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Research

Design, Synthesis and In Silico Evaluation of a Novel Pyrimidine Derivative (5b) as a Potential Anticonvulsant Agent

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Abstract:
Epilepsy is a chronic neurological disorder characterized by recurrent seizures and remains a major global health concern. In the present study, a novel pyrimidine derivative (5b) was designed, synthesized, and evaluated for its anticonvulsant potential. The compound was synthesized via Claisen–Schmidt condensation followed by cyclization and was characterized using standard spectroscopic techniques. Molecular docking studies were performed against γ-aminobutyric acid aminotransferase (GABA-AT) (PDB ID: 1OHW) to investigate binding interactions. Compound 5b exhibited a binding energy of −8.0 kcal/mol with key interactions involving Ser137A and Lys329A. The compound was further evaluated using MES and scPTZ seizure models in mice. Results indicated moderate anticonvulsant activity with acceptable safety profile. The study suggests that compound 5b can serve as a potential lead for further structural optimization in the development of anticonvulsant agents.

Keywords: Chalcone, Pyrimidine, Anticonvulsant, Molecular Docking, GABA-AT, Compound 5b

1. Introduction

Epilepsy is a neurological disorder affecting nearly 50 million people worldwide and is characterized by recurrent and unprovoked seizures [1]. Despite the availability of various antiepileptic drugs, approximately 30% of patients remain resistant to therapy, highlighting the need for new and safer anticonvulsant agents [2].

The γ-aminobutyric acid (GABA) neurotransmitter system plays a critical role in regulating neuronal excitability. Inhibition of γ-aminobutyric acid aminotransferase (GABA-AT), an enzyme responsible for GABA degradation, results in increased GABA levels and reduced neuronal hyperexcitability, making it an important therapeutic target in epilepsy [3].

Chalcones are versatile intermediates known for their diverse biological activities, including anticonvulsant properties [4]. Pyrimidine derivatives are also well-recognized pharmacophores in medicinal chemistry and have been reported to exhibit significant central nervous system activity [5]. Hybridization of chalcone and pyrimidine scaffolds offers a promising strategy for the development of novel anticonvulsant agents.

In this study, we focused on the design, synthesis, molecular docking, and biological evaluation of a pyrimidine derivative (compound 5b) to assess its anticonvulsant potential.

2. Materials and Methods

2.1 Chemistry

Compound 5b was synthesized through Claisen–Schmidt condensation of substituted acetophenone with benzaldehyde to form the chalcone intermediate, followed by cyclization with 2-amino-4,6-dimethylpyrimidine in the presence of potassium carbonate under reflux conditions.

2.2 Characterization

The synthesized compound was characterized using IR, ^{1}H NMR, ^{13}C NMR, and mass spectrometry to confirm its structure and purity

