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Review Article

Perspective on Metal-Ligand Coordination Complexes and Improvement of Current Drugs for Neurodegenerative Diseases (NDDs)

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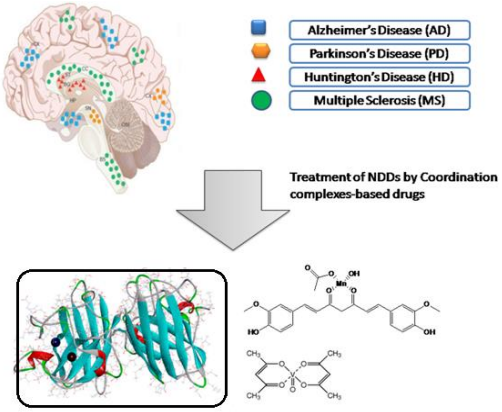
ABSTRACT

Neurodegenerative diseases (NDDs) associated with the steady loss of neural functionality by the action of irreversible damage or death of neurons are one the most serious diseases amongst human beings. The most common NDDs are including Alzheimer's disease, Prion protein disease, and Parkinson's disorder. Several coordination complexes are effective in the treatment of NDDs. In the present scenario, computational methods opened a new vista for novel drugs with theoretically improved overall effectiveness. This review highlights the current trends of computational designs of coordination complexes in developing new drug discovery options and their potential to treat different neurodegenerative diseases with up-to-date R&D exploration with future perspectives.

GRAPHICAL ABSTRACT



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Introduction: Overview and Human Impact

In general, neurodegenerative diseases (NDDs) can be defined as the progressive dysfunction and loss of neurons that cause dissimilar participation of neuronicarrangements[1,2]. The most common diseases under NDDs are Alzheimer's disease (AD): which involves acute dementia and frontotemporal dementia (FTD), Parkinson's disease (PD), demential Lewy bodies (DLB), Friedreich's ataxia (FRDA), Huntington's disease (HD), amyotrophic lateral sclerosis (ALS), and prion disorder [2-6]. Among the above-given NDDs, Alzheimer's disorder is the commonest and chiefly leads to the variable phases of dementia [4,6]. Neurodegenerative diseases account for the second-largest reason for deaths globally, with a considerable rise in disability [7]. The mortality rate for these diseases is forecasted to increase by 119-231% from 1990 to 2040 in the US alone [8]. Such an alarming increase in mortality rate points toward a better understanding of these diseases and drug development. The most common neurodegenerative diseases include Alzheimer's disease and Parkinson's disease [9]. Other diseases in this category include Huntington's disease, Spinal muscular atrophy, Lewy body disease, Friedreich's ataxia, and Amyotrophic lateral sclerosis [7]. Over time, a loss of nerve structure or function eventually leads to cell death. Unfortunately, these diseases have no known cure. However, the mental or physical symptoms associated with them can be mitigated. The symptoms of neurodegenerative diseases include memory loss, mood change, anxiety, apathy, agitation, and forgetfulness. Aging increases the probability of getting infected by these diseases by causing disarrangement in cellular homeostasis. The molecular mechanism by which neurodegenerative diseases lead to the disease includes protein aggregation (as in the case of Alzheimer's disease), protein misfolding, protein accumulation in the brain, mitochondrial impairment, proteolytic events, and nuclear trafficking.

Prions (or transmissible spongiform encephalopathies (TSEs) are a group of lethal neurodegenerative diseases that causes diseases (like Creutzfeldt-Jakob disease (CJD) in humans and animals. They have a very interesting molecular mechanism of action. They are misfolded proteins and can act as normal proteins in the brain to misfold. Several cell biology, X-ray crystallography, and NMR experiments are being conducted to understand its mode of action thoroughly. The disease originated when the normal cellular prion protein (PrPC) gets converted to its misfolded pathogenic form (PrPSc). They do not have a cure but can be slowed down using medications. Tauopathies are a particular type of neurodegenerative disease characterized by the presence of special tau (microtubule-associated protein) in the brain [10]. The function of tau protein in healthy neurons is to stabilize microtubules. Many filamentous inclusions are located in tauopathies' nerve cells (or glial cells). These diseases consist of Alzheimer's disease, frontotemporal dementia with parkinsonism-17 (FTDP-17), Pick disease (PiD), progressive supranuclear palsy (PSP), and corticobasal degeneration (CBD). Structural studies (like cryo-electron microscopy) are being carried out to understand the molecular mechanism underlying the disease progression and how different conformers play a crucial role in disease progression.

Heat shock proteins (HSPs) which play a crucial role in protein quality control, regulate the protein folding mechanism [11]. Protein misfolding, as mentioned above, is a major cause of neurodegenerative diseases. An association between the protein degradation system and heat shock protein is the key to maintaining cellular homeostasis. Another group of proteins that play lead to these diseases includes amyloid

aggregates. These proteins are formed in several neurodegenerative diseases like Alzheimer's and polyglutamine disease and possess characteristic β-sheet structures [2]. Therapeutics are being developed to understand the pathology of these diseases and cure them. Insilico studies pave the way for developing effective drugs against several diseases [12]. Molecular docking, MD simulations, and machine learning approaches are being developed to understand the system regulating these diseases. There are several natural products with the potential to cross the blood-brain barrier that is being studied using computational approaches to cure these diseases [13].

These NDDs heavily affect our human community worldwide, so much attention on the fast-track testing tools based on the design of novel diagnostic and therapeutic techniques has been undertaken worldwide [14]. Currently, several drugs are repositioned to treat AD and other NDDs. Examples are azithromycin, thalidomide, imatinib, galantamine, carmustine, tamibarotene, bexarotene, paclitaxel, etc. [1-3,12].

Several metals, such as Ca, Cu, Fe, and Zn, are essential elements that play a pivotal role in several life-cycle biochemical processes. Though aiming to develop new NDDs treatments, scientific R&D awareness has made a great diversity to develop lead compounds and target molecules. In this regard, metal homeostasis is one of the most common targets using the suitable ions of calcium, copper, iron & zinc [15]. In NDDs, protein aggregation and oxidative stress are both severe pathological stages that are commonly observed. The condition demonstrated that these processes are associated with the involvement of metal ions [16]. The rational design of multifunctional HP-based drugs targeting specific tissues or biomolecules, membrane crossing ability, delivery, and excretion capacity can be enclosed in the same molecular entity [17,18]. Metal ions perform many basic and essential biological performances leading to several significant biological functions within the brain, including synthesis/metabolism of neurotransmitters, oxygen transport, and nerve transmission [18].

