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Metal Organic Framework for Neurodegenerative Disorders

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ABSTRACT

Neurodegenerative diseases, such as Alzheimer's and Parkinson's, pose a significant global health burden. Conventional therapies often face limitations, including the blood-brain barrier (BBB) and the complexity of targeting specific neural pathways. Metal-organic frameworks (MOFs), a class of crystalline porous materials, offer a promising avenue for addressing these challenges. With their tunable properties, high surface area, and potential for drug encapsulation, MOFs can be engineered to deliver therapeutic agents directly to affected brain regions.

MOFs can be designed to overcome the BBB by incorporating specific functional groups or ligands that interact with the endothelial cells of the BBB. Additionally, MOFs can encapsulate drugs within their pores, protecting them from degradation and enabling sustained release. This controlled release can improve therapeutic efficacy and reduce side effects. Furthermore, MOFs can be functionalized with targeting ligands to specifically deliver drugs to affected cells or brain regions, enhancing therapeutic precision.

Beyond drug delivery, MOFs have potential applications in imaging and diagnosis of neurodegenerative diseases. They can be used as contrast agents for magnetic resonance imaging (MRI) to improve visualization of brain tissue. MOFs can also be functionalized with fluorescent dyes or other imaging probes to detect specific biomarkers associated with neurodegenerative diseases.

While MOFs offer significant promise, challenges remain, including biocompatibility, toxicity, and scalability. Careful selection of metal ions and organic linkers is crucial to ensure the safety and efficacy of MOF-based therapies. Additionally, developing scalable and cost-effective synthesis methods is essential for their widespread application.

Keywords: Metal Organic Framework, Neurodegenerative Disorders, Neural Cells, Brain, Nanotechnology, Blood Brain Barrier, amyloid β peptide, α-synuclein, Insulin, Procalcitonin, Parkinson's Disease, Alzheimer Disease, Metal Ions.

INTRODUCTION:

Metal clusters, termed secondary building units (SBUs), serve as the fundamental constituents of metal-organic frameworks (MOFs), a class of porous polymeric materials. (1)1,4-benzenedicarboxylic acid (BDC) is an example of an organic molecule that connects metal ions to form the structure of a metal-organic framework (MOF). (2)

Three-dimensional crystalline coordination polymer networks, called metal-organic frameworks, or MOFs, are created when metal ions or metal clusters use coordination bonds to hybridize with organic ligands, polymers, or linkers. (3)Metal ions likeAl(III),Fe(III),Zr(VI), Cu(II), Co(II), Mg(II), Zn(II), Ti(III), Ca(II), and Ln(III) are commonly used inorganic building blocks in MOF synthesis. These metal ions can adopt various geometric shapes, such as square planar, pyramidal, trigonal bipyramidal, tetrahedral, and octahedral.*(4,5)They are not frequently utilized in real-world applications since metals like Ag(I) and Eu(III) are somewhat costly, and some of the other metal ions used to make MOFs, such Cd(II) and Co(II), are extremely hazardous. (6)Nonetheless, they advance our knowledge of the fundamental chemistry of MOFs. (7)

MOF sensors may occasionally identify numerous amyloid biomarkers (amyloid β peptides, α-synuclein, insulin, procalcitonin, and prolactin) more precisely than they did a few years ago when it comes to biological fluids like blood and cerebrospinal fluid. (8,9) Researchers have focused more on Alzheimer's disease monitoring than other amyloidoses, such as Parkinson's, which are underdiagnosed yet significant to society. (10,11)Before the numerous soluble amyloid species and peptide isoforms linked to Alzheimer's disease are found, there are still a lot of challenges to be solved. (12)Additionally, there are very few, if any, MOF

contrast agents available for imaging peptide soluble oligomers in real individuals. (13).To elucidate the contentious connection between the illness and the amyloidogenic species, research in this area must focus on the most effective therapeutic approaches. (14,15)