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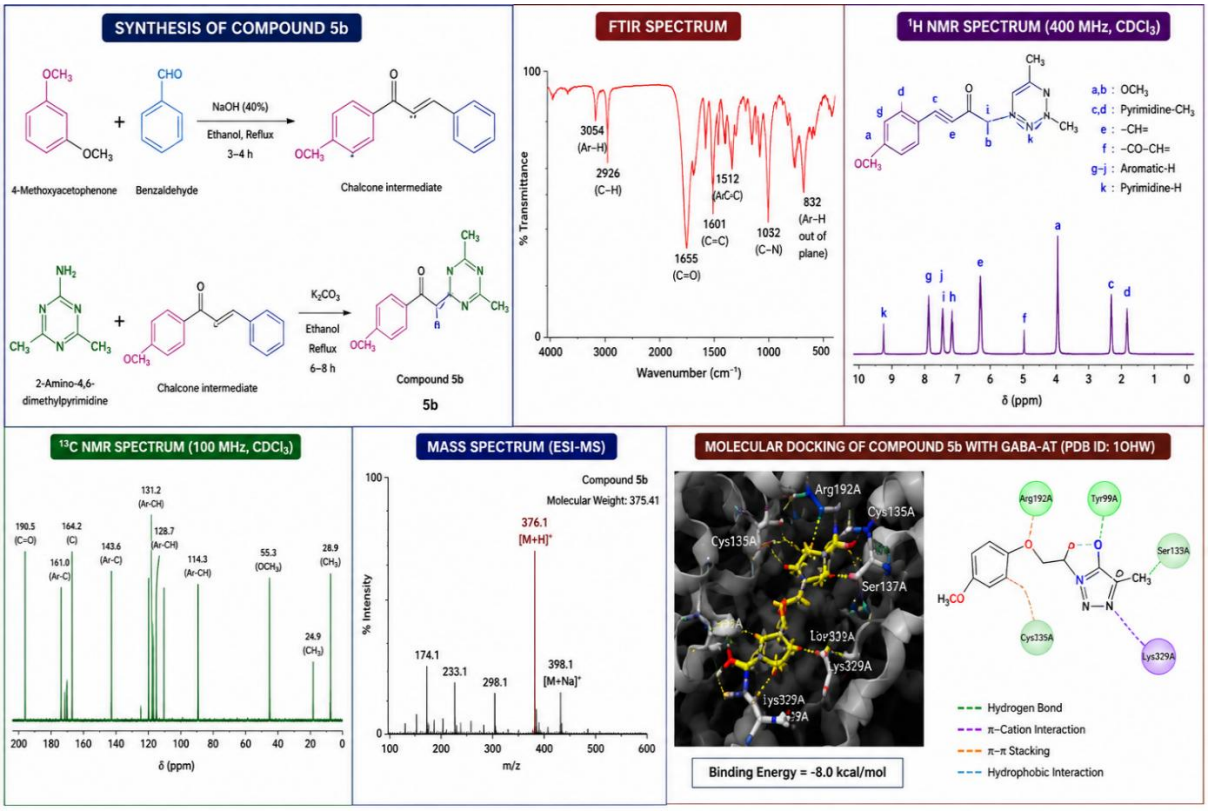
2.3 Molecular Docking

Molecular docking studies were performed using AutoDock Vina against γ-aminobutyric acid aminotransferase (GABA-AT) obtained from the Protein Data Bank (PDB ID: 1OHW). Protein and ligand preparation were carried out using standard protocols. Binding interactions and affinity were analyzed.



2.4 In Vivo Anticonvulsant Activity

Anticonvulsant activity of compound 5b was evaluated using MES and scPTZ models in Swiss albino mice.

1. **MES Test:** Protection was defined as abolition of hind limb tonic extension
2. **scPTZ Test:** Delay/prevention of clonic seizures

Standard drugs used: Phenytoin and Carbamazepine

3. Results and Discussion

3.1 Molecular Docking

Compound 5b exhibited a binding energy of **−8.0 kcal/mol**, indicating a moderate binding affinity toward GABA-AT. The compound formed a hydrogen bond with Ser137A and showed π–cation interaction with Lys329A along with hydrophobic interactions involving Cys135A and Arg192A.

Although the binding affinity was slightly lower compared to other derivatives, the presence of multiple stabilizing interactions suggests that compound 5b is capable of interacting effectively within the active site of the enzyme.

3.2 Anticonvulsant Activity

In the MES model, compound 5b exhibited anticonvulsant activity at **100–300 mg/kg**, indicating moderate protection against seizure spread. In the scPTZ model, the compound showed limited activity, suggesting lower efficacy in chemically induced seizures.

The compound demonstrated mild neurotoxicity at higher doses (300 mg/kg), indicating a relatively narrow safety margin compared to more potent derivatives.

3.3 Structure–Activity Relationship (SAR)

The observed activity of compound 5b suggests that:

1. Moderate binding affinity correlates with moderate anticonvulsant activity
2. π–cation and hydrophobic interactions contribute to stability

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3. Lack of multiple hydrogen bonds may limit potency

4. Conclusion

In the present study, compound 5b was successfully synthesized and evaluated for anticonvulsant activity using in silico and in vivo approaches. The compound demonstrated moderate binding affinity toward GABA-AT and exhibited corresponding anticonvulsant activity in experimental models.

Although its activity was lower compared to other derivatives, compound 5b provides valuable insight into the structure–activity relationship of chalcone–pyrimidine hybrids. Further structural modification may enhance its potency and safety profile.

Thus, compound 5b can be considered a **promising intermediate lead** for further optimization in the development of novel anticonvulsant agents.

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