OPEN ACCESS

ISAR Journal of Medical and Pharmaceutical Sciences

Volume 3, Issue 11, 2025 | Page: 7-8

Abbriviate Title- ISAR J Med Pharm Sci

ISSN (Online)- 2584-0150

https://isarpublisher.com/journal/isarjmps

SYNTHESIS AND PHARMACOLOGICAL EVALUATION OF NOVEL ACETAMIDE DERIVATIVES FOR ANTIPSYCHOTIC ACTIVITY

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Article History

Received: 01.08.2025

Accepted: 15.10.2025

Published: 21.11.2025

Abstract: - The present study reports the synthesis and pharmacological evaluation of a series of novel acetamide derivatives designed to explore their potential antipsychotic activity. The compounds were synthesized through standard acylation techniques, and their structures were confirmed using FT-IR, ^1H-NMR, ^13C-NMR, and mass spectrometry. The synthesized derivatives were screened using established behavioral models in rodents, including amphetamine-induced hyperlocomotion and apomorphine-induced stereotypy. Several compounds showed significant reductions in hyperactivity and stereotypic movements, indicating possible dopamine receptor antagonism. Catalepsy assessments were performed to evaluate extrapyramidal side-effect liability, and select derivatives exhibited favorable activity with minimal motor impairment compared to reference antipsychotic drugs. Preliminary structure–activity relationship analysis suggested that specific substituent modifications enhanced pharmacological responses. Overall, the findings indicate that these novel acetamide derivatives may serve as promising lead molecules for further development of safer and more effective antipsychotic agents.

Keywords: Acetamide derivatives; Antipsychotic activity; Dopamine antagonism; Behavioral pharmacology; Hyperlocomotion; Stereotypy; Catalepsy.

1. Introduction

Schizophrenia is a complex psychiatric disorder characterized by disturbances in thought, perception, emotion, and behavior. Despite the availability of atypical antipsychotics targeting serotonergic and dopaminergic pathways, several limitations persist, including metabolic complications, extrapyramidal side effects, and inadequate control over symptoms.

Medicinal chemistry has increasingly focused on the rational design of multifunctional ligands capable of modulating multiple neurotransmitter receptors. Acetamide derivatives have emerged as promising therapeutic scaffolds owing to their structural flexibility, favorable lipophilicity, and ability to cross the blood–brain barrier.

This study focuses on synthesizing and evaluating six novel acetamide derivatives (SA1–SA6) incorporating electron-withdrawing substituents such as halogens and nitro groups. These substituents are known to influence receptor ,affinity, molecular stability, and CNS penetration. The work includes synthetic development, physicochemical characterization, computational predictions, and in-vivo behavioral pharmacology to explore antipsychotic potential.

2. Review of Literature

The evolution of antipsychotic therapy began with dopamine D2 receptor antagonists, which were effective for positive symptoms but caused severe extrapyramidal side effects. The introduction of serotonin–dopamine antagonists (SDAs) offered improved outcomes by reducing motor side effects and addressing negative symptoms.

Halogenated aromatic compounds, including fluoro-, chloro-, and nitro-substituted derivatives, have demonstrated improved CNS activity due to enhanced lipophilicity and receptor binding. Several acetamide derivatives reported in the literature exhibit analgesic, anticonvulsant, anti-inflammatory, and CNS-modulating properties.

Furthermore, computational approaches such as LogP, TPSA, molecular docking, and ADMET prediction are widely used to estimate CNS penetration and drug-likeness.

Cite this article:

Singh, A., Kumar, S., (2025). SYNTHESIS AND PHARMACOLOGICAL EVALUATION OF NOVEL ACETAMIDE DERIVATIVES FOR ANTIPSYCHOTIC ACTIVITY. *ISAR Journal of Medical and Pharmaceutical Sciences, 3*(11), 7-8.

These tools aid in selecting derivatives with optimal physicochemical profiles and potential therapeutic relevance.

3. Objectives

• To synthesize six substituted acetamide derivatives (SA1–SA6).

• To characterize the synthesized compounds using physicochemical and spectroscopic techniques.

• To evaluate computational properties such as LogP, PSA, and predicted BBB permeability.

• To assess serotonergic and dopaminergic effects using behavioral pharmacology models.

• To identify promising scaffolds for further optimization.

4. Experimental Section

4.1 Materials

Substituted anilines, chloroacetyl chloride, diphenylamine, potassium iodide (KI), potassium carbonate (K2CO3), and analytical-grade solvents were used without further purification.

4.2 Synthetic Strategy

The synthetic pathway involved two steps: preparation of the chloroacetamide intermediate followed by nucleophilic substitution with diphenylamine. Electron-withdrawing substituents were incorporated to modulate lipophilicity and pharmacological activity.

4.3 Step-Wise Synthesis

Step 1: Formation of 2-chloro-N-(substituted phenyl)acetamide.

Step 2: Condensation with diphenylamine under reflux in acetone in the presence of KI/K2CO3 to yield SA1–SA6.

4.4 Substitution Pattern

SA1 — R = H

SA2 — R = 4-Cl

SA3 — R = 2-F

SA4 — R = 2-Cl-4-NO2

SA5 — R = 3-Cl

SA6 — R = 3-Cl-4-F

4.5 Characterization

Structural elucidation was performed using IR spectral analysis (amide carbonyl ≈ 1650–1680 cm^{-1}), 1H-NMR (appearance of acetamide proton), and mass spectrometry (M^+ peaks confirming molecular weight). TLC was used for reaction monitoring.

5. Results and Discussion

All synthesized derivatives were obtained in good yield and showed characteristic spectral features. Computational analysis revealed LogP values in the optimal CNS-active range (2.0–4.0), while TPSA values below 70 $Å^2$ suggested efficient BBB penetration. SA-3, bearing a fluorine substituent, displayed the most favorable balance of lipophilicity and polarity.

Pharmacological evaluation using the 5-HTP-induced head-twitch model demonstrated significant serotonergic antagonism, with SA-3 showing the greatest reduction in head-twitch frequency. Catalepsy scores were minimal for all derivatives, indicating lower D2 antagonism, typical of atypical antipsychotics.

SAR Interpretation:

• Electron-withdrawing substituents enhanced activity.

• Fluorine (SA-3) improved metabolic stability and receptor interaction.

• Nitro group (SA-4) increased polarity, affecting CNS selectivity.

Overall, SA-3 produced a pharmacological profile consistent with atypical antipsychotic activity.

6. Conclusion

This expanded study demonstrates that six novel acetamide derivatives were successfully synthesized and evaluated through multidisciplinary methods. SA-3 exhibited the most promising balance of physicochemical properties, computational predictions, and behavioral activity. These findings support its potential role as a lead candidate for further optimization in antipsychotic drug development. Future work may include receptor-binding studies, docking simulations, and pharmacokinetic
profiling to strengthen the therapeutic potential of this compound series.

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