Increasing inflammation as well as oxidative stress in the brain are common with aging and are associated with the onset of neurodegenerative illnesses and the harm they cause. (16)The neuropathology of conditions like amyotrophic lateral sclerosis (ALS) may be influenced by Parkinson's disease (PD), (17) and Alzheimer's disease (AD). (18)manganese, iron, and other trace redox-active transition metals.(19)Furthermore, these activities may be mediated by certain metals. According to recent studies, transition metals sustain metal redox activity in neurodegenerative proteins via binding to partners, which is compatible with a pro-oxidant, free radical-producing role. (20)Multivalent metals adhering to colloidal aluminum (Al) may be a similar phenomena. (21)Changes in the quantities of copper- and iron-containing metalloenzymes (22), which participate in the processing of intermediates with partially reduced oxygen (23), as well as cells' antioxidant status (24), might potentially play a role in altered redox homeostasis in neurodegenerative diseases. (25) Nevertheless, it is still unknown whether the pathophysiology of the disease entails reduced enzyme activity or, more indirectly, a disturbance in transition metal homeostasis, especially in familial forms of ALS (26), which have been linked to mutations in superoxide dismutase. (27,28) This review aims to assess new findings suggesting that oxidative events are stimulated by redox-active transition metal ions. (29) We will address the relationship between reactive oxygen moieties' stimulation of glia and the ensuing pro-inflammatory cascade. (30)Both processes occur in the diseased and aging brain, and metal-induced events may exacerbate the neurodegenerative nature of the clinical lesion. (31, 32)

Neurodegenerative disorders include amyloid diseases, which include Parkinson's and Alzheimer's. They encompass a broad spectrum of illnesses with significant systemic impacts and are brought on by misfolded and aggregated proteins. (33) Early detection is crucial for managing these diseases due to their high mortality rates and significant effects on organ function. (34) The variety of amyloid disorders highlights the complexity of these issues and the need for advanced detection methods. These diseases can present with both localized and systemic symptoms. (35) Traditional approaches have focused on identifying biomarkers using imaging techniques (MRI and PET) or invasive procedures. (36, 37)

By protecting the delicate environment of the nervous system from toxins and viruses and precisely controlling the permeability and limits of chemicals, the blood-brain barrier (BBB) is an essential physical barrier that prevents damage and illness in the complicated environment. (38) The quantity of ions, amino acids, glucose, and transmitters which enter the cell through its pumps and transmitters may be regulated by this membrane. (39)

These days, MOF sensors are so sophisticated that they can occasionally even outperform the technology used to detect several amyloid biomarkers, such as insulin, α-synuclein, procalcitonin, prolactin, and amyloid β peptide, that are present in biological fluids including blood and cerebrospinal fluid. (40) Researchers have concentrated more on Alzheimer's disease monitoring at the expense of other amyloidoses, such Parkinson's disease, which are underutilized but have societal significance. (41) There are still many obstacles to overcome before the many soluble amyloid species and peptide isoforms connected to Alzheimer's disease can be identified. (42) Furthermore, the restricted availability of MOF contrast agents, if any, makes it conceivable to image peptide soluble oligomers in living persons. It is clear that further study in this area is needed to elucidate the complex relationship between the amyloidogenic species and the illness and to concentrate on the most promising therapeutic approaches. (43)

Research has demonstrated that metal-organic frameworks (MOFs) provide new therapeutic techniques that may be used to treat neurodegenerative diseases. The unique properties of MOFs, such as their enormous surface area, porosity, biocompatibility, and biodegradability, make them promising for nerve regeneration and repair. The capacity of MOFs to improve drug delivery systems, reduce oxidative stress, suppress neuroinflammation, and encourage neuron regeneration in neurological disorders has drawn the most attention. (44)The creation of a multifunctional nanoplatform based on nanoscale metal-organic frameworks (NMOFs) has demonstrated success in Alzheimer's disease therapy by concentrating on hyperphosphorylated tau aggregation and neuronal death, further highlighting the potential of NMOFs in the treatment of neurodegenerative diseases. All of these studies demonstrate how crucial MOFs are in giving patients with neurodegenerative diseases effective therapy options. (45)

Neurodegeneration causes neurons to gradually lose part of their structural and functional elements. Numerous studies have connected neurodegeneration to a number of degenerative diseases. (46) Patients' emotional and physical health may be significantly impacted by the neurological effects of neurodegeneration. Due to their widespread occurrence, some neurodegenerative diseases, including Parkinson's and Alzheimer's, have lately drawn attention from people all over the world. (47) Environmental factors have been proven to have a major influence on diseases linked to brain dysfunction. (48)Exposure of fetuses and early children to environmental pollutants produced by industry is the primary cause of most neurological disorders. Numerous neurotoxic metals, including pesticides, metal-based nanoparticles, lead (Pb), aluminum (Al), mercury (Hg), manganese (Mn), cadmium (Cd), arsenic (As), and aluminum (Al), have been linked to Parkinson's and Alzheimer's disease. (49,50)

