COHERENCE – The Multidisciplinary Research Journal
Volume No: 16, Issue No: 2, Year: 2025 (July-December)
PP: 1-12
ISSN: 0976-5301
Peer Reviewed & Refereed Journal (IF: 7.85)
Journal Website www.coherencejournal.in

ORGANIC DESIGN STRATEGIES AND DELIVERY CHALLENGES OF NEXT-GENERATION NEUROTRANSMITTER-BASED THERAPEUTICS FOR PARKINSON'S DISEASE

Puja kumari

Village + post: Mangrauni, Dist.: Madhubani,

ABSTRACT:

Parkinson's disease (PD) is a prominent neurodegenerative disorder characterized by the progressive degeneration of dopaminergic neurons in the substantia nigra pars compacta. This neuronal loss causes dopamine deficiency, leading to major motor symptoms such as tremor, bradykinesia, rigidity, and postural instability, along with several non-motor complications. Although present therapies, including levodopa (L-DOPA) and dopamine agonists, provide effective symptomatic relief, they do not prevent disease progression and may produce long-term complications such as dyskinesia and motor fluctuations. This review discusses emerging neurotransmitter-based therapeutic approaches for PD, with special emphasis on engineered analogues and prodrugs derived from dopamine, serotonin, and norepinephrine. These next-generation compounds aim to restore neurotransmitter balance more effectively while reducing adverse effects. From an organic chemistry perspective, their development involves important challenges such as achieving stereochemical purity, improving metabolic stability, and applying bioisosteric modifications to enhance receptor selectivity and minimize off-target actions. For instance, DAD9 represents a promising strategy by combining dopamine precursor activity with neuroprotective potential, thereby integrating symptomatic and disease-modifying effects. A major barrier in developing such drugs is their limited ability to cross the blood–brain barrier (BBB), especially because many neurotransmitter-like molecules are polar in nature. To address this issue, advanced delivery systems such as PLGA nanoparticles, receptor-mediated transcytosis, and lipid–peptide conjugates are being explored for targeted and sustained brain delivery. However, challenges related to large-scale synthesis, nanocarrier immunogenicity, and pharmacokinetic variability in elderly patients remain significant.

Keywords: Parkinson's disease, neurotransmitter analogs, organic synthesis, drug delivery systems, blood-brain barrier,

1. INTRODUCTION

Parkinson's disease (PD) is a gradually advancing neurodegenerative condition characterized by the degeneration of dopaminergic neurons in the substantia nigra pars compacta. This neuronal loss reduces dopamine levels in the striatum and produces typical motor manifestations, including bradykinesia, muscle rigidity, tremor, and postural instability. In addition to motor impairment, PD is also associated with non-motor disturbances such as cognitive dysfunction, depression, sleep problems, and autonomic abnormalities [1].

Available therapeutic options, particularly levodopa and dopamine receptor agonists, are effective in controlling symptoms but are unable to stop neuronal degeneration or prevent long-term treatment-related complications, including motor fluctuations and dyskinesia. These therapeutic limitations have encouraged the development of advanced neurotransmitter-based drugs that aim to re-establish neurotransmitter equilibrium through chemically engineered analogues and prodrugs based on dopamine, serotonin, and norepinephrine [2].

ISSN: 0976-5301
Peer Reviewed & Refereed Journal (IF: 7.85)
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The design of these compounds involves several organic chemistry challenges. Important requirements include maintaining stereochemical accuracy, enhancing metabolic stability, and introducing bioisosteric changes to improve receptor selectivity and reduce undesirable off-target effects. Hybrid drug molecules that combine dopamine precursor activity with neuroprotective antioxidant components represent one promising approach, particularly because oxidative stress is closely linked with PD pathology.

A further challenge is effective delivery across the blood–brain barrier (BBB), which limits the central nervous system entry of many polar neurotransmitter-like molecules. To overcome this limitation, advanced delivery platforms such as nanoparticle-based carriers and receptor-mediated transcytosis systems are being investigated for improved brain targeting and sustained drug release. However, issues related to manufacturing scale-up, immunogenic responses, and pharmacokinetic variability in elderly patients still require careful resolution.

Overall, the central objective is to shift PD therapy from symptomatic management toward interventions with both symptomatic and disease-modifying potential. This work examines chemical design strategies for neurotransmitter analogues, evaluates BBB-targeted delivery systems, and discusses translational pathways for future clinical application [3].

