dysfunction, Xu and co-workers proposed a new series of deferiprone-resveratrol hybrid compounds (**73**, Fig. **34**) as potential multifunctional ligands of interest. Their aim was to obtain a new molecular scaffold and innovative ligands with metal chelating ability, antioxidant and inhibitory Aβ self-aggregation activities mediated by biometals. In a preliminary screening for their ability to chelate Fe^{3+}, compounds **73a** and **73b** showed a remarkable inhibition of (2,2′-azino-bis(3-ethylbenzthiazoline-6-sulfonicacid) ABTS radical with IC_{50} values of 4.02 and 1.73 μM, respectively. In addition, both compounds evidenced their multi-target properties, showing significant inhibition of Aβ self-induced aggregation with similar potencies (IC_{50} values of 8.94 and 10.72 μM, respectively), aside from their ability to inhibit Aβ aggregation mediated by Fe^{3+} and Cu^{2+}, along with good BBB permeability [156].

In another study, Jeřábek and co-workers synthesized a new family of hybrids that have been designed as potential AChE inhibitors and immunomodulators based on the structures of resveratrol (**2**) and tacrine (**53**). The combination of tacrine molecule and a two-functionalized aromatic rings system, interconnected by an alkyl or alkenyl linker as in the resveratrol scaffold, led to a new hybrid molecular architecture represented by scaffolds **74** and **75** (Fig. **35**). Pharmacological screening led to the identification of compounds **74a** and **75a** as the most potent selective *h*AChE inhibitors with IC_{50} values of 1.3 and 8.8 μM, respectively. Moreover, both compounds exhibited moderate inhibitory activity of Aβ aggregation (37.3% for **74a** and 31.2% for **75a** at 50 μM), besides good BBB permeability. However, considerable hepatotoxicity was observed, probably due to tacrine fragment, but compound **74a** also showed neurotoxic effects on primary rat cerebellar granule neurons (CGNs). Despite these toxic effects, **75a** was additionally assayed for anti-inflammatory effects, showing an interesting modulatory

effect on microglia and astrocyte cells, with significant iNOS inhibitory activity. These data highlight compound **75a** as a promising ligand to be considered in further studies for optimization of toxicity effects in the development of therapeutical agents against NDs [157].

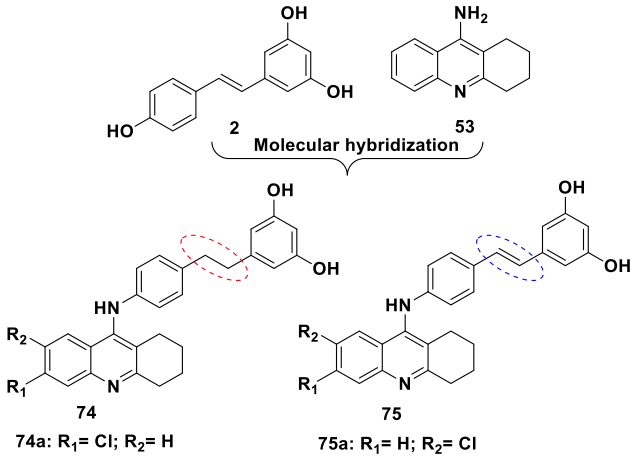

Fig. (35). Structural design of a new family of hybrid compounds based on the molecular hybridization of resveratrol (**2**) and tacrine (**53**) to generate compounds **74a** and **75a** as AChE and Aβ aggregation inhibitors.

In the search for drugs with improved antioxidant and neuroprotective effects, Deck and co-workers synthesized a new family of fluorinated (**76**) and non-fluorinated (**77**, Fig. **36**) analogues of resveratrol, varying the nature and position of different substituents in both aromatic rings of the stilbene scaffold present in the parent structure of **2**. The rationale of this work was based on the role of inflammation and OS in the pathophysiology of many chronic diseases, including NDs, which strongly supports the concept that activation of antioxidant Nrf2 signaling may represent a relevant disease-modifying therapeutic approach. In fact, a number of natural and synthetic Nrf2 activators have been investigated in the recent years, with some drug candidates undergoing clinical trials. Nrf2 is abundant in CNS and exists in the cytosol complexed with the thiol-rich redox-sensing protein Keap-1. In response to OS condition, some cysteine residues of Keap-1 are modified, leading to the rupture of the Nrf2/Keap-1 complex and, in turn, releasing NRf2 that is then translocated to the nucleus. Once in the nucleus, Nrf2 exerts an antioxidant effect, which leads to an increase in GSH production [40, 158]. In this context, numerous Nrf2-activating small molecules have been studied for their electrophilic nature, which is susceptible to nucleophilic attack from cysteine residues of Keap-1, often in a Michael addition fashion, leading to activation of Nrf2. In a preliminary screening, a series of fifty-six stilbene-like compounds, including forty mono- and polyfluorinated and sixteen non-fluorinated analogues, were tested in an Nrf2-ARE reporter-HepG2 stable cell line assay. Biological results led to identification of a number of substituted *trans*-stilbene-like compounds as activators of Nrf2, highlighting some derivatives with fluorine and/or methoxy ring substituents. Particularly, the polyfluorinated compounds **76a-c** (Fig. **36**) exhibited strong effects on the activation of Nrf2 with EC_{50} values of 0.3, 0.45 and 0.65 μM, and a 10.7, 8.2 and 4.5-fold activation at 15 μM, respectively. In addition, methoxy-substituted resveratrol analogues **77a** and **77b** (Fig. **36**) exhibited the 69-fold and 65.5-fold activation of Nrf2 at 15μM, in spite of their moderate EC_{50} values of 3.3 and 2.2 μM, respectively. In conclusion, the authors highlighted the absence of linearity in the structure-activity relationship (SAR) among all tested compounds, suggesting that not only the nature but also the position of a given substituent is responsible for the antioxidant effect. Moreover, there are other Keap1-independent pathways that could be involved in the Nrf2 activation and, in turn, result in a cascade of cellular changes, which culminate in antioxidant, anti-inflammatory and neuroprotective effects, and that trans-stilbene substituted derivatives could be studied to innovate findings in the drug discovery for NDs [159].