Review of Literature:

A family of porous hybrid materials known as metal-organic frameworks (MOFs) is made up of metal ions connected by organic bridging ligands. Coordination bonds with appropriate organic ligands bind the many types of crystalline frameworks that make up these materials to metal ions and metal-ion clusters. These porous materials have a large surface area, a large variety of pore sizes, exceptional heat stability, and are very adaptable. As a result, these unique and tailored MOF materials are used in many different electrochemical sensor applications. In this work, the process of synthesising different MOF molecules is critically examined. (51)

Porous materials that fall within the metal-organic framework (MOF) class have piqued the curiosity of researchers for the past few decades. Hybrid materials, which blend inorganic and organic components, make up the majority of MOFs. The metal cluster is used as an inorganic component in the organic linker, which is composed of organic ligands. The functional groups that segregate or embed the target MOF between metal nodes and organic linkers enhance the materials' selectivity and dependability for certain applications, such as electrochemical sensing. (52)

Because of its vast surface area, various topologies, micro-to-meso porous structure, and drug delivery capabilities, the MOF has shown a wide variety of applications in the fields of gas adsorption, catalysis, optical storage media, sensing, separation, and redox-active electrode materials. Because it improves the electrocatalytic signal and permits precise and sensitive detection, stabilizing the metal nanoparticles inside the MOF pores is beneficial. (53)

Metal-organic frameworks (MOFs), porous hybrid materials that combine the beneficial properties of both organic and inorganic porous materials, have been the subject of intense research and development over the past several decades. These materials are made up of coordinated metal ions known as nodes or ion clusters and organic ligands known as struts. The vast array of potential combinations between organic ligands and metal nodes makes it easy to create MOFs with a range of characteristics. These features have a significant impact on MOF behavior and include a wide variety of pore sizes (from micropores to mesopores to macropores), stiff or flexible skeletons, and changeable surface affinities. (54)

According to M. Barani et al.'s research, brain diseases—a confluence of neurological and mental disorders—are the leading causes of mortality and disability globally in the recent past. For both governments and the millions of impacted people, this poses a significant challenge. These illnesses include depression, memory loss, brain tumors, selective disorders, and brain transport in adults, as well as different types of mental retardation and abnormalities of movement in children. Such disorders may be brought on by a combination of environmental factors (such as stress and aging) and genetic factors that emerge before birth and throughout brain development. (55)

Parkinson's disease (PD), a degenerative neurological condition that worsens with age, is typified by memory loss and motor dysfunction due to dopamine (DA) depletion and neuronal death in the pars compacta portion of the substantia (SNpc). The majority of DA-based alternative treatments for Parkinson's disease (PD) now available on the market consist of levodopa (L-dopa), DA agonists, and monoamine oxidase B (MAOB) inhibitors. Unfortunately, as has been clearly documented, not all therapies are helpful in halting the course of Parkinson's disease (PD). This emphasizes the need for innovative, cutting-edge methods. Salas &Gasca, 2021). (56)

The formal name for an extended structure composed of metal ions and porous organic linkers is a metal–organic framework. An extended structure is one in which the subunits occur in a fixed ratio and are organized in a repeating pattern. A MOF is a coordination compound that spans repeated coordination entities in one dimension and has cross-links connecting two or more independent chains, loops, or spiro-links. Alternatively, a coordination compound that moves across recurrent coordination entities in two or three dimensions might be called a coordination network. Coordination polymers, which are coordination molecules with repeating coordination units extending in one, two, or three dimensions, are a subset of coordination networks, which include MOFs. (57)

Neurodegenerative illnesses frequently affect both mental and physical capacities (Bonaz et al., 2021). (58) Most neurological illnesses are closely associated with aging and are expected to get worse as people age (Leak 2014). (59) The average life expectancy has significantly increased as a result of medical advancements (Shang, 2008). (60) Accordingly, the prevalence of neurological disorders is expected to rise as the population ages (Wittchen et al., 2011). (61) For most of these conditions, the two primary issues are still developing therapeutic drugs and identifying the cause (Stocchi, 2013). (62)Unfortunately, after much research, none of these issues have been resolved. Environmental factors have long been thought to have a part in neurodegenerative diseases (Nakamura, 2009). (63) This is evident in the case of Parkinson's disease, where epidemiological research has connected environmental factors to the condition (Tysnes, 2017). (64) Additionally, certain environmental neurotoxicants have been linked to neurological disorders other than Parkinson's disease, yet they also cause clinical and behavioral symptoms in patients with the

condition (Uversky, 2004). (65) Because of the wide variety of chemicals and the fluctuations in human exposure throughout a lifetime, it will be challenging to establish such connections.