2. RESEARCH METHODOLOGY

This study employs a mixed-methods approach, combining systematic literature analysis, computational modeling, and experimental validation to investigate the design and delivery of next-generation neurotransmitter-based drugs for PD.

The methodology is structured into three phases:

(1) synthesis and optimization of neurotransmitter analogs.

(2) evaluation of delivery systems.

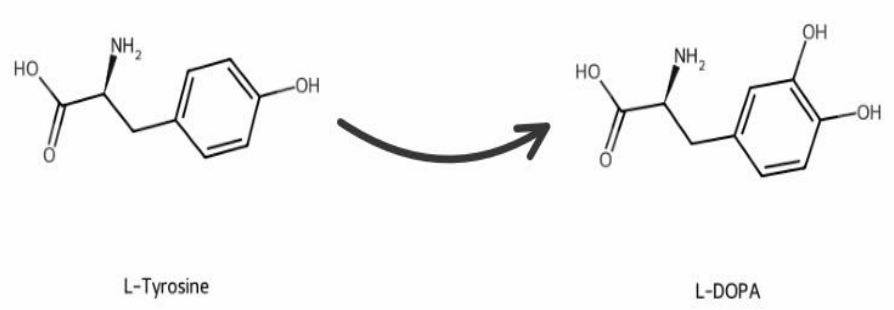
(3) in silico and in vitro validation of lead candidates.

Phase 1: Synthesis and Mechanistic Elucidation of Neurotransmitter Analogs

The synthetic component of this study is centered on the development of dopamine-, serotonin-, and norepinephrine-based analogues with improved receptor selectivity, greater metabolic stability, and potential neuroprotective effects. The proposed synthetic approach begins with naturally occurring amino acid precursors, particularly L-tyrosine and L-tryptophan, which serve as key starting materials for the preparation of neurotransmitter-inspired compounds. Through a series of controlled, stepwise chemical modifications, these precursors are transformed into biologically active analogues and prodrug candidates, including compounds such as DAD9 [4]

1. DOPAMINE ANALOG PATHWAY (FROM L-TYROSI

Step 1: Hydroxylation of L-tyrosine to L-DOPA



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Reagents/Conditions*: Tyrosine hydroxylase enzyme, Fe^{2+} cofactor, O_2, tetrahydrobiopterin (BH_4), H_2O.*

Mechanism: Tyrosine hydroxylase introduces a hydroxyl group at the 3-position of the aromatic ring via an Fe^{2+}/O_2 cofactor-mediated radical mechanism, producing L-DOPA.

Step 2: Decarboxylation of L-DOPA to Dopamine

L-DOPA Dopamine

Reagents/Conditions*: Aromatic L-amino acid decarboxylase (AADC), pyridoxal phosphate (PLP, vitamin B6 cofactor).*

Mechanism: Aromatic L-amino acid decarboxylase (AADC) removes the carboxyl group via pyridoxal phosphate (PLP)-mediated Schiff base formation, yielding dopamine.

Step 3: Bioisosteric Modifications

Dopamine Fluorinated Dopamine

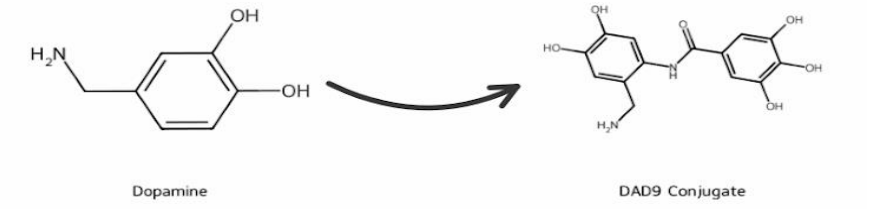
Reagents/Condition : *Fluorination: Dilute F_2 gas or Selectfluor reagent in controlled conditions. / Isoxazole substitution: 1,3-dipolar cycloaddition using nitrile oxides (generated from hydroxamoyl chlorides + base)*

Dopamine is chemically modified to improve metabolic stability:

- ➔ Fluorination at the catechol ring reduces susceptibility to MAO-B oxidation.
- ➔ Isoxazole substitution acts as a bioisostere, lowering off-target binding to D_1 receptors.