Computer-Aided Drug Designing (CADD)

Essential for CADD

Today, antibiotic resistance leads to the development of new antibiotic-based research [19]. Toward the design of novel drugs,computer-aided drug design (CADD) can be combined with wet-lab techniques to elucidate the mechanism of drug resistance in search of promising-antibiotic targets and designedas novel antibiotics for both known and new targets. On the other hand, many repurposed drugs have already been FDA-approved and therefore face a cheaper and quicker journey to the clinic. Considerable CADD-based methods can produce an atomic level structure-activity relationship (SAR) used to facilitate the drug design process, thereby minimizing time and costs. On the other hand, many repurposed drugs have already been FDA-approved and therefore face a cheaper and quicker journey to the clinic [20-23]. In general, computational drug repurposing paid attention owing to the economically high costs and several obstacles with experimental setups can be reduced with excellent results [24-27].

Approaches applied in CADD

Molecular Dynamics(MD) Simulations

Principally, the drugs are developed through computational methods using the postulate that pharmacologically active compounds act by interaction with their macromolecular-level targets,such as peptides and proteins/nucleic acids. The influencing factor for these interactions is molecular surfaces and various

chemical and physical bonding, for example, hydrophobic interaction, hydrogen bonding, and electrostatic forces [28]. In general, CADD involves two significant kinds of processes, (a) Structure-based CADD: The goal of structure-based CADD is to design a compound that binds tightly to the target protein that is with low free energy, improved ADMET (absorption, distribution, metabolism, excretion, and toxicity) properties and are target specificity design molecule/drug according to target protein structure and structure of target protein must be known, and (b) Ligand-based CADD: If a series of active ligand molecule is known for the target protein, but little or no structural information exists for target protein then this method can be applied. This method is used to discover new or improved drugs when receptors with common properties concerning the known ligands' quantitative structure-activity relationship (QSAR) and pharmacophore methods [29].

Molecular Dynamic simulations have been utilized to study ligand-target interactions at an atomic level, generate conformational ensembles for the target in combination with other methods, and estimate relative free binding energies [30]. Using this technique, parameters such as the structural, dynamic, and thermodynamical properties of a molecular system are under investigation. Simply, a biomolecule (solute) like a protein, an enzyme, or a collection of lipids forming a membrane immersed in an aqueous media/solvent (most common: water or electrolyte). Select the biomolecules (*i.e.,* proteins and enzymes) that are being deposited in the Protein Data Bank (PDB) [31], which serves as a starting point for MD simulation studies. Additionally, if no structure is available in the data bank, modeling (predicting) with the structure for which several techniques are available is considered, such as homology or comparative modeling [32]. Following most typical examples of MD simulation software: such as VASP, GROMACS, AMBER, Adalone, CHARMM, NAMD, OpenMM, ADF, and many more.

Artificial Intelligence and virtual screening

Computational drug design has aided in developing many new anti-cancer drugs, making it a watershed moment in the field. Gefitinib [33], Erlotinib [34], Sorafenib [35], Lapatinib [36], Abiraterone [37], Crizotinib [38] are all approved drugs that have been discovered based on computational drug methods. Until now, anti-cancer drug development has progressed quickly, with recent promising findings coming from analytical and AI approaches. Artificial intelligence (AI) is becoming more widely used in drug production and design. This was made possible by the availability of broad chemical and biological databases, which are needed to create precise predictive models. According to scientists, AI can revolutionize the drug development process by allowing billions of potential molecules to be screened for hits, proposed alternatives to be prioritized, and biological targets to be validated. In the later stages of drug development, it can also be used to direct lead optimization and inform the design and execution of clinical trials. As a result, strategic AI implementation could greatly aid R&D efforts to develop new, reliable, safe drugs to alleviate human suffering caused by unmet clinical needs [38]. Deep learning networks with generative capabilities can formulate completely new molecules with the desired physical and biological properties, which can aid in developing drugs for difficult-to-treat diseases. They may also be involved in the improvement of existing molecules. They may also be involved in the improvement of existing molecules. Machine learning is used in the multi-objective optimization of lead molecules, allowing for the identification of compounds with a healthy balance of the required collection of

physicochemical, biological, and pharmacokinetic characteristics [39].

The rapid development of computing tools and small molecule databases has resulted in significant advances in the development of lead compounds in recent years. Computational approaches are rapidly being used to speed up the drug development process as the number of potential drug targets grows exponentially. As a result, computer-assisted drug design and chemical bioinformatics techniques such as high-throughput docking, homology search, and pharmacophore search in databases for virtual screening (VS) technology are being used more frequently [23,39]. Computer-aided drug design approaches use virtual screening as a critical component. It may be the most cost-effective method of identifying possible lead compounds, and several successful cases have used this technology. Physical screening of large chemical libraries for biological targets is the most popular method for discovering new lead compounds in drug discovery. High-throughput screening detects active molecules in experiments by conducting independent biochemical analyses of over one million compounds. However, this technology comes at a high price and takes time to develop new assumptions. As a result, virtual high-throughput screening, a less expensive and more efficient calculation tool, was developed [40-42].

Molecular docking and modeling

The molecular docking technique can interpret the interaction between a small molecule or ligand and a protein at the atomic level, enabling us to better understand and explain small molecule activity in target proteins' binding sites. The process for MD has 3 connected constituents binding site recognition, performing a search procedure to find the best-suited ligand to the receptor or protein, and then obtaining the scoring feature to compare the various binding conformation energies given off by each ligand-protein interaction [4,10,43]. There is various docking software available such as DOCK [44], AutoDock [45], GOLD [46], AutoDockVina [12,47], ConsDock, SymmDock, UCSF Dock [48], and many others are some of the docking software programs available.

The molecular docking procedure is divided into three steps. First, small molecules' and target proteins' structures should be planned ahead of time. In this step, the open-access PDB database [49] (http://www.rcsb.org) contains many experimentally solved structures that can be used to study several crystal structures, as well as homologous template models if docking structures are within the desired interest. Second, it can be used as an indicator for conformations, orientations, and positional spaces in the ligand-binding site [50]. By using systematic and stochastic methods, conformational search algorithms predict the conformations of binary complexes. Exhaustive search, fragmentation, and conformational ensemble are systematic analysis methods. Stochastic methods, on the other hand, involve (i) Monte Carlo (MC) techniques, (ii) Tabu search techniques, (iii) Evolutionary Algorithms (EA), and (IV) Swarm optimization (SO) techniques [51]. Finally, these methods measure the putative binding-free energy, which is used to assess the preliminary idea during molecular docking [52].