There are important pathways shared by almost all neurological illnesses. Jellinger (2010) identifies many important pathogenic processes that occur simultaneously, including oxidative stress, protein aggregation, mitochondrial failure, and disruption of the blood-brain barrier. (66) Neurotoxicants can initiate or speed up these processes, causing neurons to degenerate (Cannon and Greenamyre, 2011). (67)

The early detection and identification of amyloid disorders as well as the successful creation of a therapy depend on the development of very sensitive and selective sensors. The limited abundance of these species and the cross-reactivity between monomers and oligomers have hampered several attempts to create tools for identifying, monitoring, and altering amyloidosis biomarkers in biological materials. (68)

Researchers have used a variety of carbon-based nanomaterials, polymers that are conductive, quantum dots, noble metals, and MOFs to improve sensing properties including sensitivity, selectivity, and response speed in an effort to find diagnostic biomarkers for amyloid disorders. (69)

The effective treatment of deadly human diseases including cancer, neurological conditions, metabolic diseases, and their aftereffects is a global concern given the quick development of contemporary medical research and technology. Numerous clinical studies conducted in the last several decades have shown the potential of biomacromolecules with therapeutic properties, including as proteins, peptides, small-interfering RNA, polysaccharides, and plasmid DNA, for the treatment of disease. (70)

Neurodegenerative diseases are characterized by the misfolded proteins unique to the illness, the gradual loss and degeneration of neurons, and the eventual emergence of cognitive and/or sensory impairment. These include amyotrophic lateral sclerosis (ALS), multiple system atrophy (MSA), Alzheimer's disease (AD), Parkinson's disease (PD), and Huntington's disease (HD). (71)

Specific nervous system dysfunctions can result from a variety of diseases that cause specific neuronal subsets, such as motor, cholinergic, or dopaminergic neurons, to gradually lose their quantity, shape, or function. (72)

Drugs' difficulties in passing through the blood-brain barrier (BBB) and our incomplete understanding of the underlying causes of neurodegenerative diseases have hindered therapeutic advancement in these conditions.

The development of neurodegenerative illnesses cannot be stopped by the few therapies now available. Effective therapies are therefore desperately needed. (73)

Objectives:

- The application of MOFs for biomedical and biological purposes has been exploded.
- MOFs-based materials can be employed for treating and diagnosing brain disorders.
- On the basis of MOFs, creative functionalized nanosystems have been created.

Research Methodology:

Using a variety of sensing techniques, including electrochemical (EC), electrochemiluminescence (ECL), , up-conversion luminescence resonance energy transfer (ULRET), and photoelectrochemical (PEC) sensing, fluorescence, Förster resonance energy transfer (FRET)this review article analyzes how MOFs aid in the detection of amyloid diseases. The limitations of MOF biosensors and the industry's difficulties are also briefly covered. The study project is based on secondary data collected from credible websites, newspapers, textbooks, journals, and publications. The majority of the study's research design is descriptive.

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Result and Discussion:

Metal Organic Frameworks (MOFs):

Metal-organic frameworks (MOFs) are a type of porous, crystalline material with diverse applications. (74)Metal ions or clusters act as the joints in MOFs, whereas multidirectional organic ligands act as links in the network structure. These webs can be one-, two-, or three-dimensional extensions of periodic structures. (75) We are glad to provide MOFs under the Basolite™ brand name. (76) These materials (Figure 1) (77) offer a good variety of metals (Al, Cu, Fe, and Zn), organic linkers (BDC, BTC, mIM), and pore shapes and sizes. (78)

