WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
Coden USA: WJPRAP Impact Factor 8.63
Volume 15, Issue 12, 810-819. Research Article ISSN 2277–7105

DESIGN AND *IN-SILICO* EVALUATION OF NOVEL ZURANOLONE DERIVATIVES FOR THE TREATMENT OF POSTPARTUM DEPRESSION

P. Chithra*, Khadeejath Amana C. K., Lubna Harif, Mariyam Bashreena

Department of Pharmaceutical Chemistry, Malik Deenar College of Pharmacy, Kasaragod, Kerala.

Article Received on 13 May 2026,
Article Revised on 03 June 2026,
Article Published on 16 June 2026,

https://doi.org/10.5281/zenodo.20696845

***Corresponding Author**

P. Chithra

Department of Pharmaceutical Chemistry, Malik Deenar College of Pharmacy, Kasaragod, Kerala.

How to cite this Article: P. Chithra*, Khadeejath Amana C. K., Lubna Harif, Mariyam Bashreena. (2026). Design and In-Silico Evaluation of Novel Zuranolone Derivatives For The Treatment Of Postpartum Depression. World Journal of Pharmaceutical Research, 15(12), 810–819.

ABSTRACT

Postpartum depression (PPD) is a serious mood disorder that affects millions of women worldwide, often emerging in the months following childbirth. Unlike the transient "baby blues," PPD can persist and disrupt maternal well-being, infant bonding, and family dynamics. Current treatments, such as SSRIs and SNRIs, act slowly and do not directly address the neurosteroid imbalance thought to underlie PPD. Zuranolone, a synthetic neurosteroid that enhances GABA-A receptor activity, has shown faster symptom relief, but its pharmacokinetic limitations highlight the need for improved derivatives. In this study, novel Zuranolone derivatives were designed using bioisosteric replacement of the pyrazole ring with imidazole, thiadiazole, and oxadiazole heterocycles. Their physicochemical properties were predicted using SwissADME, and blood–brain barrier permeability was assessed with logBBpred. Molecular docking against the native GABA-A receptor (PDB ID: 8FOI) revealed stronger receptor interactions than allopregnanolone, with the imidazole derivative (ZI1) showing the most favourable profile, including optimal lipophilicity, high gastrointestinal absorption, and superior docking affinity. These findings suggest that structural modification of Zuranolone may enhance its therapeutic potential in PPD. However, as the results are based solely on computational predictions, laboratory synthesis and experimental validation are essential to confirm feasibility, activity, safety, and clinical

relevance.

KEYWORDS: Postpartum depression, Zuranolone, GABA receptor, allopregnanolone, imidazole.

INTRODUCTION

Postpartum depression (PPD) is a chronic mood disorder that commonly arises in the first few months after childbirth, affecting 17.2% of women worldwide.[1] Postpartum Depression (PPD) is characterised by a persistent low mood, feelings of worthlessness, and a sense of despondency, which differs from the brief "baby blues." Major diagnostic manuals recognise that PPD can begin within the first month after childbirth, although some guidelines extend this timeframe up to a year.[2] This condition can significantly affect maternal functioning, infant bonding, and family dynamics, potentially leading to serious consequences if left untreated. Remission rates vary: approximately 30% of mothers recover by 6 months, and about 94% by 24 months. Longitudinal studies indicate that around 30% of mothers may continue to meet the criteria for depression up to three years postpartum.[3] Neurosteroids are steroids produced within the brain that play a crucial role in regulating brain function. They are released during mild stress, acting as natural "stress-busters" by modulating the brain's response to stress.[4]

Allopregnanolone is a neurosteroid derived from progesterone. It enhances the activity of GABA-A receptors, which are the brain’s main inhibitory receptors. By boosting GABA signalling, it promotes calmness, relaxation, and emotional stability — essentially acting like the brain’s natural anti-anxiety and anti-stress agent. When this GABAergic system is dysfunctional, the brain loses part of its natural calming mechanism. This imbalance is implicated in major depressive disorder (MDD) and postpartum depression (PPD), where reduced neurosteroid activity contributes to heightened stress sensitivity and mood instability. During pregnancy, levels of neurosteroids (including allopregnanolone) rise significantly. This surge helps buffer the mother against stress, stabilising mood and protecting mental health during the demanding physiological changes of pregnancy. After childbirth, neurosteroid levels drop sharply. This sudden decline can leave the brain more vulnerable to stress and emotional instability. For some women, this neurochemical shift contributes to postpartum depression, characterised by sadness, anxiety, and difficulty bonding with the baby.[5]

Traditional antidepressants (SSRIs, SNRIs) mainly act on serotonin or norepinephrine. PPD, however, is strongly linked to the sudden drop in neurosteroids (like allopregnanolone) after childbirth. Zuranolone is designed to restore neurosteroid activity at GABA-A receptors, addressing the underlying mechanism rather than just symptoms. Standard antidepressants often take weeks to months to show effect. Zuranolone has been shown to alleviate symptoms within days, which is critical for mothers struggling with bonding, caregiving, and emotional stability.[6] There is an increased need for novel neurosteroids with more selectivity and increased half-life. This study aims to generate novel Zuranolone-heterocyclic derivatives by utilising the bioisosteric replacement methods.