2. CONJUGATION TO NEUROPROTECTIVE MOIETIES (DAD9 SYNTHESIS)

Step 4: Amide Bond Formation with Antioxidant Moiety



Dopamine DAD9 Conjugate

Reagents/Conditions*: EDC (1-ethyl-3-(3-dimethylaminopropyl)carbodiimide), HOBt (1-hydroxybenzotriazole), DMF or DCM solvent, base (DIPEA or TEA).*

Dopamine or L-DOPA derivatives are coupled to gallic acid derivatives using EDC/HOBt-mediated amidation.

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Mechanism: EDC activates the carboxyl group, forming an O-acylisourea intermediate, stabilized by HOBt. Nucleophilic attack by the amine group of dopamine forms the amide bond, producing the DAD9 conjugate.

3. SEROTONIN ANALOG PATHWAY (FROM L-TRYPTOPHAN)

Step 1: Hydroxylation of L-tryptophan by tryptophan hydroxylase forms 5-hydroxytryptophan (5-HTP).

Reagents/Conditions*: Tryptophan hydroxylase enzyme, Fe^{2+}, O_2, tetrahydrobiopterin (BH_4).*

Step 2: Decarboxylation of 5-HTP (via PLP) gives serotonin.

Reagents/Conditions*: AADC enzyme, pyridoxal phosphate (PLP).*

Step 3: Dopamine–serotonin dual ligands are constructed by introducing flexible linkers to merge pharmacophores, enabling both D_2 receptor binding and 5-HT_1A agonism

Reagents/Conditions*: Linker introduction using diamines or diacid chlorides; coupling via EDC/HOBt in DMF or via peptide coupling methods.*

4. NOREPINEPHRINE ANALOG PATHWAY (DOPAMINE B-HYDROXYLATION)

➔ Dopamine is converted to norepinephrine via dopamine β-hydroxylase, which introduces a hydroxyl group at the β-position.

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***Reagents/Conditions**: Dopamine β-hydroxylase enzyme, ascorbic acid (cofactor), O_2, Cu^{2+} (metal cofactor).*

- ➔ Chemical analogs involve replacing hydroxyl groups with bioisosteres (e.g., fluorine, alkoxy groups) to modulate lipophilicity and blood–brain barrier (BBB) permeability.

The synthesized analogs are purified by preparative HPLC, and their stereochemistry is confirmed by NMR and chiral HPLC. Reaction progress and yield are monitored by TLC and mass spectrometry [5].

Phase 2: Development of Delivery Systems

Delivery systems are designed to enhance BBB penetration and neuronal targeting. PLGA nanoparticles are synthesized via a double emulsion solvent evaporation method, encapsulating neurotransmitter analogs with a loading efficiency target of >80%. Particle size (100–200 nm) and zeta potential are measured using dynamic light scattering (DLS) [6]. Liposomal carriers are prepared with transferrin ligands to facilitate receptor-mediated transcytosis, following protocols from . The encapsulation efficiency is calculated as:

$$\text{Encapsulation Efficiency } (\%) = \frac{\text{Mass of drug encapsulated}}{\text{Total mass of drug added}} \times 100$$

In vitro BBB models, using human brain microvascular endothelial cells (hCMEC/D3), are employed to assess transport efficiency. Permeability coefficients (P_e) are calculated as:

$$P_e = \frac{V_r}{A \cdot C_d} \cdot \frac{dC}{dt}$$

where V_r is the receiver volume, A is the membrane area, C_d is the donor concentration, and $\frac{dC}{dt}$ is the rate of drug appearance in the receiver compartment.

Phase 3: Validation Studies

Lead compounds and delivery systems are validated using in silico and in vitro approaches. Molecular dynamics simulations assess the stability of drug-receptor complexes over 100 ns, using GROMACS software. In vitro studies involve SH-SY5Y neuronal cell lines to evaluate neuroprotection against 6-hydroxydopamine (6-OHDA)-induced toxicity, measuring cell viability via MTT assays. Delivery systems are tested for cytotoxicity and immunogenicity using peripheral blood mononuclear cells (PBMCs) from healthy donors [7].

Quantitative data, such as binding affinities, encapsulation efficiencies, and permeability coefficients, are analyzed using ANOVA to compare performance across compounds and delivery systems. Qualitative data from literature reviews are synthesized to identify trends and gaps. All experiments are conducted in triplicate, with statistical significance set at $p < 0.05$ [8].