Liu and Wang [52] categorize them into three groups: (a) Binding affinity is determined using force field-dependent functions derived from physical atomic contacts in the target-ligand complex. It is also possible to determine solvation and entropy concepts. (b) Empirical-based functions suit experimental binding affinity data with simpler energy terms, like hydrogen bonding and hydrophobic interactions. (c) Knowledge-based activities derive binding energy from statistical measurements of protein-ligand atom pair frequencies in a training set [21,22]. New scoring technologies have also been

developed, such as (i) machine learning technologies, (ii) interactive fingerprints, and (iii) quantum mechanical scores [23].

Pharmacophore Modelling

Ehrlich was the first to suggest the idea of a pharmacophore in 1909. The pharmacophore is the essential feature responsible for a drug's biological activity, and it is the first step to understanding the interaction between a receptor and a ligand [53]. A pharmacophore is defined as "a set of spatial and electronic properties required to ensure optimal supramolecular interactions with specific biological targets and to trigger (or block) their biological reactions," according to the International Union of Pure and Applied Chemistry (IUPAC) [54, 55].

A pharmacophore is a molecular structure describing the basic properties contributing to a compound's biological activity. Pharmacophore models can be developed using the structural features of active ligands that bind to the drug target when structural knowledge about the drug target is minimal or unknown [56]. Pharmacophore screening aims to find compounds with different scaffolds but a similar three-dimensional arrangement of main interacting functional classes [57].

When the target structure's 3D information is identified, the binding site information can also generate pharmacophore models [58,59]. Pharmacophore models that use chemical characteristics like acidic/basic residues, hydrogen bond acceptors, and donors are considered the most efficient pharmacophore models. Digital drug screening in broad databases has also used pharmacophore modeling [32]. DISCO, GASP, and Catalyst are examples of programs that have been developed to recognize and develop pharmacophore models. GASP and Catalyst have been shown to work better than DISCO in reproducing pharmacophore models [60]. I3C (indole-3-carbinol) is a naturally occurring anti-cancer enzyme detected using QSAR. Because of its poor efficacy, this molecule has never advanced beyond clinical trials. The highly potent analog SR13668 was developed using ligand-based pharmacophore modeling to develop a novel drug that has been shown to be highly potent against many cancer forms [54]. The steps in developing a pharmacophore model can be summarized as follows [54-56]:

1. A literature search or a database search is used to identify active compounds known to bind to the desired target and have the same interaction mechanism.
2. Important atom types and their connectivity are described for a 2D pharmacophore model. (b) The conformations of a 3D pharmacophore model are described using IUPAC nomenclature.
3. Ligand alignment, also known as superimposition, is a technique for identifying common characteristics required in binders.
4. Development of pharmacophore models.
5. Assessment and selection of the best pharmacophore models.
6. Pharmacophore models Validation.

Pharmacophore modeling depends on the assumption that molecules with identical configurations of associated chemical groups, like hydrogen-bond donors or acceptors, or aromatic rings, can make comparable interactions with a receptor both spatially and geometrically and thus have similar chemical and biological activity. When chemical knowledge of several active ligands is available, creating a typical pharmacophore model may be possible. This model, in principle, represents the main molecular characteristics needed for action, including lipophilic, aromatic, hydrogen bonding, and charged groups. After the pharmacophore model has been developed, it can scan compound databases for molecules with similar properties. When the target structure is unavailable, pharmacophore modeling is widely used. Since

specific drug discovery targets, like ion channels, transporters, and G protein-coupled receptors (GPCRs), are difficult to crystallize, pharmacophore models are instrumental in searching for possible hits [57].

Coordination Complexes Targeting NDDs

Transition metal complexes tend to have many unique virtues, for example, various photochemical and photophysical properties, environment-responsive ligand exchange kinetics ability to generate particular interactions/linkages with macro and biomolecules, which make them exciting stands and suitable for drug delivery applications [22-26]. Herein we described metal-coordination complexes that showed efficiency to combat NDDs.

Platinum Complexes

Over the past few years, the functionalization and modification of platinum-based coordination compounds have gained attention due to their biochemical and biomedical applications around the globe. Most known platinum-based complexes have been used to prepare different drug targeting and delivery strategies in chemotherapy. Platinum-based anti-cancer drugs play a crucial role in treating various malignant tumors [58, 59]. The primary causative peptide, Amelyoid-β peptide (Aβ), is recognized for Alzheimer's disease because that contains a high-affinity metal-binding site which leads to aggregation/ modulation and toxicity evaluation [11, 12].