MATERIALS AND METHODS

Drug design and bioisosterism

Zuranolone is a synthetic neurosteroid acting as a positive allosteric modulator of GABA-A receptors (figure.1). It is used as a lead molecule for designing novel derivatives for the treatment of PPD (postpartum depression). The bioisosteric modification method is used to design derivatives.

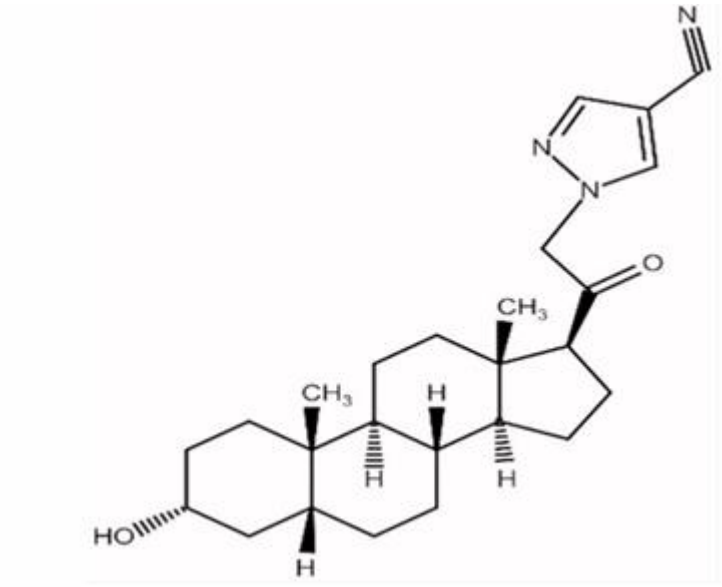
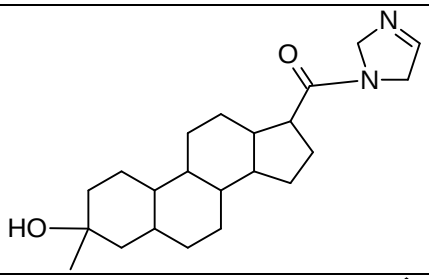
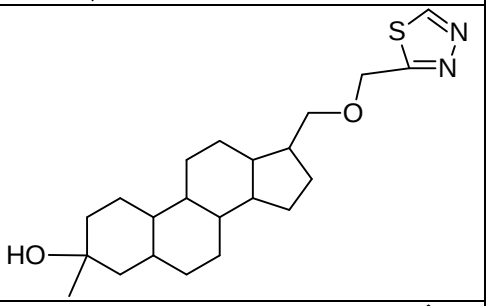
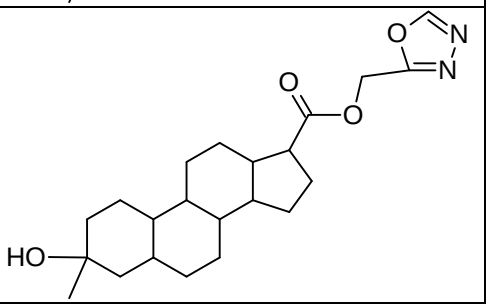


Figure 1: The structure of Zuranolone.

The pyrazole ring of Zuranolone is replaced with various 5-membered heterocycles like imidazole, thiadiazole and oxadiazole in order to design molecules with better therapeutic values. (Table.1)

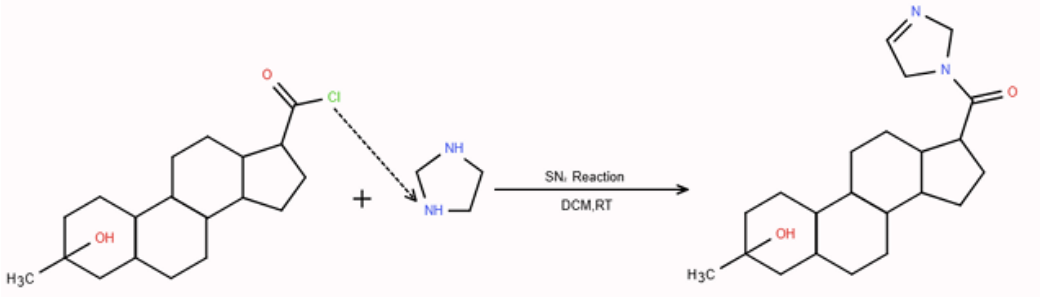
Table 1: The structures of various designed derivatives.