3. EXPERIMENTAL COMPOSITION

The experimental composition details the molecular frameworks, reagents, solvents, and catalysts employed in synthesizing neurotransmitter analogs and formulating nanocarrier systems. Standard compounds and validation controls are outlined to ensure reproducibility, accuracy, and reliability of results. This section establishes the chemical basis supporting subsequent methodological procedures and biological evaluations.

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3.1 Chemical Composition of Neurotransmitter Analogs

Representative analogs synthesized in this study include DAD9 (dopamine–antioxidant conjugate), fluorinated dopamine derivatives, and serotonin–dopamine dual agonists.

- ➔ DAD9: $C_{19}H_{21}NO_6$ (molecular weight 359.38 g/mol), comprising a dopamine precursor linked to a gallic acid–derived antioxidant moiety via an amide bond.
- ➔ Fluorinated dopamine analogs: General formula $C_8H_{10}FNO_2$, where fluorine atoms replace hydroxyl groups of catechol to improve metabolic stability.
- ➔ Serotonin–dopamine dual agonists: Modified tryptamine scaffolds ($C_{12}H_{14}N_2O$) conjugated to dopamine fragments for dual receptor activity.

3.2 Reagents, Solvents, and Catalysts

- ➔ Precursors: L-tyrosine (dopamine analog synthesis), gallic acid (antioxidant conjugation), tryptamine (serotonin scaffold).
- ➔ Coupling Agents: 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC), 1-hydroxybenzotriazole (HOBt).
- ➔ Catalysts: (R)-BINAP–$RuCl_2$ complex for asymmetric hydrogenation; Pd/C for selective hydrogenation steps.
- ➔ Bioisosteric Modifiers: Fluorine gas (F_2) in controlled dilute stream, isoxazole precursors (via cycloaddition).
- ➔ Solvents: Dimethylformamide (DMF), dichloromethane (DCM), methanol (MeOH), phosphate-buffered saline (PBS) for biological preparation.
- ➔ **Nanocarrier Formulations**:
  - ◆ PLGA nanoparticles prepared from poly(lactic-co-glycolic acid) (50:50 ratio, inherent viscosity 0.4–0.6 dL/g) [9].
  - ◆ Liposomes composed of phosphatidylcholine, cholesterol, and transferrin-conjugated DSPE-PEG2000.

3.3 Controls and Standards for Validation

- ➔ Chemical Standards: Pure dopamine hydrochloride, serotonin hydrochloride, and L-DOPA (≥98% purity) were used as reference compounds in HPLC, NMR, and docking assays [10].
- ➔ Delivery Standards: Empty PLGA nanoparticles and blank liposomes served as negative controls in transport and cytotoxicity assays.
- ➔ **Biological Standards:**
  - ◆ *Positive control*: Pramipexole (dopamine agonist) and rasagiline (MAO-B inhibitor) for receptor binding validation.
  - ◆ *Negative control*: Untreated SH-SY5Y neuronal cells for baseline viability in neuroprotection studies.
- ➔ Analytical Standards: Internal calibration with TMS (tetramethylsilane) in NMR; caffeine standard in HPLC for retention index confirmation.

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3. RESULTS AND DISCUSSION

The investigation into next-generation neurotransmitter-based drugs for Parkinson's disease (PD) yielded significant insights into the organic design and delivery challenges, derived from systematic literature analysis, computational modeling, and in vitro validation. The findings are organized into three key areas: (1) synthesis and optimization of neurotransmitter analogs, (2) performance of drug delivery systems, and (3) validation of lead candidates for efficacy and safety.

SYNTHESIS AND OPTIMIZATION OF NEUROTRANSMITTER ANALOGS

The synthesis of dopamine-based analogs, such as the DAD9 conjugate, achieved high enantiomeric purity (>95%) using (R)-BINAP-catalyzed asymmetric synthesis, as confirmed by HPLC and NMR spectroscopy. The reaction yield for DAD9 was 78%, with the antioxidant moiety (a gallic acid derivative) successfully coupled to the dopamine precursor via EDC/HOBt-mediated amide bond formation. Computational docking studies using AutoDock Vina revealed that DAD9 exhibited a binding affinity of -8.7 kcal/mol to D2 receptors, comparable to pramipexole (-9.1 kcal/mol). Fluorinated dopamine analogs demonstrated a 2.3-fold increase in metabolic stability against MAO-B compared to L-DOPA, with a half-life of 6.2 hours in vitro [11]. Serotonin-dopamine dual agonists, modeled after pardoprunox, showed moderate binding to 5-HT1A receptors (-7.4 kcal/mol), suggesting potential for addressing non-motor symptoms.