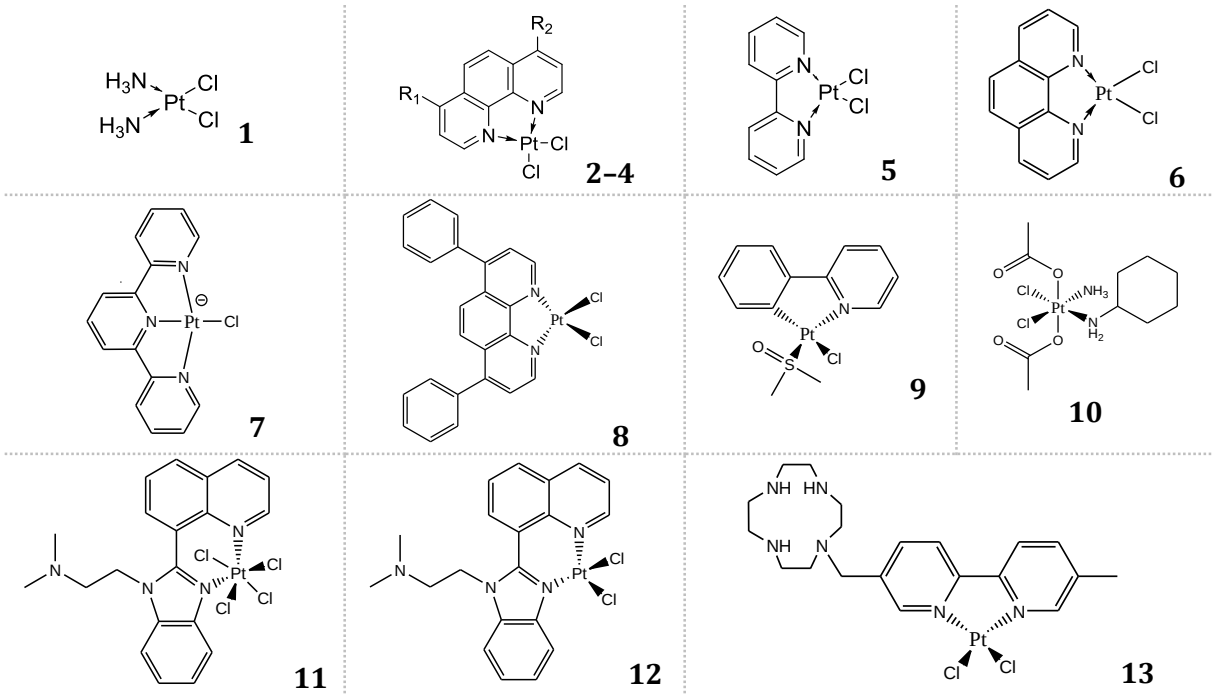


Figure 1. Structure of the Pt(II) complexes showing potential to treat NDDs through the interaction with the Aβ peptide, disrupt metal binding, and show promise in cell and animal models. *Cis*-platin (1), R_1=R_2=H=Pt(1,10-phenanthroline) chloride (2), R_1=R_2= =Pt(4,7-diphenyl-[1,10]-phenanthroline) chloride (3) R_1=R_2= = Pt(4,7-diphenyl-[1,10]-phenanthrolinedisulfonate) chloride (4), 2,2′-bipyridine (5), 1,10-phenanthroline (6), 2,2′:6′,2′′-terpyridine (7), Pt(ϕ-phen)Cl_2 (8), Pt(ϕ-MePy)(DMSO)Cl (9), Satraplatin (10), Pt1(11), Pt2(12), PtC(13).

Platinum-based transition complex *cis*-platin (**1**) is well known, and the first compound used to treat cancer disease. Other higher analogs were also reported to have the anti-cancer potential [59,60]. Despite this, there is limited evidence that Pt-based drugs are viable therapeutics for other diseases so far. In some studies, Pt-based complexes are observed to have significant therapeutic responses combating for NDDs, most likely AD [61].

Transition metal complexes are believed to treat AD due to their modulating/inhibiting effects on amyloids' aggregation under three prominent mechanisms: (a) coordination chemistry, (b) oxidative, and(c) proteolytic reactions [62-64]. Derrick *et al*. proposed that the responses depend on the tunable virtues of these investigated complexes, including the coordination geometry of the metal center and the oxidation state of the corresponding transition metal ion [63]. According to the study investigated by Barnham et al., the potent effects of Pt-complexes (**1–4**) have definedthe histidine residues of Aβ as a viable therapeutic target to inhibit the neurotoxic and synaptotoxic actions of Aβ [59]. In addition, Manna *et al*. [64] recently investigated Pt(II)-based coordination complexes (**5–7**) on β-Amyloid aggregation to assess the neurogenic potential thereof (Fig. 1).

Based on the obtained data corroborated, the hypothesis to enlarge the application field of already known metal-based agents to neurodegenerative diseases can be suitable alternatives as drugs with neuro-treatment. In this study, investigated complexes were found to have a significant affinity to repress amyloid aggregation in a dose-dependent way using Thioflavin T (ThT) binding assays. Moreover, Barnham reported other higher analogs of *cis*-platin (Fig. 1), and they were also found to show good Aβ-repressing behavior [61]. In the presence of Pt(ϕ-MePy)(DMSO)Cl complex (**9**), the interaction with Aβ results to a significant extent. Satraplatin, a Pt(IV) complex (Fig. 1, **10**), exhibits slow ligand exchange kinetics that has been found in its biological stability as well as orally bioavailability reported by Carr *et al*. in their earlier work [65]. In this regard, Kenche *et al*. (2013) prepared orally bioavailable Pt(IV) pro-drugs as modulators of Aβ peptide with a hydrophobic diamine (Pt1:**11**), and its Pt(II) analog (Pt2:**12**) [66]. Consequently, PC1 (**13**) was synthesized as a bifunctional complex consisting of one or two cyclen metal-binding moieties attached to a bipyridine Pt(II) binding unit [67]. PC1 complex exhibit overall good performance towards aggregation through binding and metal scavenging ability.

The Pt(IV) complex uptake was noticed in comparison to its Pt(II) complex [70]. Fig. 1 Pt1 complex depicted the treatment of an APP/PS1 mouse model of AD showed a statistically significant reduction in CSF $A\beta_{1-42}$ levels and a reduction in the plaque loading phase. Thus, the Pt(II &IV)-based drug strategies are believed to hopefully develop Pt-complexes that can selectively target on Aβ peptide chain. Therefore, they have highly promising capabilities to treat NDDs rather than AD with more clinical studies [67-70].

Copper Complexes

Copper-containing complexes have been found of great importance in medicines for centuries. Aβ plaque binding capacities have been reported for ^{64}Cu (half-life of the 64Cu isotope = 12.7 h) complexes that incorporate amyloid-binding moieties into the molecule and are currently used in approved plaque imaging agents (Fig. 2; **14**&**15**) [71]. Studies revealed that both**14**&**15** have applicability and feasibility for brain imaging applications [6,71]. Several studies indicated that copper-based chelators play vital therapeutic responsibility in inheriting disorders as well as in neurodegenerative diseases, for example, Alzheimer's, Wilson's, Parkinson's, and Menkes. [72,73], and prion diseases [73]. Further

associated works indicated that the phenolic-OH in curcumin was found to have biological properties. In addition, the intrinsic antioxidant activity of curcumin was associated with a favorable non-planar coordination geometry of the complex Cu(Curc)(OAc)(OH) (**16**) investigated through the superoxide (O^{2-}) reducer. Furthermore, a good NO free radical scavenging ability of Cu-derivative (**17**) becomes a neuroprotective and a potential agent in treating epilepsy and other NDDs induced by oxidative stress [74].

Generally, the prion diseases that develop as a result of the conformational conversion of the normal form of the transmissible prion protein (PrP^{C}) into the disease-associated form (PrP^{Sc}) belong to the family of rare and progressive neurodegenerative disorders (NDDs). An *In vitro* study was performed by Kou *et al*. based on a multi-target strategy to design and synthesize assessment for anti-Alzheimer's profiling on Cu-based xanthone derivatives (**18**&**19**) [72]. In the study, all Cu-based xanthone derivatives were observed to have a significant metal chelating property and exhibited selective inhibitory activity against Acetylcholinesterase (AChE). Notably, amongst all the tested compounds, complex (**18**) showed considerable AChEinhibitory action (IC_{50} value = (0.193 ± 0.003) μM) as standard comparable with tacrine. Consequent work was further progressed by Lim *et al*. and Noor *et al*. to evaluate the Amyloid-β Plaques binding capacities of Cu-*Bis*(thiosemicarbazonato) and stilbene-based complexes (**19-21**) [73-75]. More R&D work is needed focusing on ^{64}Cu complexes with clinical extrapolation.