The structures of resveratrol (**2**) and its natural analogue, pterostilbene (**78**), a natural resveratrol-like product extracted from blueberries with a number of biological properties, including antioxidant, anti-inflammatory, inhibition of the self-induced Aβ aggregation and neuroprotective properties, were used as molecular models by Zheng and co-workers in the design of novel improved multifunctional anti-AD ligands. Considering that resveratrol lacks AChE inhibition and that tertiary amines are important pharmacophore units for molecular recognition in the AChE catalytic active site (CAS), the authors explored the fragment hybridization of the common scaffold of **2** and **78** with a β-amino alcohol subunit to obtain multifunctional neuroprotective and AChE inhibitors (Fig. **37**). Among fourteen novel pterostilbene-β-amino alcohol hybrid derivatives, biological data led to identification of compound **79** as the most potent and selective AChE inhibitor (IC_{50}= 24.04 μM), also inhibiting 40.2 % of Aβ self-aggregation (at 25 μM). Additionally, **79** exhibited a significant antioxidant activity in ORAC assay (1.2 Trolox eq.) and 74.9% of neuroprotection at 10 μM in H_2O_2-induced neurotoxicity model. These biological results strongly suggest that the insertion of a tertiary amine into the pterostilbene scaffold can decisively contribute to the AChE inhibitory effect, which was corroborated by molecular docking studies, preserving the other relevant anti-AD properties of resveratrol and pterostilbene [53].

Seeking novel multifunctional neuroprotective compounds, Martínez and co-workers designed and synthesized a series of five ionophore polyphenol derivatives based on MH of stilbene-like scaffold of resveratrol (**2**) and the selective Cu^{2+} chelating agent **80** (Fig. **38**). Evaluation of metal ion binding ability showed that all tested compounds **81a-c** and **82a-b** (Fig. **38**) were capable of selectively binding to Cu^{2+}, forming 2:1 (compound:Cu^{2+}) complexes with association constants with the log Ka ranging from 12 to 16, and the imino derivatives **82a-b** showing a slightly better selectivity than the parent amino analogues **81a-c**. In a binding assay, compound **81b** showed the best affinity for βA_{1-40} (1.55×10^{-5} M^{-1}), with a comparable value as resveratrol (1.65×10^{-5} M^{-1}). In addition, the overall results related to antioxidant activity as evaluated by different radical scavenging assays highlighted compound **81c** for its remarkable antioxidant activity, inhibiting a 60% extension of Cu^{2+}-βA_{1-40} catalyzed production of ·OH. Furthermore, compound **81c** showed an improved activity to reduce or eliminate DPPH and AAPH free radicals in comparison to resveratrol and ascorbic

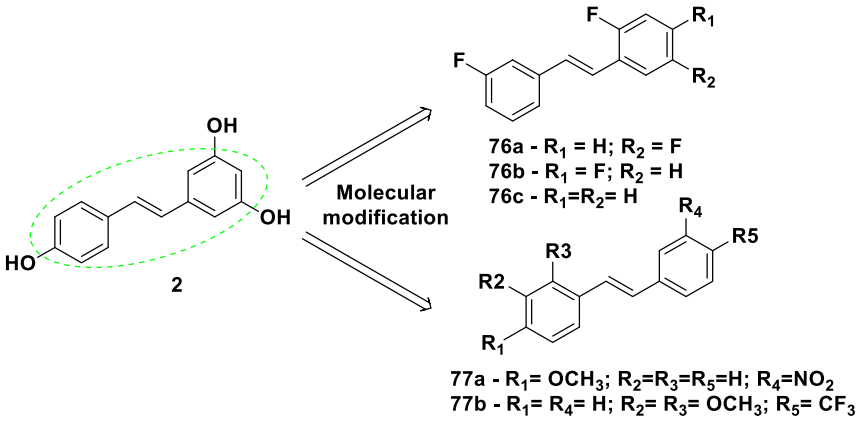

Fig. (36). Chemical structures of substituted stilbene-like derivatives **76a-c** and **77a-b** with remarkable effects on Nrf2 activation and antioxidant activity.

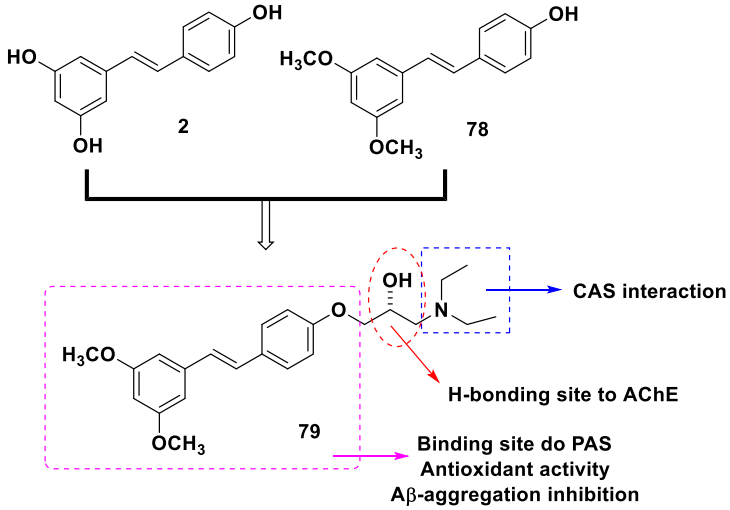

Fig. (37). The design of pterostilbene-β-amino alcohol hybrid compound **79** with multifunctional neuroprotective, antioxidant and selective AChE inhibitory properties.

acid. Compound **81c** also prevented 50% of the formation of induced total Cu^{2+} aggregates and misfolding $\beta A_{1\text{-}40}$ in its amorphous, and a 67% of the fibrillary setup, inducing a better effect than that observed for resveratrol. Moreover, in the thioflavin-T (ThT) assay, all target compounds, and particularly compound **81c**, inhibited the formation of mature $\beta A_{1\text{–}40}$ fibrils in a 67-92% range, similarly to resveratrol, showing no toxic effects on healthy eukaryotic cells of *T. thermophile.* Collectively, all these results highlight **81c** as a promising, non-toxic and effective neuroprotective candidate for further *in vivo* studies aimed at anti-AD drug development [160].