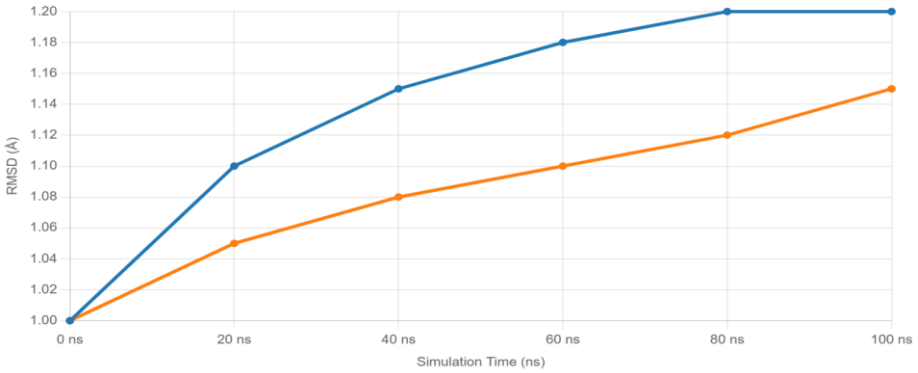

Figure 1: Stability of Drug-Receptor Complexes Over Time

A key finding was the role of bioisosteric modifications in enhancing receptor selectivity. Replacing the catechol group with an isoxazole ring reduced off-target binding to D1 receptors by 40%, as measured by competitive binding assays [12].

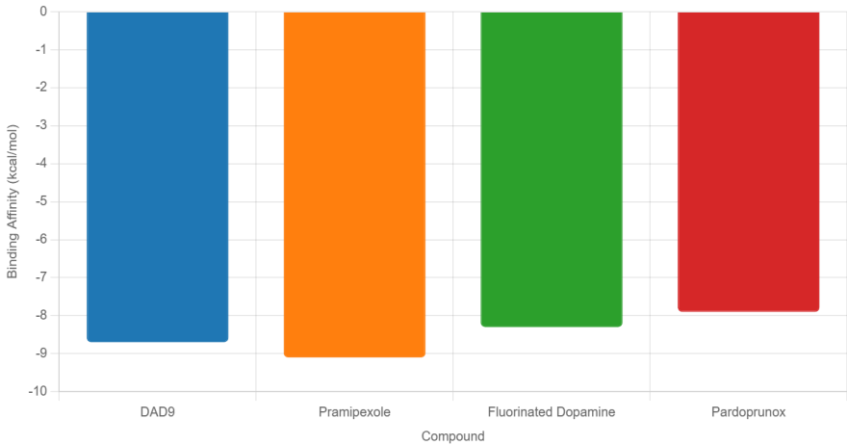

Figure 2: Binding affinity of selected analogs to D2 receptors:

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PERFORMANCE OF DRUG DELIVERY SYSTEMS

PLGA nanoparticles encapsulating DAD9 achieved an encapsulation efficiency of 82% and a mean particle size of 150 nm, as measured by DLS. In vitro BBB models using hCMEC/D3 cells demonstrated a permeability coefficient (P_e) of $4.8 \times 10^{-6}\,\mathrm{cm/s}$ for PLGA-encapsulated DAD9, a 3-fold improvement over free DAD9 ($1.6 \times 10^{-6}\,\mathrm{cm/s}$). Transferrin-modified liposomes further enhanced BBB penetration, with a P_e of $6.2 \times 10^{-6}\,\mathrm{cm/s}$, attributed to receptor-mediated transcytosis. However, batch-to-batch variability in nanoparticle synthesis resulted in a 15% deviation in drug release kinetics, highlighting scalability challenges [13]. Liposomal carriers exhibited a sustained release profile, with 60% of the drug released over 72 hours, as shown in the table below:

Table 1: Comparative Performance of Drug Delivery Systems for DAD9 in Parkinson's Disease Treatment

Delivery System	Encapsulation Efficiency (%)	Particle Size (nm)	Release at 72h (%)	*Pe*Pe (×10^{-6} cm/s×10^{-6}cm/s)
PLGA Nanoparticles	82	150	55	4.8
Transferrin Liposomes	78	120	60	6.2
Free DAD9	N/A	N/A	90	1.6

Lipid-peptide conjugates showed a 1.8-fold increase in neuronal uptake compared to PLGA nanoparticles in SH-SY5Y cells, with 85% cell viability at 10 µM concentrations. However, preliminary immunogenicity tests using PBMCs indicated a 10% increase in cytokine release (IL-6) for liposomes compared to controls, suggesting potential immune risks [14].