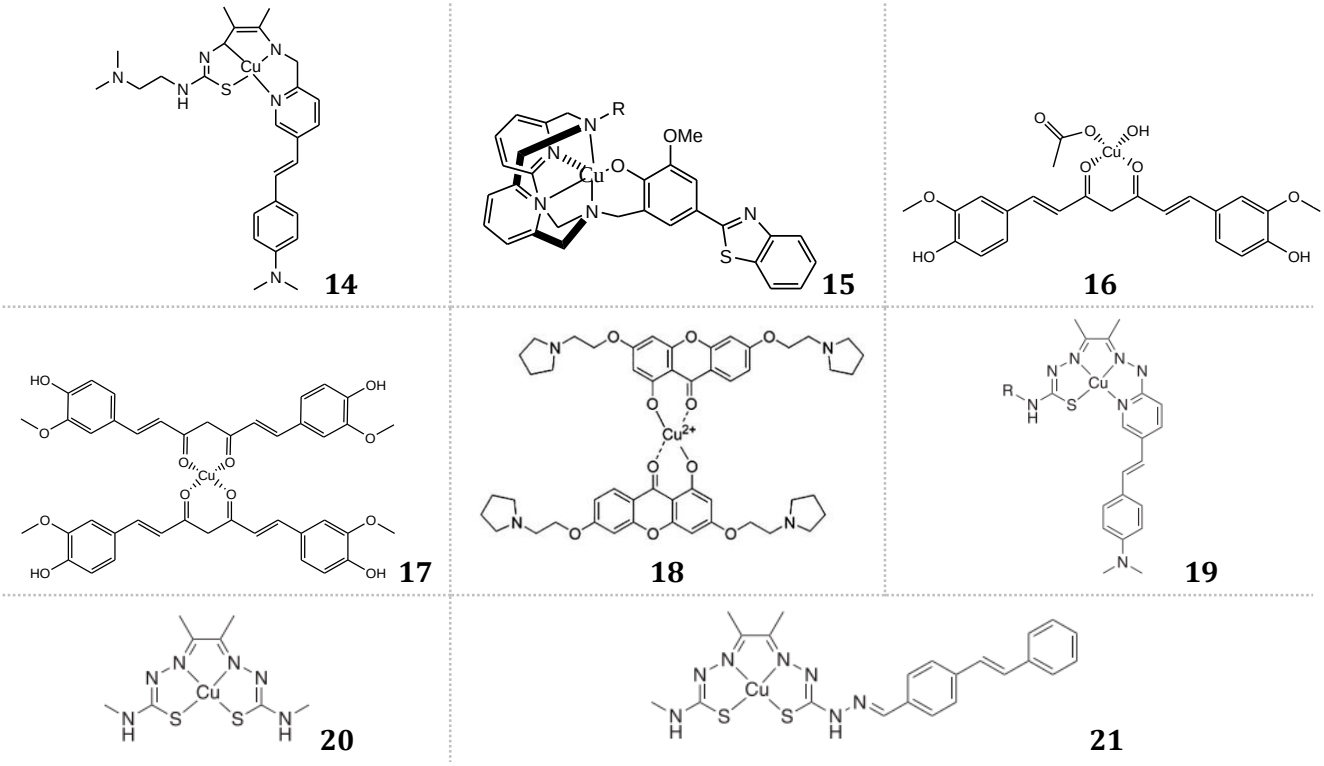
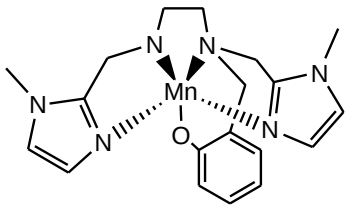


Figure 2. Cu-complexes used as plaque imaging agents and showed remarked biological activities towards NDDs. ^{64}Cu-styrylpyridine derivative (**14**), ^{64}Cu-benzothiazole derivative (**15**), Cu-curcumin chelate derivative (**16**), Cu-curcumin chelate complex derivative (**17**), Cu-xanthone derivative **(18)**, Cu-(thiosemicarbazone-styrylpyridylhydrazone) complexes [R = CH_3 or $-(CH_2)_2N-(CH_3)_2$] (**19**),[Cu(atsm)] (**20**), [Cu(atsm/a-stilbene] (**21**)

Manganese Complexes

Manganese is recognized as an essential trace element. Manganese has been utilized as a cofactor in several enzymes and metalloenzymes. It is profoundly referred to as an essential transition metal that actively participates in many life processes, such as growth, development, and neuron functioning [71,72]. Additionally, previously well-defined effects of lithium over neurodegenerative disorders transition metals such as Pt, Cu, Zn, and Mn have demonstrated promising effects in treating NDDs [70]. Lab coworkers of Hureau research's group have evaluated an Mn(II) (**22**) superoxide dismutase (SOD) mimic complex for the viable therapeutic target to neurotoxicity and synaptotoxicity for the inhibition of Aβ aggregation [76]. However, Mn curcumin complex (**23**) of Cu-curcumin (**17**) has shown more excellent performance towards the inhibition of Aβ aggregation [77].



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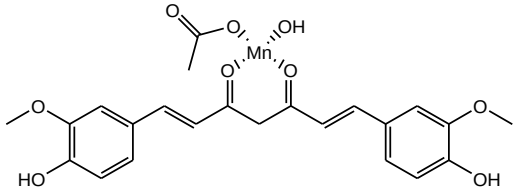

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Figure 3. Mn-complexes promising for the treatment of NDDs. Mn (II) SOD mimics the complex (**22**) and Mn(II) complex of curcumin as an organic framework

Ruthenium Complexes

Generally, Ru complexes are considered to be less toxic than Pt complexes with excellent biological activities. This attitude made them attractive candidates for further development to treat NDDs. Firstly, Valensin *et al*. reported a *fac*-[$Ru(CO)_3Cl_2(N^1$-thz)] complex (**24**) (Fig. 4) that selectively targeted His residues on Aβ aggregation [77]. Wang *et al*. reported further Ru-pyridine-based complexes (**25**&**26**) and found positive results regarding prion protein ($PrP_{106–126}$) inhibitory activity [78]. Both the Ru-pyridine-based complexes were found successful in inhibiting action against Aβ peptide aggregation as well as prion protein inhibition.