In a more recent study, Martínez and co-workers explored the MH strategy between resveratrol (**2**) and previously identified metal chelating and neuroprotective derivatives with a general scaffold represented by **82a-b** (Fig. **38**) and a β-secretase (BACE-1) inhibitor fragment (**83**, Fig. **39**), aiming to obtain novel multifunctional BACE-1 inhibitors. In addition, two other 4-amino-quimoline derivatives previously studied for their anti-malarial activity were also investigated for their potential BACE-1 inhibitory activity. As a result, compounds **84** and **85** were identified to exert significant inhibitory activity of 100 and 91% at 50 μM on BACE-1, with IC_{50} values of 4.4 and 1.7 μM, respectively; they were also predicted to possess good *in silico* BBB properties. In fact, computational studies evidenced much better non-covalent interactions with BACE-1 of compounds **84** and **85**. As expected, both the compounds also showed antioxidant and selective Cu^{2+} chelating abilities, being capable of inhibiting Cu^{2+}-Aβ catalyzed ROS formation at 68.5% and 36.2%, respectively. Interestingly, compounds **84** and **85** exhibited remarkable inhibiting activity of Cu^{2+}-induced and Aβ self-aggregation, with **84** showing better inhibition of Cu^{2+}-induced Aβ aggregation model while **85** being most effective in inhibiting Aβ self-aggregation. Overall, these results clearly suggest that functionalized polyphenols, such as **84** and 4-aminoquinoline derivative **85**, should be further investigated as promising lead compounds for the development of anti-AD drug candidates [161].

Considering the previously described synthetic derivatives **70** (Fig. **33**) and **72** (Fig. **34**) as AChE and Aβ inhibitors, respectively, and their structural similarity with the metal chelator matol (**86**, Fig. **40**), Cheng and co-workers designed a new family of resveratrol-based hybrid compounds as potential MTDLs. Biological results highlighted compounds **87** and **88** (Fig. **40**) for their best antioxidant

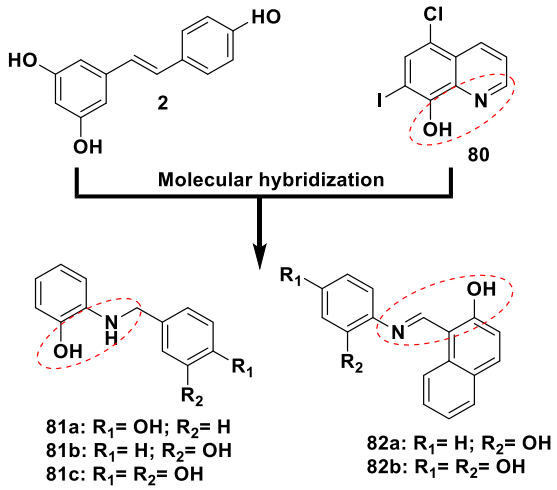

Fig. (38). Molecular design of the hybrid azo-derivatives **81a-c** and **82a-b** with improved neuroprotective, selective Cu^{2+}-chelating, and antioxidant properties.

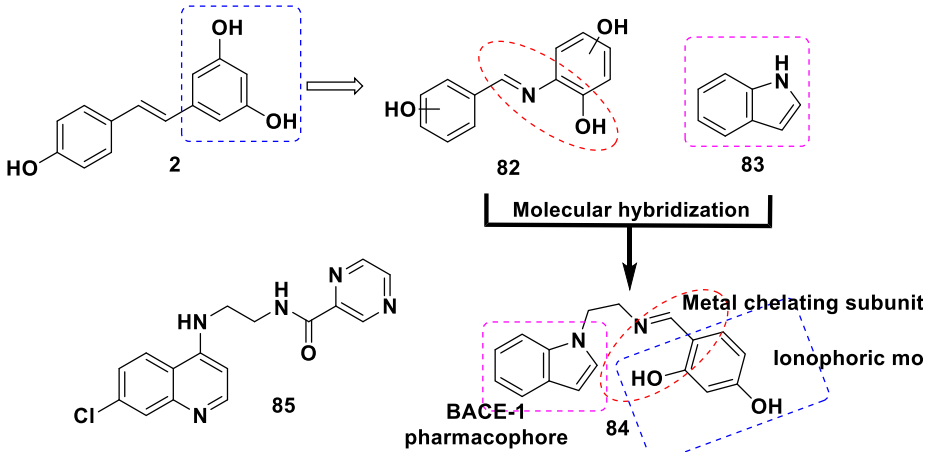

Fig. (39). Molecular hybridization strategy used for the design of compound **84** as a multifunctional antioxidant and BACE-1/Aβ-aggregation inhibitor and chemical structure of the antimalarial compound **85** with multifunctional anti-AD properties.

activity in the ABTS assay with IC_{50} values of 1.94 and 1.18 μM, respectively. In addition, both compounds were found capable of inhibiting Aβ self-aggregation in a micro molar range (IC_{50} values of 7.20 and 8.29 μM for **87** and **88**, respectively) and showed selective chelation ability for Fe^{3+}, which is an important biometal involved in Fenton reaction and ROS production. Moreover, both compounds showed the ability to inhibit Fe^{2+}-mediated Aβ aggregation as well as Aβ fibrils disaggregation effect at 50 μM [162].

Focusing on MAO inhibition as an additional target of interest in the AD clinic, Lan and co-workers designed novel hybrid inhibitors of Aβ-aggregation and MAO, based on the combination of structural fragments of resveratrol (**2**) and the MAO inhibitor indazole derivative **89** (Fig. **41**). Biological studies led to the selection of compound **90** (Fig. **41**) as the most promising MAO-B inhibitor into the series, with IC_{50} values of 1.14 μM and 30.4 μM for MAO-B and MAO-A, respectively, and showing 26.7-fold higher selectivity for MAO-B. In order to characterize its multi-target pharmacological profile, as expected in the molecular design approach, compound **90** was also evaluated for its Aβ inhibitory activity, exhibiting a significant effect on Aβ-self aggregation (IC_{50} value of 19.5 μM). Moreover, **90** showed an adequate CNS permeability in a predictive PAMPA-BBB model and no toxic effects on PC12 cell line in a range of 6.25 to 100 μM [163].

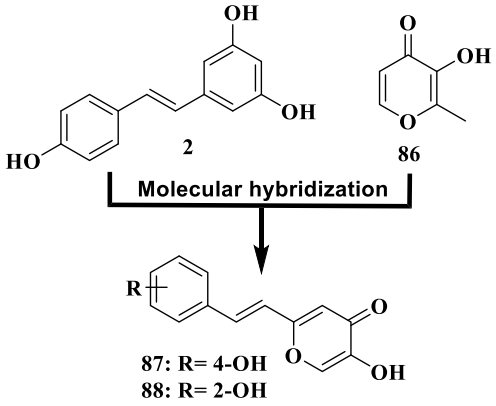

Fig. (40). Molecular design of the hybrid compounds **87** and **88** as new MTDLs with antioxidant and anti-Aβ activities.