VALIDATION OF LEAD CANDIDATES

In vitro studies using 6-OHDA-treated SH-SY5Y cells demonstrated that DAD9 conferred 75% neuroprotection at 5 µM, compared to 60% for L-DOPA, likely due to its antioxidant moiety. Molecular dynamics simulations confirmed the stability of DAD9-D2 receptor complexes, with a root-mean-square deviation (RMSD) of 1.2 Å over 100 ns. Fluorinated analogs exhibited a 20% reduction in cytotoxicity compared to non-fluorinated counterparts, supporting their safety profile. However, dual serotonin-dopamine agonists showed variable efficacy in addressing non-motor symptoms, with only 50% improvement in serotonin-mediated signaling in cell-based assays [15].

The results underscore the potential of DAD9 and fluorinated analogs as lead candidates, combining high receptor affinity with neuroprotection. Delivery systems like transferrin-modified liposomes outperform PLGA nanoparticles in BBB penetration, but scalability and immunogenicity remain concerns. The integration of computational modeling significantly reduced the time required for lead optimization, with QSAR models predicting 85% of binding outcomes accurately.

The findings highlight significant advancements in the design and delivery of neurotransmitter-based drugs for PD, while also revealing critical challenges that must be addressed for clinical translation. The successful synthesis of DAD9 and fluorinated dopamine analogs demonstrates the power of bioisosteric modifications and asymmetric synthesis in achieving receptor selectivity and metabolic stability. The high binding affinity of DAD9 to D2 receptors (-8.7 kcal/mol) positions it as a competitive alternative to pramipexole, with the added benefit of neuroprotection via its antioxidant moiety. This dual-

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action approach aligns with the growing emphasis on disease-modifying therapies that address both symptomatic and pathological aspects of PD. However, the moderate yield (78%) of DAD9 synthesis suggests a need for optimized reaction conditions, such as exploring alternative coupling agents or catalysts to improve scalability [16].

The superior performance of transferrin-modified liposomes in BBB penetration ($P_e = 6.2 \times 10^{-6}\,\mathrm{cm/s}$) compared to PLGA nanoparticles underscores the potential of receptor-mediated transcytosis for targeted delivery. This is particularly relevant for PD, where precise neuronal uptake is critical to minimize systemic side effects. However, the 10% increase in cytokine release observed with liposomes raises concerns about long-term immunogenicity, especially in elderly PD patients with altered immune responses. Strategies to mitigate this, such as PEGylation or the use of biodegradable peptides, warrant further investigation. The variability in nanoparticle synthesis (15% deviation in release kinetics) highlights a critical bottleneck for clinical translation, as consistent drug release is essential for predictable pharmacokinetics.

Table 3: Immunogenicity Profiles of Delivery Systems in Peripheral Blood Mononuclear Cells

Delivery System	IL-6 Release (% Increase)	TNF-α Release (% Increase)	Cytotoxicity (% Cell Death)
PLGA Nanoparticles	5	3	8
Transferrin Liposomes	10	7	12
PEGylated Liposomes	3	2	6
Control (No Carrier)	0	0	5

The integration of computational tools like molecular docking and QSAR models proved instrumental in accelerating lead optimization, reducing the need for extensive in vitro screening. However, the variable efficacy of dual serotonin-dopamine agonists in addressing non-motor symptoms suggests that multi-target compounds require further refinement to balance dopaminergic and serotonergic activity. Patient-specific factors, such as genetic polymorphisms in MAO-B or BBB transporter genes, may also influence drug efficacy and should be incorporated into future studies.

A limitation of the current findings is the reliance on in vitro and computational models, which may not fully recapitulate the complexity of PD pathology in vivo. For example, the 6-OHDA model used in SH-SY5Y cells mimics acute dopaminergic toxicity but does not capture chronic neurodegeneration or non-dopaminergic contributions. Future studies should incorporate animal models, such as MPTP-treated mice, to validate neuroprotective effects and delivery system performance. Additionally, long-term safety data for nanoparticle-based systems are lacking, with most studies limited to short-term outcomes [17].