Owing to the interesting electrochemical, photophysical, and biological properties, Ru(II) polypyridyl complexes have been extensively under consideration for the last few decades. Messori *et al*., in a consequent study, investigated Ru(III) complex, PMRu20 (**27**), as inhibitor of $Aβ_{42}$ aggregation and obtained fine observations combating AD [79]. In another study performed by Vyas *et al*., theoretical and experimental data of two Ru-pyridine-based complexes (**28**&**29**) showed potential for AChE inhibition and Aβ aggregation blocking [80]. The results from the study proposed that the complexes have the potential to be applied for NDDs treatment. Several Ru(II&III) polypyridyl complexes (**31–36**) (Fig. 4) have been reported to have the ability to interact with Aβ peptide aggregation. Their functionality was believed to be due to the hydrophobic nature of the bpy/phen ligands [69,81-83].

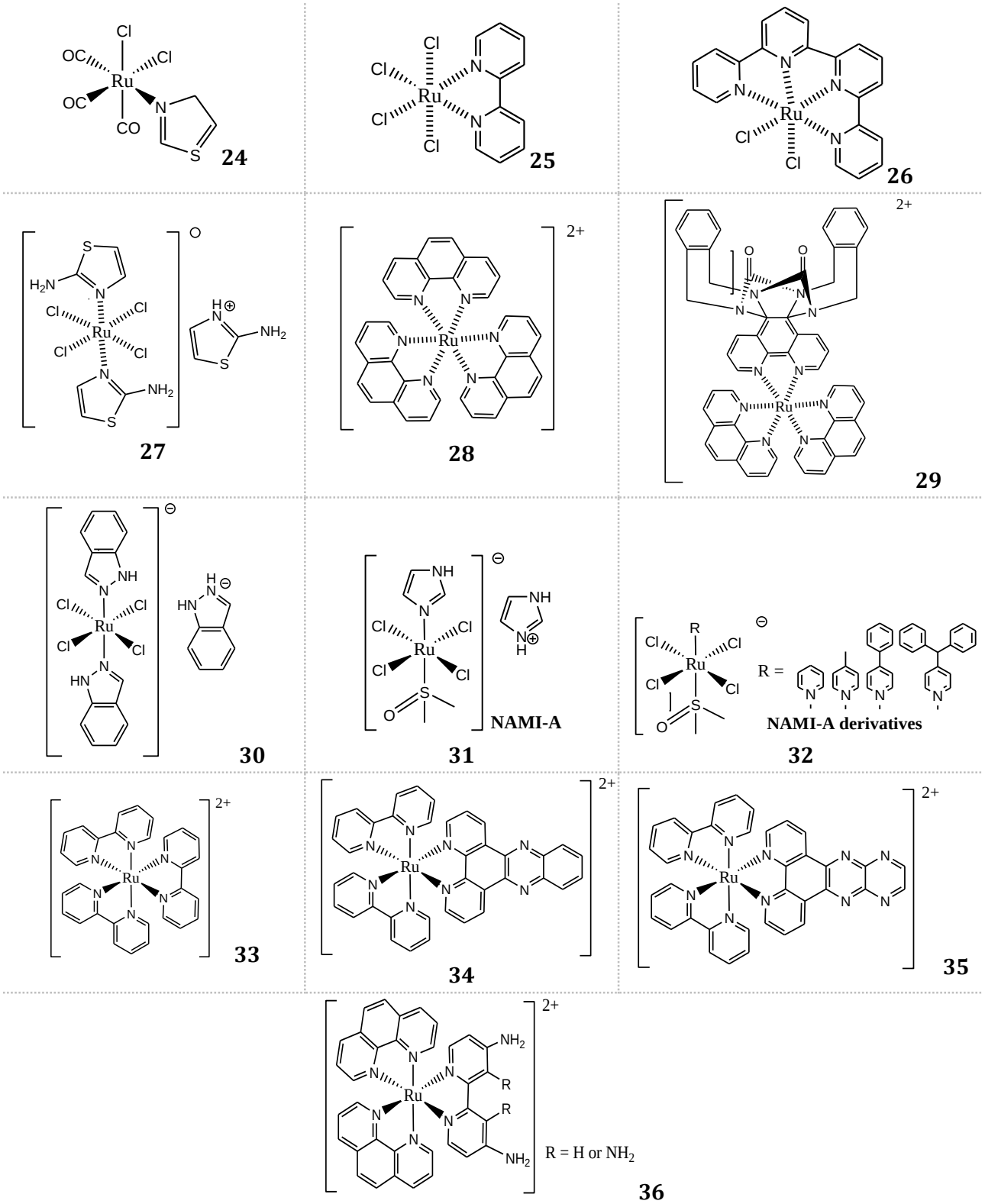


Figure 4. Ru-complexes promising for the treatment of NDDs [77-88].*fac*-$[Ru(CO)_3Cl_2(N^1\text{-thz})]$ complex (**24**)**,** [Ru-dipy] complex (**25**), [Ru-tetrapy] complex (**26**), Rh-PMRu20 (**27**), Rh-polypyridinyl complexes (**28**&**29**), Ru-KP1019 (**30**), Ru-NAMI-A complex (**31**), Ru-NAMI-A derivatives (**32**), $[Ru(bpy)_3]^{2+}$ (**33**), $[Ru(bpy)_2(dppz)]^{2+}$ (**34**), $[Ru(bpy)_2(dpqp)]^{2+}$ (**35**), $[Ru(Apy)]^{2+}$ (**36**).

Rhenium and Technetium Complexes

Fundamentally, both the rhenium and technetium find their applications as promising future diagnostic and therapeutic radiopharmaceutical agents. The metal complex plays an essential role in the biological behavior of a radiopharmaceutical and is decisive for success or failure [84,85]. In the present scenario, many complexes of Re and ^{99m}Tc have been investigated for their possible probing abilities to combat NDDs. Several reported complexes of Re and ^{99m}Tc are shown in Fig. 5 (**37-46**) targeting Aβ aggregation for the development of ^{99m}Tc analogs for diagnostic imaging of AD, and these studies have provided vital information on the peptide aggregation process *via* luminescence [69, 84-86]. Recent developments in the relevant coordination chemistry of Re and Tc have been explored for the past few decades resulting in excellent biomedical applicability. In this regard, beta-emitting isotopes of rhenium offer a possible method for the in situ treatment of cancerous tissue using analogous targeting strategies to those for technetium [85].