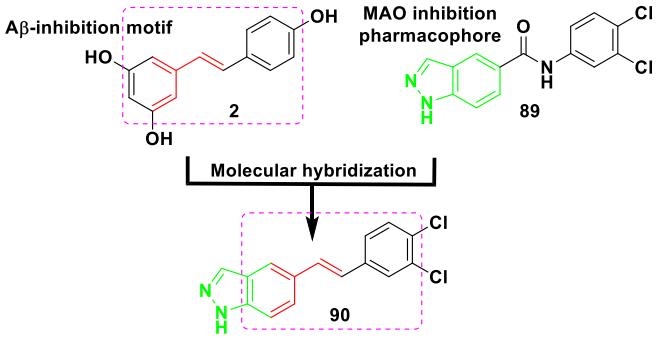

Fig. (41). Design of compound **90** as MAO-B and anti-Aβ aggregation inhibitor by molecular hybridization between the resveratrol (**2**) and MAO-inhibitor **89** substructures.

Aiming to improve anti-inflammatory and antioxidant activities reported for resveratrol (**2**), and considering that *trans*-viniferin (**91**, Fig. **42**) is a better antioxidant than **2**, Tang and co-workers investigated a new family of resveratrol-viniferin based derivatives. All five synthetic compounds were tested for their inhibition of MAO isoforms and antioxidant activity in the three DPPH, ABTS and (ferric ion reducing antioxidant power) FRAP radical scavenging approaches. Biological and chemical results pointed out compound **92** (Fig. **42**) for its 2.82-fold selectivity for *h*MAO-A inhibition (IC_{50}= 2.60 and 0.92 μM for MAO-A and MAO-B, respectively), in addition to antioxidant activity in DPPH assay with an IC_{50} value of 46.95 μM and 1.43 and 1.74 trolox equivalent by ABTS and FRAP methods, respectively. Interestingly, compound **93** also showed selective inhibition of *h*MAO isoforms (IC_{50} values of 8.12 and 3.93 μM for MAO-A and MAO-B, respectively), but with an opposite 2-fold MAO selectivity in comparison to its opened-ring analogue **92**. In addition, compound **93** (Fig. **42**) exhibited a slightly weaker antioxidant activity in the DPPH assay (IC_{50}= 35.3 μM), but similar trolox equivalents in ABTS (1.70) and FRAP (1.97) tests, in comparison to **92**. In order to confirm such antioxidant profile in biological systems, both compounds were assayed in cellular models and showed neuroprotective effects against ROS generation, H_2O_2-induced apoptosis, and a significant *in vitro* anti-inflammatory activity. In this study, mouse microglia BV2 cells were used to establish cell OS injury model with H_2O_2 and to explore the protective effect and possible mechanisms of action of **92** and **93**. Both compounds showed low toxicity and were resistant to H_2O_2, rotenone and oligomycin-A-induced oxidative neurotoxicity. Overall, the biological data and the adequate BBB permeability in the PAMPA test highlighted compounds **92** and **93** for further consideration as potential anti-AD drug candidates [164].

Based on the antioxidant properties exhibited by pyridoxine (vitamin B6, **94**), which is a known enzymatic cofactor for at least 140 enzymes with an important regulatory role [165], Li and co-workers synthesized a number of pyridoxine-based derivatives and identified the pyridoxine-resveratrol hybrid **95** (Fig. **43**) as an MAO inhibitor in previous works. However, this compound showed some pharmacokinetic (PK) restrictions, including poor lipophilicity and BBB permeability. More recently, the authors re-investigated the structure of **95**, in the light of its structural similarity with resveratrol (**2**) and its potential in the design and discovery of novel MAO inhibitors with multifunctional anti-PD properties. Thus, a new family of thirteen pyridoxine-resveratrol hybrids was synthesized and biologically evaluated for MAO inhibitory and antioxidant properties. Compounds **96a-c** (Fig. **43**) were identified as promising multifunctional agents, exhibiting strong and highly selective inhibition of MAO-B with IC_{50} values of 0.01, 0.01 and 0.02 μM, respectively, and IC_{50} values of 24.1, 28.0 and 12 μM, respectively for MAO-A. In addition, compounds **96a-c** showed expressive antioxidant activity with ORAC values of 2.89, 2.53 and 2.43 μM of trolox equivalents, with high BBB permeability in the PAMPA assay. Furthermore, compounds **96a-c** showed neuroprotective effects on H_2O_2-induced PC-12 cell injury and no toxic effects at low doses, suggesting their wide therapeutic safety range and great neuroprotective effects, and the potential to be considered as promising and representative MAO-B inhibitors for the treatment of PD [166].

In previous studies, Fukuhara and co-workers studied some structural features of the catechin scaffold that could be modified to enhance the antioxidant effects, and developed the planar catechin analogue **97** (Fig. **44**) with the significant hydroxyl radical-scavenging and DNA-protective effect against Fenton reaction by-products [167]. More recently, the same group reported the effect of methyl substitution on the antioxidant and genotoxicity of resveratrol analogues, leading to the identification of compounds with 6- to 60-fold higher ability of radical scavenging than resveratrol (**2**), especially the dimethyl-substituted analogues **98** and **99** (Fig. **44**) as the most potent and less toxic antioxidants [57, 168]. Based on these findings, Imai and co-workers developed the hybrid dimethyl-catechol catechin **100** (Fig. **44**) as a mimic of resveratrol analogues **98** and **9**, aiming to obtain new potent antioxidant candidates to combat OS in NDs. Evaluation of the radical scavenging activity of compound **100** revealed its 28-fold increased radical scavenging activity in comparison to **97**, clearly demonstrating the enhanced effect of methyl-substituted catechin and its potential to be considered in the development of anti-OS therapy to prevent OS-related NDs [169].

Li and co-workers used MH between resveratrol (**2**) and clioquinol (**69**) for generating a series of resveratrol-based imine hybrid derivatives (Fig. **46**). Among twenty new hybrid compounds screened for their activity as Aβ self-aggregation inhibitors, and their antioxidant and metal chelating abilities, compound **101** (Fig. **45**) was identified as the most potent DPPH radical scavenger (IC_{50}= 14.1 μM), with metal chelation ability for Cu^{2+} and Fe^{3+} and inhibitory activity of 64. 6% for Aβ self–aggregation and 68.1% for Cu^{2+}-induced $A\beta_{1-42}$ aggregation (at 20 μM). Moreover, compound **101** significantly reduced Cu^{2+}-Aβ-induced ROS formation and showed significant neuroprotective effects on human neuroblastoma SH-SY5Y cells [170].