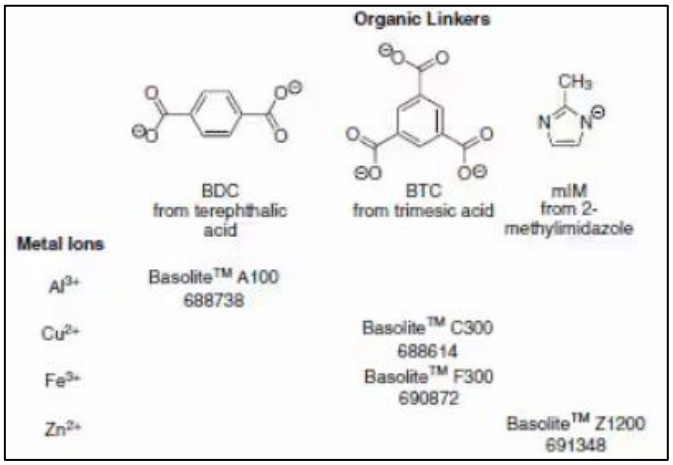

Figure 1.Organic linkers (79)

Amyloid Biomarkers

Early diagnosis is crucial to slowing the advancement of amyloid illnesses, which is a major lesson to be learned from their management and therapy. (80)In some cases, elevated levels of certain proteins or abnormal protein variants can be detected in bodily fluids years or even decades before any noticeable symptoms of disease appear. (81) Because the molecular mechanisms behind the production of amyloid fibrils in most cases of amyloidosis are similar, robust tests to reduce the threshold for detecting these biomarkers may be developed using the same principles (Figure 2). (82)

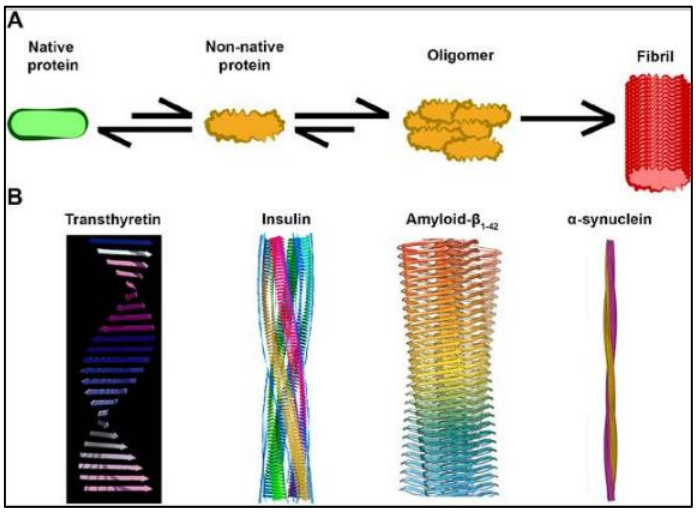

Figure 2:(A) A schematic representation of the mechanism by which amyloid is created. This process may be initiated by denaturation, overexpression, or cleavage of a normally folded protein, or by the formation of an intrinsically disordered protein. The figure's icons were obtained from reference (3). The unique makeup of the β strand is exemplified by structural models of amyloid protofilaments with different sources, including insulin, transthyretin, amyloid-β peptide, and α-synuclein. (4). Elsevier Copyright 1996. Reproduced by permission of ref (83)

Currently, around 20 human amyloid diseases are known to exist. These diseases are associated with the accumulation of protein aggregates that can occur spontaneously or be inherited and accumulate in localized tissues (medullary thyroid cancer, localized insulin-derived amyloidosis), the central nervous system (Parkinson's disease, Alzheimer disease), or the system (apolipoprotein amyloidosis, hereditary non-neuropathic systemic amyloidosis). According to estimates from the World Health Organization, people with Alzheimer's disease account for 60–70% of dementia cases that are currently being diagnosed globally. 6 metal-organic framework (MOF-based) sensorshave been created, the majority of which are meant to be utilized for Alzheimer's disease monitoring; a few are also targeted towards Parkinson's disease and other amyloid-related diseases. (84)

Parkinson's Disease Biomarkers

Parkinson's disease (PD) is the second most common neurodegenerative disorder after Alzheimer's, affecting approximately 10 million people globally. (85)Bradykinesia, resting tremors, and dementia are common symptoms of Parkinson's disease. The underlying cause is the degeneration of dopamine-producing neurons in the substantia nigra. A hallmark of the disease is the presence of Lewy bodies, which are protein aggregates containing α-synuclein. α-synuclein is a protein that can misfold and form harmful clumps, leading to neuronal damage. (86)Oligomers of α-synuclein are believed to be toxic to neurons by generating reactive oxygen species and damaging cellular vesicles. By the time symptoms appear, a significant number of dopamine-producing neurons have already been lost. Early detection of these oligomers is crucial, as they are present in very low concentrations in bodily fluids. (87)