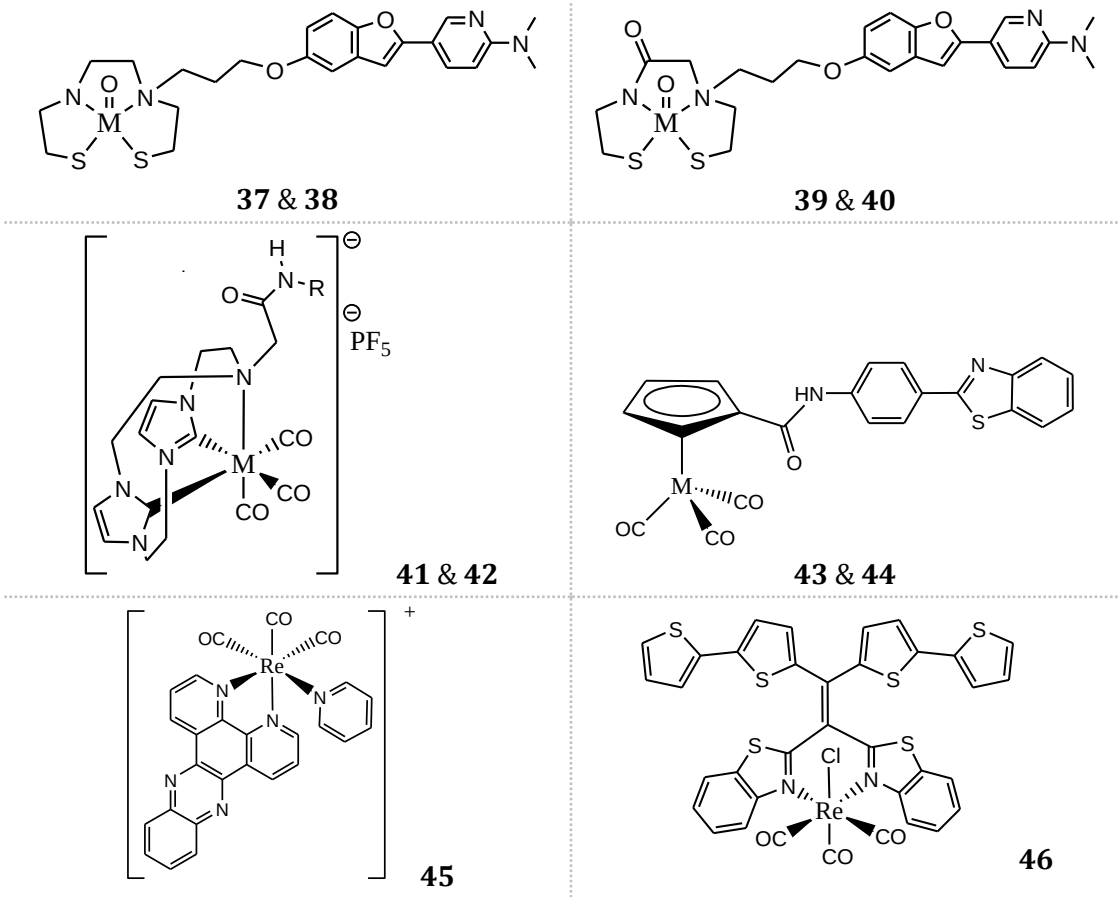
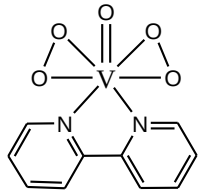


Figure 5. Re and ^{99m}Tc-complexes promising for the treatment of NDDs [77,90]. BAT chelate M=Re (**37**); M=^{99m}Tc (38), MAMA chelate =Re (39); M=^{99m}Tc (**40**), Carbene ligated M=Re (**41**); M=^{99m}Tc (**42**), *Cp*-ligated =Re (**43**); M=^{99m}Tc (**44**), Re-Luminescent probes (**45**&**46**).

Vanadium Complexes

Vanadium-based complexes, especially oxovanadium complexes, have been known to exhibit many biological functioning such as anti-cancer properties [86] and anti-diabetic properties; dioxidovanadium(V) complex cis-$[VO_2(obz)py]$ on renal function in diabetic rats [87] as they have demonstrated the ability to induce apoptosis in cancer cells. Due to their biological activities, their use could be a promising route to take in the fight against cancer and AD disorder. Comparatively to other metal complexes, there is a limited number of studies on the interaction of vanadium complexes with the Aβ peptide aggregation. He *et al*. recently investigated V(V) peroxo complex (**47**) $[VO(O_2)_2(bipy)]^-$(Fig. 6) for the Aβ peptide inhibition and fibril formation *via* Met-35 oxidation [86]. Consequently, this research group also reported a familiar approach to modifying the prion protein aggregation and human islet amyloid polypeptide framework [87,88]. In a meaningful work, Dong *et al*. [89] investigated the potential effects of the anti-diabetic vanadium, vanadyl(IV) acetylacetonate (VAC), on AD through *in vitro* and *in vivo* models. Hence, additional research dimensions should be required to encourage the vanadium complexes in NDDs treatment strategies.



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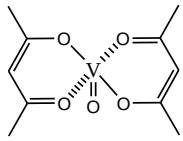

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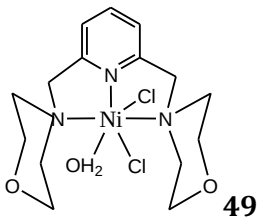
Figure 6. Vanadium complexes showing prominent anti-NDDs potential. $[VO(O_2)_2(bipy)]^-$ (**47**), $[VO(acac)_2]$ (**48**)

Nickel Complexes

Although nickel plays many vital roles in biological systems, nickel has been found to be less investigated to treat NDDs. Metals such as ruthenium, zinc, and copper are known to modulate Tau conformation and enhance its aggregation. In the current work, emphasis on understanding the interaction of nickel complex (**49**) (Fig. 7) with *Tau*protein was investigated by Gorantla *et al*. [90]. In this study, it was concluded that nickel and its synthetic conjugate (**49**), being non-toxic to neuro2a cells and preventing *Tau* aggregation, might help overcome AD and related disorders.