In another approach, Jiang and co-workers also used resveratrol (**2**) and clioquinol (**69**) as molecular prototypes in a structural combination with the stilbene-like imine **102** (Fig. **49**), which was reported as a modulator of metal-induced Aβ aggregation and ROS production, for the reduction in metal-Aβ neurotoxicity in living cells. Their purpose

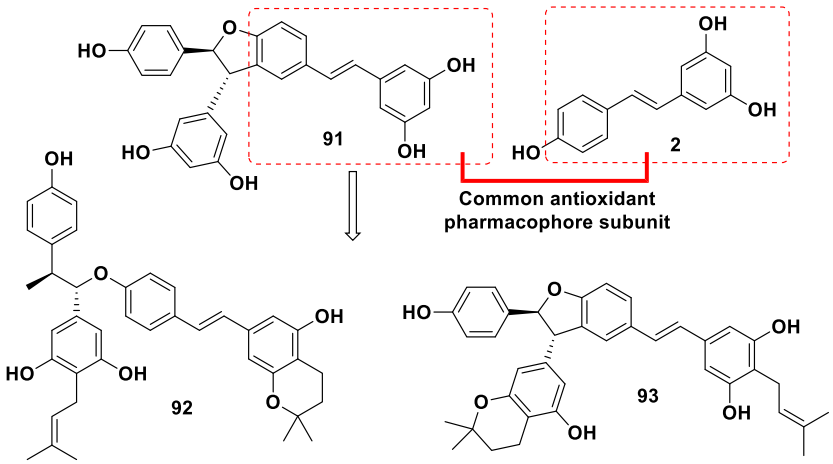

Fig. (42). Molecular optimization of the resveratrol (**2**)-parent viniferin (**91**) to generate the optimized antioxidant and neuroprotective derivatives **92** and **93**.

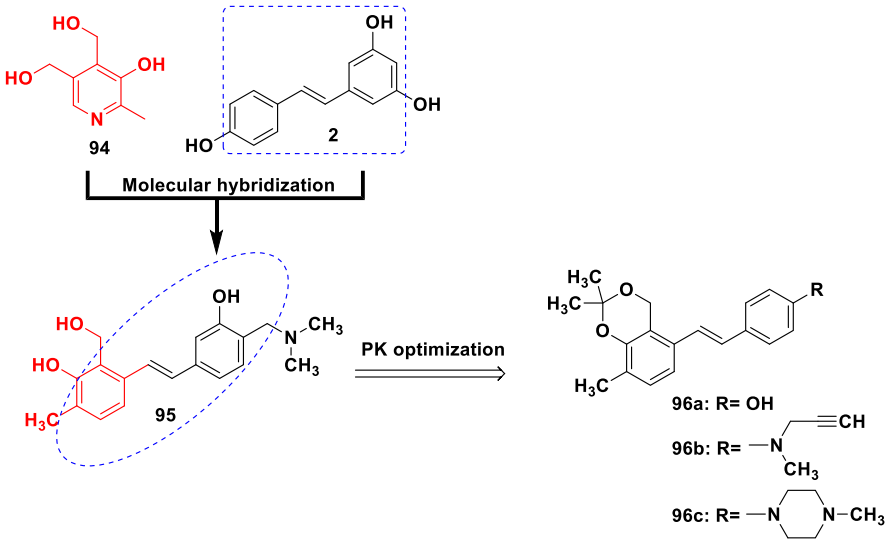

Fig. (43). Chemical structure of the pyridoxine (**94**)-resveratrol (**2**) hybrid **95** and its optimized neuroprotective and selective MAO-B inhibitors **95a-c**.

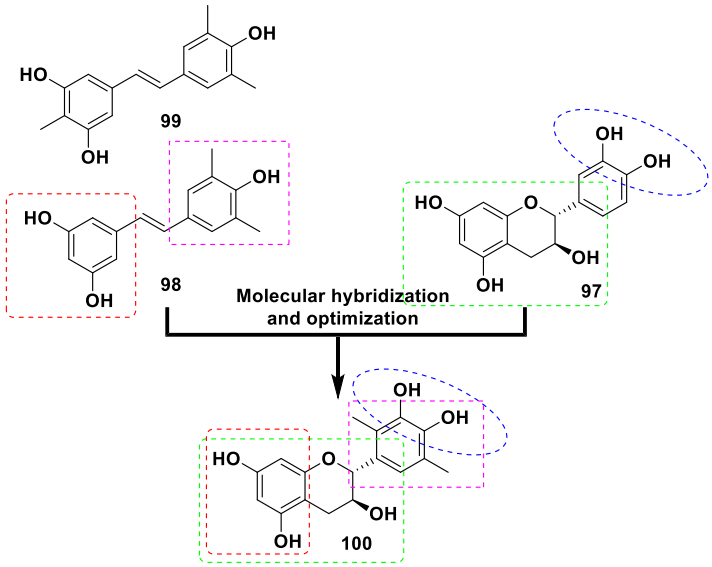

Fig. (44). The chemical structure of dimethylcatechol catechin **100** with improved safety and antioxidant properties.

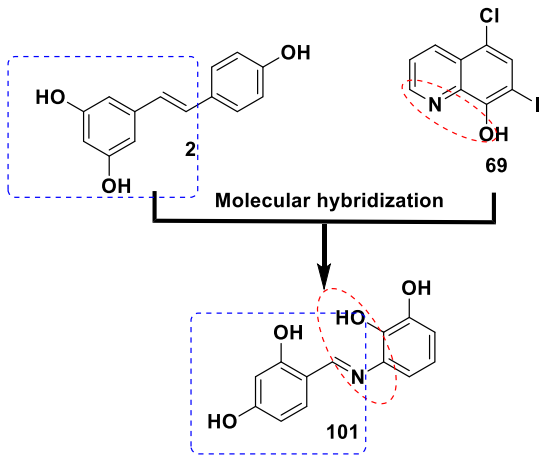

Fig. (45). Design strategy for resveratrol-based imine derivative **101** with improved metal-chelating, antioxidant and neuroprotective effects.