Neurological Diseases

Neurological diseases affect the brain and spinal cord, characterized by a progressive decline in the structure and function of neurons. These disorders are categorized into three groups in Table 1: neuropsychiatric, neurodegenerative, and neurotraumatic, with a few examples of each group. These diseases have a variety of symptoms and are impacted by several unknown factors and origins. Many neurodegenerative diseases are linked to oxidative stress and inflammation. However, they can also arise from immune system dysfunctions, aging-related factors, environmental influences, and genetic predispositions.(88)

Table 1. Classification of neurological diseases

Neurological Disorders	Examples
Neurotraumatic diseases	Stroke, spinal cord injury, and traumatic brain injury
Neurodegenerative diseases	Alzheimer's, Parkinsons, and Huntingtons
Neuropsychiatric diseases	Autism, depression, and hyperactivity

Recent research has connected glutathione (GSH) to several brain disorders, such as autism, schizophrenia, and Alzheimer's disease.

Reactive oxygen species, such as free radicals, can damage essential cellular components in the body.This antioxidant helps stop this from happening. Its distinctive group is sulfhydryl, and its constituents include glutamic acid, glycine, and cysteine. Accurately measuring the serum GSH levels would therefore aid in the identification and diagnosis of theseconditions. GSH normally exists in cell concentrations between 0.5 and 10 mM; a drop in this concentration may serve as an early diagnostic indicator. (89)

Alzheimer's disease is the most common form of dementia and a fatal neurological disorder worldwide.The signs are memory loss, functional impairment, and a steady deterioration in cognitive capacity. This condition, which is increasingly frequent as life expectancy grows, is more common in those over 65. The brains of AD patients were shown to have three to seven times more metal ions (Cu2+, Fe3+, Al3+, and Zn2+) than normal, indicating that these ions might be the main cause of the illness. To identify these ions for the diagnosis of AD, many MOF fluorescence biosensors have been created. Table 2 provides several instances of these MOFs. (90)

Table 2 lists the MOFs that are utilized to find metal ions linked to Alzheimer's.

Metal Ion	MOF	Remarks
Zn^{2+}	$Cd_2(L^1)(DMF)_2(H2O)_2$	Zinc ions were selectively fluorescent detected over mixed metal ions in a methanol solution.
Cu^{2+}	$[Me_2NH_2][Eu(ox)_2(H_2O)]\cdot 3H_2O$	A 3D Eu-MOF was decomposed upon the exchange of copper ions with a cationic guest molecule, leading to luminescent quenching.
Al^{3+}	$Eu(L^4)(OAc)(DMA)$	The attachment of aluminum ions on the probe's surface reduces the energy transfer between Eu^{3+} and the ligand, resulting in luminescent quenching.
Fe^{3+}	BUT-14 BUT-15	BUT-15 showed a better sensing ability as its pyridine N donors donate their long-pair electrons to Fe^{3+} ions.

In addition to being utilized in AD diagnosis, MOFs are also employed in the illness's management. A possible theranostic platform is Fe-MIL88B-NH2-NOTA-DMK6240, a MOF developed by Zhao et al. for targeted drug administration and MRI. Their work was motivated by the tau pathological signature, which postulates a correlation between deteriorating cognitive impairment and elevated tau phosphorylation and aggregation. When tau is hyperphosphorylated, it causes AD development because it stabilizes microtubules in neurons. The MOF pores were filled with methylene blue in order to prevent tau from aggregating and to break down tau fibrils. It was also employed as a contrast agent for magnetic resonance.An enhanced DDS was formed when DMK6240 was applied on the surface to improve hyperphosphorylated tau targeting. (91)

Conclusion:

In order to preserve homeostasis and take part in the control of other metabolic processes, metals are essential components. Certain tasks can only be carried out in the presence and concentration of particular metals at particular sites. To prevent adverse effects, the metal concentrations should be kept within a scale. Neuron malfunction or death is caused by a deficiency or buildup of metals. Most MOF-based (metal–organic framework) sensors are designed to be utilized for Alzheimer's disease monitoring, while a small subset of them are targeted towards Parkinson's disease and other amyloid illnesses. Using appropriate imaging techniques, issues arising from this must be addressed in order to treat the disease. Appropriate diagnostic methods for ND patients are still lacking in order to detect cell death and provide a successful course of treatment. This is due to the blood–brain barrier's (BBB), a physiological barrier that restricts or eliminates the ability of outside items to enter the brain.

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