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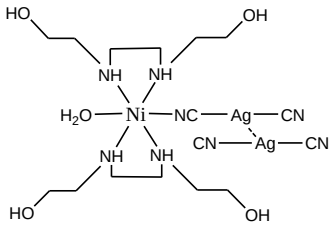

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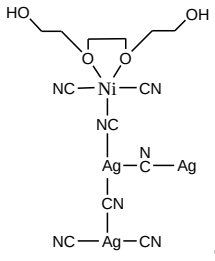

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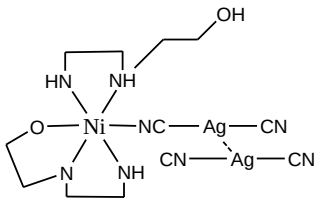
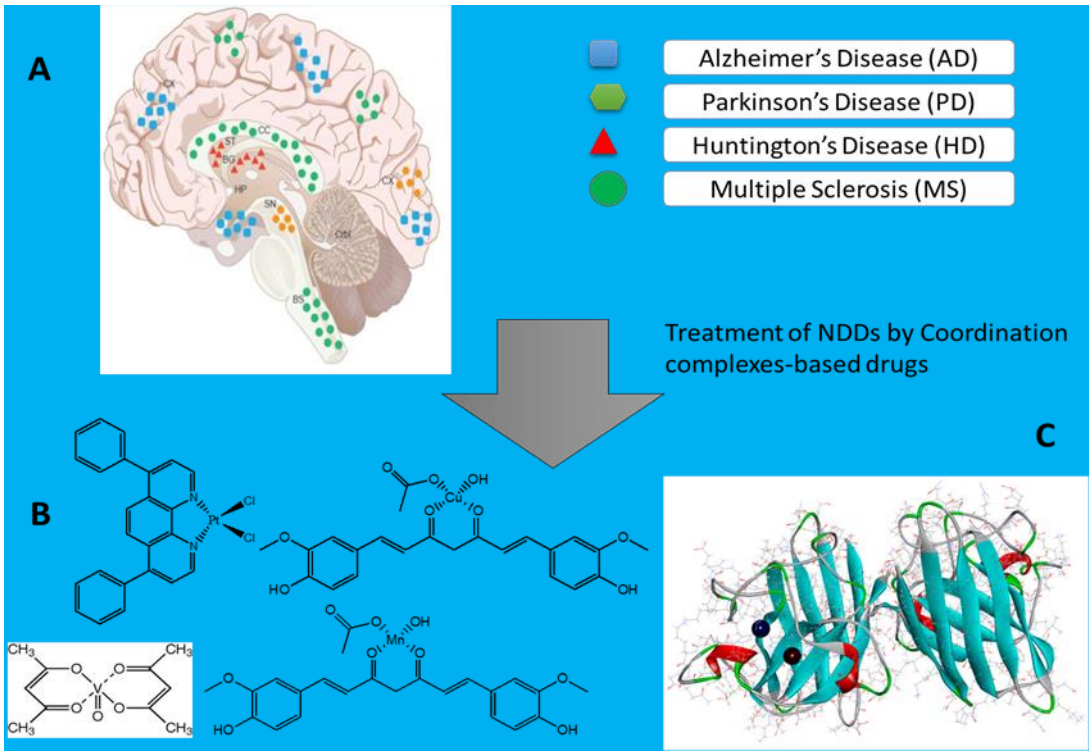


52

Figure 7. Nickel complexes showing anti-NDDs potential to *tau* protein aggregation and AChE inhibitors. DSA1:[Ni(bis-hydeten)$_2$] $[Ag(CN)_2]_2.H_2O$ (**50**), DSA2: $[Ni(edbea)Ag_3(CN)_6]$ (**51**), DSA3: $[Ni(hydeten)_2Ag(CN)_2][Ag(CN)_2]$ (**52**)

Kisa *et al*. reported the computational design of nickel complexes as novel analogs (**50–52**) (Fig. 7) for treating Alzheimer's, glaucoma, and epileptic diseases. The primary neurodegenerative diseases and their treatments using coordination complexes-based drugs (A) and, Promising candidates based on Coordination entities to treat NDDs (B) [91]. Notably, neurodegenerative diseases are characterized by abnormal protein/tissue protein formation, i.e., β-amyloid in AD, Huntington-defective proteins in HD, a combination of ubiquitous proteins in amyotrophic lateral sclerosis, Tau and β-amyloid in MS accumulation, α-synuclein accumulation in PD, and tau neurofibrillary tangles in traumatic brain injury. Evidence suggests that the proliferation of well-mixed proteins from cell to cell profoundly affects disease progression. Moreover, in the present scenario, more research is recommended with systematic clinical trials combating for NDDs based on the latest approaches, more likely computational methodologies [92].



Scheme 1. Major Neurodegenerative diseases and their treatments using Coordination complexes-based drug effects. **(A)** Major Neurodegenerative diseases, and their associated regions; Abbreviations: Basal ganglion (BG), Brain Stem (BS), Cerebellum (Crbl), Corpus callosum (CC), Cortex (Cx), Hippocampus (Hp), Striatum (St), Substantia Nigra (SN) (Adapted from Ref. [94] under CCBY Creative Commons), **(B)** Promising candidates based on Coordination entities to treat NDDs, and **(C)** Human superoxide dismutase structure—SOD1 with copper (brown) and zinc (deep blue) ions; PDB Code 2C9V.

Conclusions and Future Prospects

The review encompasses an overview of some of the favorable alternatives currently being developed to combat neurodegenerative diseases (NDDs) concerning transition metal-based complexes and chelating agents with recent computational approaches. Previously well-defined effects to overcome neurodegenerative disorders, transition metals such as platinum,

copper, manganese, ruthenium, and rhenium have shown considerable ability to treat NDDs/disorders. Described complexes have the significant ability and potential to be used in combating for NDDs treatment by targeting Aβ peptide, tau, and prion protein aggregation. As we continue learning more about neurodegenerative disorders, new opportunities will be presented for transition metal complexes, primarily via computational approaches. Although some prion and Aβ-targeted metal complexes have been found promising for further research as anti-AD drugs. The toxicity *in vivo* and unclear pharmacodynamics and pharmacokinetic profiles are other tuff challenges. It should be noted that they are still in the very early stage of development and therefore want to proceed further before the phases of clinical trials. Towards future R&D, it would be pretty interesting if the scientific world would introduce a transition metal nanoparticle-based delivery system embedded/ doped into the complexes to improve future medicines to the contest of NDDs.

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Disclosure statement

The authors reported no potential conflict of interest.

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