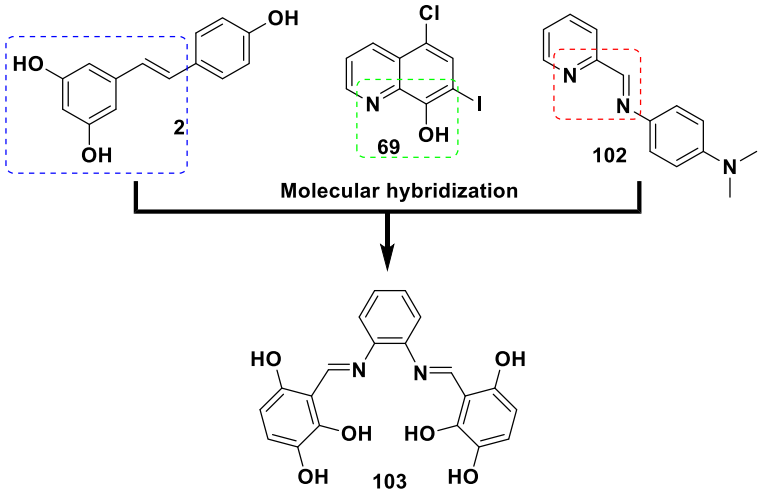

Fig. (46). Structural design of the multifunctional ligand **103** by MH of resveratrol (**2**), clioquinol (**69**) and stilbene-like imine **102** with remarkable metal chelating ability, antioxidant activity and neuroprotective effects.

was to generate an innovative scaffold for new multifunctional ligands with potential effects against Aβ aggregation, metal-βA interaction, metal chelating ability, the control of ROS generation, and antioxidant activity. Among twenty-six synthetic compounds, pharmacological data led to the identification of derivative **103** (Fig. **46**) with a pronounced 5.2-fold higher antioxidant activity in DPPH assay (IC_{50}= 21.0 μM) in comparison to **2** and a 2.6-fold Trolox equivalent in ABTS test. Compound **103** also inhibited 70.3% of self-induced $AβA_{1-42}$ aggregation and 85.7% of Cu^{2+}-induced $AβA_{1-42}$ aggregation (at 20 μM), aside from the chelating ability of Cu^{2+}, Zn^{2+} and Fe^{3+}. In addition, compound **103** showed significant effects in reducing Cu^{2+}-Aβ-induced cellular ROS production, neuroprotection in human SH-SY5Y neuroblastoma cells and low cytotoxicity. Interestingly, compound **103** showed a much better neuroprotective capacity than resveratrol (**2**) at a concentration of 10 μM and showed good BBB permeability. Overall, these properties highlight compound **103** as a new promising candidate for anti-AD multifunctional drugs [171].

Chao and co-workers investigated the neuroprotective effects of four synthetic methylated resveratrol derivatives (**104-107**) for their potential use in the clinic for PD. The study of their effects on dopaminergic human SH-SY5Y cells by monitoring changes in the level of lactate dehydrogenase (LDH) release and the activity of caspase-3 triggered by 6-OHDA revealed compound **106 (**Fig. **47**) as the unique derivative with a potent neuroprotective effect. Notably, in comparison to resveratrol (**2**), **106** showed a higher neuroprotective effect in a wide concentration range. Additional data suggested **106** to have higher cell permeability than **2** and, thus, could result in a higher effective intracellular dosage. Furthermore, Western blot analysis of the JNK–c-Jun and mTOR pathways and GSK-3β signaling in neuronal cells treated with **2** and **104** indicated that inhibition of 6-OHDA-activated JNK pathway and modulation of mTOR kinase activity may be involved in the neuroprotective mechanism of **106.** These findings contribute significantly to the future design and development of stilbene-like small molecules with potential disease-modifying use against PD and other NDs [172].

Literature data suggest that studies on resveratrol (**2**) metabolism in human beings produce similar results to those obtained from rodent models. In addition, sulfation and glucuronidation of resveratrol in the human liver seem to be the main metabolic conjugation reactions, whereas sulfation is

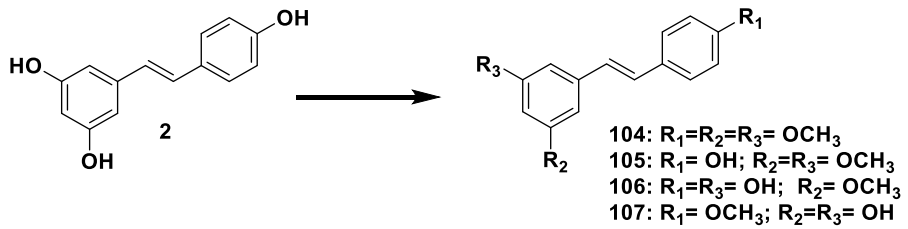

Fig. (47). Chemical structures of methylated resveratrol derivatives **104-107**.

predominant in a human duodenum preparation. These findings are corroborated by other studies that evidenced glucuronide and sulfate conjugates in urine and serum as main resveratrol metabolites after oral or i.v. administration [173-175]. Based on these data, Hoshino and co-workers developed a series of sulfate-conjugated resveratrol metabolites and assessed them in a set of cell-based assays indicative of chemoprevention, including inhibition of TNF-α-induced NF-κB activity, COX-1 and COX-2, NO production in macrophages and aromatase, induction of quinone reductase 1 (QR1), DPPH radical scavenging, and cytotoxicity in KB and MCF7 cells. In general, all sulfate metabolites **108-113** (Fig. **48**) showed to be less active than **2**, except for resveratrol 3-sulfate **111**, which exhibited antioxidant, COX-1 inhibitory activity and mediated comparable or even greater QR1 induction, and resveratrol 4'-sulfate **113**, which inhibited COX-1, COX-2 and NF-κB induction. The authors highlight that since serum concentrations of sulfated metabolites are higher than those of resveratrol, the residual bioactivity showed by some metabolites could be addressed in further studies in the search for new effective multi-target candidates to combat neuroinflammation, OS and neuronal death in NDs [176].

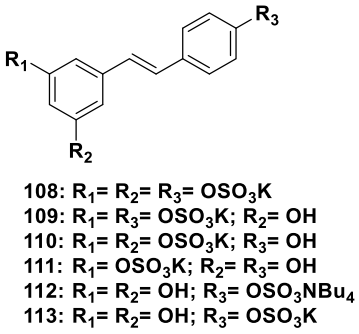

Fig. (48). Chemical structure of multi-target bioactive sulfate-conjugated resveratrol metabolites (**108-113**).