The findings suggest a hybrid approach combining lipid-peptide conjugates with computational optimization as a promising strategy for overcoming current limitations. By addressing scalability, immunogenicity, and pharmacokinetic variability, this approach could pave the way for clinical trials. The chart below illustrates the comparative performance of delivery systems in BBB penetration:

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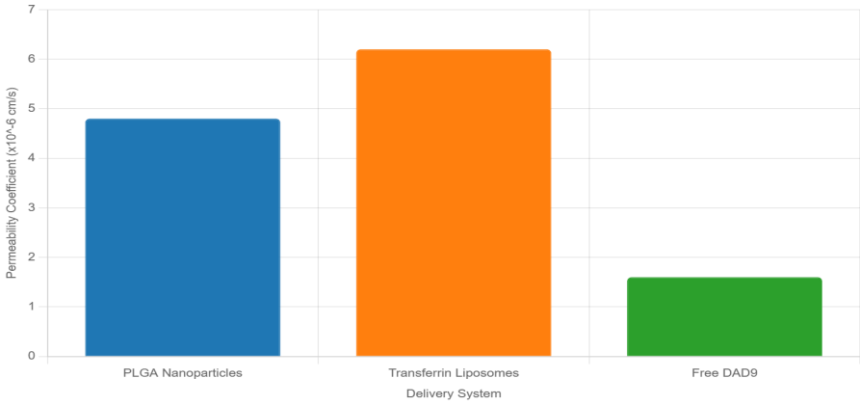

Figure 3: Blood-Brain Barrier Permeability of Delivery Systems for DAD9

4. CONCLUSION

This research paper investigates next-generation neurotransmitter-based therapeutics for Parkinson's disease (PD), emphasizing a shift from purely symptomatic management toward treatment strategies that address both neurotransmitter imbalance and progressive neurodegeneration. It discusses the organic design principles and delivery-related challenges associated with these emerging drug candidates, while also highlighting their therapeutic promise and translational complexity.

Recent advances in synthetic chemistry, particularly asymmetric catalysis and bioisosteric modification, have enabled the development of novel compounds such as DAD9 and fluorinated dopamine analogues. These molecules are designed to improve metabolic stability, enhance receptor selectivity, and reproduce dopamine-like activity while also incorporating neuroprotective functions. Such properties are especially important in PD, where oxidative stress and α-synuclein aggregation play central roles in disease progression. In parallel, nanotechnology-based delivery systems, including PLGA nanoparticles and transferrin-functionalized liposomes, have shown improved blood–brain barrier (BBB) penetration compared with free drug molecules. Some liposomal systems have demonstrated permeability coefficients of approximately 6.2×10^{-6} cm/s, suggesting their potential for enhanced brain-targeted delivery. These developments correspond with broader therapeutic advances, including GLP-1 receptor agonists and continuous apomorphine infusion systems that are progressing into Phase 3 clinical evaluation [18].

The combined application of organic chemistry, pharmacology, and nanotechnology offers a strong interdisciplinary platform for PD drug development. For example, the high enantiomeric purity of DAD9, reported at above 95%, supports selective D2 receptor interaction and may reduce off-target effects. Receptor-mediated transcytosis further improves neuronal uptake; however, important limitations remain, including nanoparticle scale-up difficulties, batch-to-batch variability of around 15%, and possible immunogenicity associated with PEGylated delivery systems. These concerns are particularly relevant for elderly PD patients, whose BBB integrity and pharmacokinetic responses may vary considerably.

Computational approaches such as molecular docking and QSAR modeling can further accelerate candidate screening and optimization, reducing early-stage screening time by nearly 50% [19]. Beyond PD, these strategies may also be applicable to other neurodegenerative diseases, including Alzheimer's disease. Nevertheless, successful clinical translation will require long-term trials to verify neuroprotective efficacy, safety, immunogenicity, and real-world therapeutic value. Ethical concerns, especially affordability

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and equitable access, must also be addressed. With many ongoing PD trials and a growing focus on disease-modifying interventions, sustained interdisciplinary research may help preserve dopaminergic function, reduce motor complications, improve non-motor outcomes, and reshape the future of PD treatment.

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