5. CANNABIDIOL (CBD) SYNTHETIC DERIVATIVES AND ANALOGUES

During the last few years, CBD (**3**) has been intensively investigated for its potential therapeutic benefits for NDs due to many reported pharmacological properties, including anti-inflammatory, neuroprotective and antioxidant, in addition to its effects on ECS modulation. Thus, considering the multi-target effects evidenced for CBD (**3**), it has been explored as a starting material and molecular prototype in the development of novel multifunctional candidates against NDs.

Breuer and co-workers investigated the neuroprotective properties of 4-fluoro-cannabidiol (**114**) and 10-fluoro-cannabidiol diacetate (**115**, Fig. **49**), and assessed the SAR contribution of the structural modification of CDB (**3**) by insertion of a fluorine atom as a substituent in different positions of its structure. Pharmacological evaluation based on a set of behavioral assays in mice predictive of anxiolytic, antidepressant, antipsychotic and anticompulsive activity evidenced compound **114** as considerably more potent than CBD (**3**). In addition, **114** showed anti-compulsive effects, similar to CBD, probably due to interactions with cannabinoid receptors [177]. In a more recent study, Perez and co-workers investigated compound **114** for its neuroprotective activity in motor and sensory neurons from neonatal rats. Biological data evidenced a significant neuroprotective effect of **114** at 2.5 and 5 mg/kg, leading to an increase of 42% in neuronal survival, showing a 3- and 6-fold higher dose-dependent neuroprotective effect in comparison to CBD (**3**). Moreover, compound **114** elicited an 80% down regulation in PPARγ, which is a bioreceptor broadly involved in the anti-inflammatory response, besides complete depletion of expression gene p53 that is an OS modulator and implicated in apoptotic events. These findings suggest that, at least in part, the higher neuronal survival promoted by **114** could be due to the modulation of anti-apoptotic pathways, and highlight compound **114** as a new promising CBD analogue of interest in the development of neuroprotective drug candidates for NDs [178].

Modifications in the structure of CBD (**3**) were also explored by Kinney and co-workers to obtain a series of resorcinol-like analogues with improved PK properties. Studies regarding neuroprotective effects on hippocampal neurons subjected to ammonium acetate and ethanol-induced OS of twelve CDB derivatives led to the identification of compounds **116-118** (Fig. **50**) as the most promising in terms of cell viability. The acylazetidine analogue **117** exhibited the best nanomolar potency in the prevention of damage to hippocampal neurons induced by both OS-inducers, with EC_{50} values ranging from 0,004 to 0,008 μM, followed by the ethoxy formyl-azetidine analogue **118** (EC_{50}= 0,02-0,11μM) and the triazole **116** (EC_{50}= 1-5 μM), with slight toxic effects only above 100 μM [179]. Due to its promising therapeutic relevance, considering the significant neuroprotective effects on hippocampal neurons, aside from showing better potency, safety, aqueous solubility and permeability than **3**, compound **117** was further investigated in different cellular models for neuroprotection, exhibiting a 31-fold higher potency and 5-fold less toxicity than CBD (**3**). The mechanism of action underlying neuroprotection promoted by **117** was evidenced to involve mitochondrial Na^+/Ca^{2+} exchanger-1 (mNCX-1), since intracellular Ca^{2+} plays an important role in OS [180, 181].

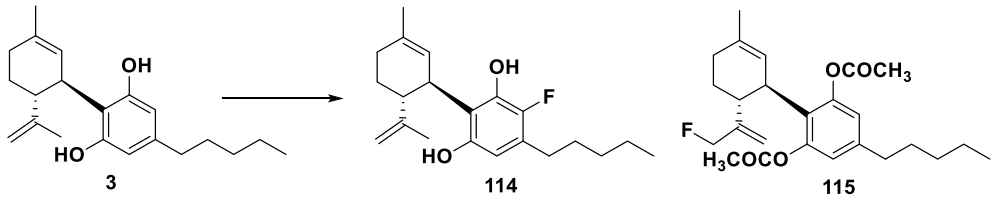

Fig. (49). Chemical structures of fluorinated CBD derivatives **114** and **115**.

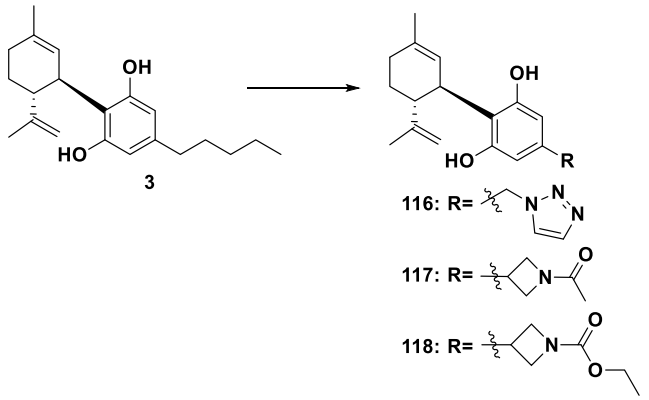

Fig. (50). Chemical structures of CDB-analogues **116-118** with enhanced neuroprotective and physical-chemistry properties.

(-)-Dimethylheptyl-cannabidiol (DMH-CBD, **119**, Fig. **51**), a non-psychoactive synthetic analogue of CBD (**3**), has been investigated for its anti-inflammatory and other beneficial effects on NDs. Studies on microglial cells of BV-2 mice stimulated by LPS evidenced a pronounced dose-dependent reduction in the expression of pro-inflammatory genes related to cytokine production, including IL-1β (88%), IL-6 (82%) and TNFα (48%) under treatment of **119** (10 μM). In addition, compound **119** led to upregulation of several genes related to OS and GSH homeostasis, including tribbles homologue 3 (Trb3), heme oxygenase 1 (Hmox1), and solute carrier family 7, member 11 [cystine/glutamate transporter subunit (Slc7a11/xCT)] by 10-folds, 4-folds and 5.4-folds, respectively, evidencing a reduction in the induced oxidative damage. Moreover, in previous studies, the same group has reported that CBD inhibited the *in vitro* MOG-induced proliferation of MOG35–55-reactive T cells (TMOG), which is an experimental autoimmune encephalomyelitis (EAE), commonly used as a model of multiple sclerosis (MS). These findings demonstrate that CBD is able to ameliorate the severity of EAE in myelin oligodendrocyte glycoprotein 35–55 (MOG35–55)-immunized mice and attenuate microglial activation and T-cell recruitment, and markedly reduce their Th17 inflammatory phenotype [182-184]. Based on the same experimental protocol, compound **119** also exhibited a similar inhibitory effect in TMOG assay at various doses (0.1–10 μM) and, overall, these biological data clearly suggest that derivative **119** may effectively assist in neuroprotection and respond in a modulatory manner to oxidative and inflammatory signaling [185].

Appendino and co-workers developed a new series of CBD-based aminoquinone derivatives as potential drug candidates for NDs. Among nine synthesized compounds, ligands **120-123** (Fig. **52**) exhibited pronounced activity in controlling gene expression related to neuroinflammation and neurotoxicity. These compounds were assessed for their agonist activity on PPARs, which are involved in the control of homeostasis in lipid and glucose metabolism and inflammation, showing significant effect, especially for analogues **120-122**. However, data from the literature suggest that long-term use of CBD-quinone structural analogues could enhance cytotoxicity due to their electrophilic nature and the possibility of alkylation of crucial cellular proteins and/or DNA and, in turn, the risk of adverse side effects. On the other hand, quinones are well-known highly redox-active molecules and may be responsible for increased ROS formation and OS; however, some quinone-based drugs have been approved for clinical use [186, 187]. Thus, considering that effects on keap1/Nfr2 pathway could be indicative of OS exacerbation, compounds **120-123** were investigated for their ability to activate Nrf2, and no significant activity was observed. In addition, the MTT test involving human oligodendrocyte cells (MO3.13) showed compounds **120-123** to exhibit cell viability of 80-100% at 25 μM, suggesting their cellular safety. In the light of these promising results, these quinone derivatives were further studied for their action on PPARs, highlighting compound **120**, which showed a high agonistic effect on PPARγ [188].

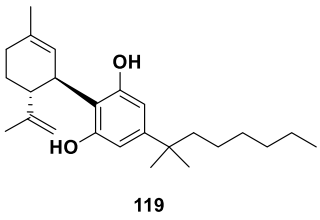

Fig. (51). Chemical structure of CDB-analogue **119** with effective antioxidant, neuroprotective and anti-inflammatory effects.

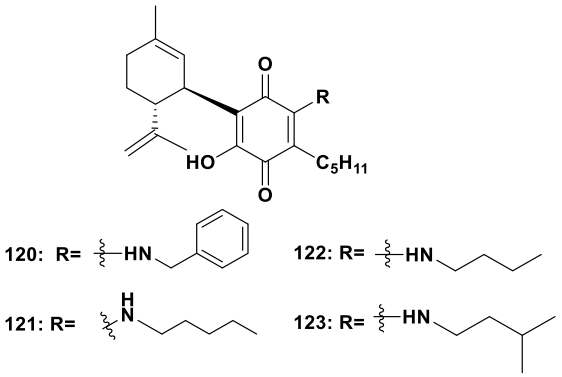

Fig. (52). Chemical structures of CBD-based aminoquinone derivatives **120-123**, with agonist effects on PPARs without significant cytotoxicity.

In order to better characterize the pharmacological profile and the therapeutic potential against inflammatory-related chronic illnesses, such as NDs, new studies were conducted on the CBD-quinone prototype **120**, also known as VCE-004.8. The molecular docking showed that **120** binds to the active PPAR site and exhibits different conformational effects. *In vitro* results confirmed that compound **120** effectively bound to PPARγ with IC_{50} value of 1.7 μM [188, 189], and also exhibited a high affinity for CB2 (Ki= 170 nM). Furthermore, compound **120** showed no cytotoxicity on NIH-3T3 cells in the MTT assay; in addition, it did not play any role as an ROS-inducing agent as the electron-donating substituent eliminates thiophilicity [189].

In another study, Navarrete and co-workers studied the potential effects of compound **120** on multiple sclerosis (MS), aiming to confirm its anti-inflammatory action. It was suggested that **120** could modulate the hypoxia-inducible factor pathway (HIF), and the transcriptional activity of the erythropoietin (EPO) gene, which is regulated by HIF-$_{1α}$ and HIF-$_{2α}$. In fact, experimental results confirmed that compound **120** strongly activated HIF pathway in a concentration-dependent manner (0,1-10 μM) through EPO gene expression in mRNA qt-PCR and MO3.13 cells, in turn, leading to neuroprotection. Evaluation of its anti-inflammatory properties by using primary cells of pre-incubated microglia with **120**, stimulated or not by LPS, evidenced its strong ability for COX-2 inhibition. In addition to the inhibition of hydroxylation of HIF-$_{1α}$ and a strong chelating ability for iron ions, probably due to the presence of the hydroxy and amino-enone functionalities in its structure, compound **120** showed to be a partial PPAR agonist, once it failed to induce an M2 polarization in the presence of IL-4, with a positive regulation of ARg-1, which could counteract the pro-inflammatory effects of iNOS. In conclusion, the authors suggest that the anti-inflammatory activity of **120** is mediated by PPARγ and CB_2 receptors, in addition to its neuroprotective activity mediated by the induction of VEGF and EPO genes [190].

CONCLUDING REMARKS

The use of curcumin (**1**), resveratrol (**2**) and CBD (**3**) as structural prototypes and starting materials or fragment-based strategies for MH have led to the development of a number of novel chemical entities with improved properties for NDs. In most cases, new neuroprotective, antioxidant and anti-inflammatory agents have been identified with multi-functional properties, which have been considered as promising starting points for new generations of neuroactive disease-modifying drug candidates for NDs. The large number of papers reporting the use of curcumin (**1**) and resveratrol (**2**) as structural prototypes in the design and optimization of new biologically active chemical entities makes it clear that they are widely recognized for their biological importance in the generation of chemical and pharmacological diversity, leading to novel hybrids of structurally modified molecules with enhanced pharmacological and PK properties. In a more recent scenario, molecular and pharmacological studies focused on CBD (**3**) as a non-psychotropic cannabinoid drug candidate have demonstrated a crescent global interest in the singular structural feature for drug design of novel multi-functional molecules capable of modulating ECS and other molecular targets involved in the pathogenesis of NDs. Overall, the combination of the singular multi-target biological properties of these three natural products has empowered the chemical intuition and creativity of medicinal chemists worldwide in the never-ending search for innovative, more effective and less toxic ligands that could be further developed as therapeutics for NDs.

CONSENT FOR PUBLICATION

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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