Name of derivative	The heterocyclic ring present	Structure
ZI-1	Imidazole	
ZT-1	Thiadiazole	
ZO-1	Oxadiazole	

Proposed synthetic scheme for the synthesis of derivatives

1. Synthesis of Zuranolone-imidazole derivative

The nitrogen atom of the heterocycle attacks the carbonyl carbon of the steroid acid chloride. Chloride leaves, forming a new amide bond between the steroid and the nitrogen-containing ring. This reaction is called nucleophilic acyl substitution.[7] (Scheme.1)

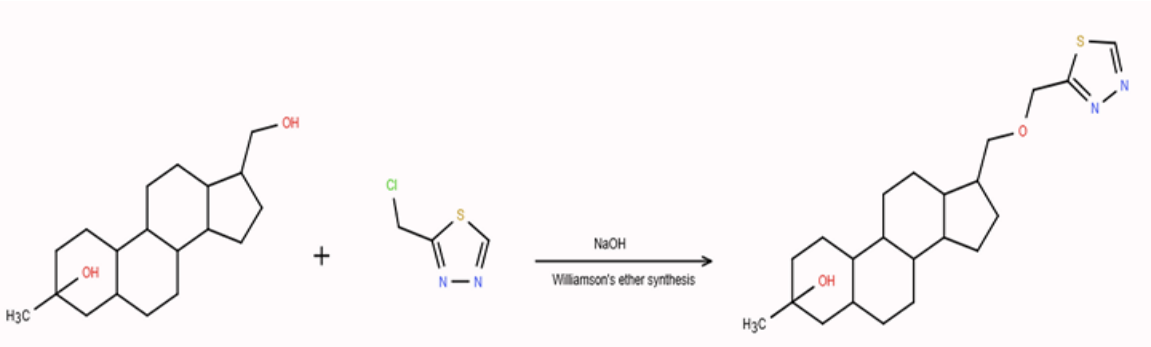


Scheme 1: Synthesis of Zuranolone imidazole derivative (ZI1).

2. Synthesis of Zuranolone-Thiadiazole derivative

The steroid's –OH group is converted into an alkoxide by NaOH, which then replaces Cl in the Chloromethyl thiadiazole to form an ether linkage (Williamson ether synthesis).[8]

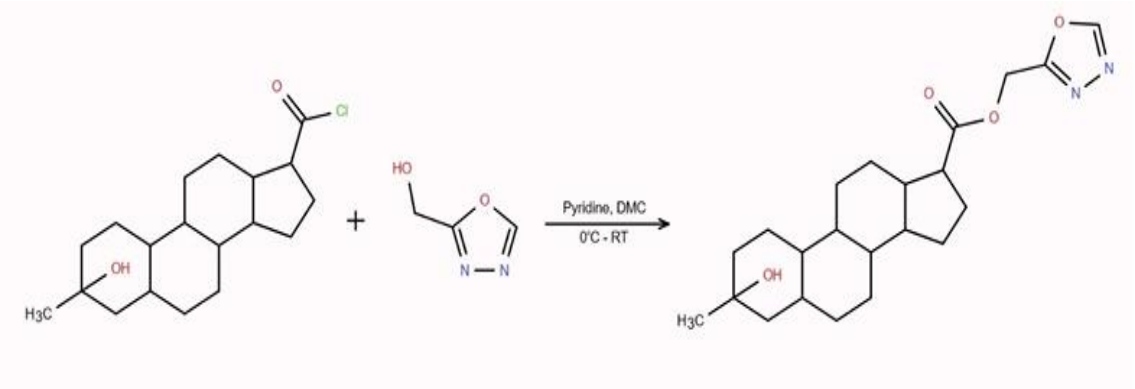
(Scheme.2)



Scheme 2: Synthesis of Zuranolone-thiadiazole derivative (ZT1).

3. Synthesis of Zuranolone-oxadiazole derivative

An acid chloride on the steroid reacts with the hydroxymethyl Oxadiazole in the presence of pyridine and DMC to form an ester, linking the heterocycle to the steroid via ester linkage.[9] (Scheme 3)



Scheme 3: Synthesis of Zuranolone-Oxadiazole derivative (ZO1).

Determination of Physicochemical Properties

The physicochemical properties are very important in the ADME characteristics of a drug and thereby affect the biological properties of a molecule. The determination of physicochemical properties is carried out using the software Swiss ADME.[10] The BBB permeability is an important factor for a molecule to act on the CNS. The BBB permeability can be evaluated using the Software logBBpred.[11]

Molecular docking

Molecular docking was carried out using Autodock Vina and visualisation by Biovia Discovery Studio. The target protein was selected from the Protein Data Bank[12]. Native

GABA A receptor from the mouse brain complexed with allopregnanolone (PDB ID: 8FOI) is selected as the target receptor.

RESULTS

Physicochemical properties of the proposed derivatives

The molecular weight, log p values, TPSA and BBB permeability are evaluated using software. (Table 2)

Table 2: molecular properties of proposed derivatives.

Properties	ZI1	ZT1	ZO1
Molecular Formula	$C_{22}H_{34}N_2O_2$	$C_{22}H_{34}N_2O_2S$	$C_{22}H_{32}N_2O_4$
Molecular weight	358.52g/mol	390.58 g/mol	388.50 g/mol
Topological polar surface area	$52.90A^2$	$83.48\ A^2$	$85.45\ A^2$
GI absorption	High	High	High
Log p	3.24	3.94	3.36
BBB permeability, value	Yes, -0.18331	Yes, 0.04688	Yes, -0.45933
Lipinski rule Violation	No	No	No

According to the physicochemical properties, ZI1 is a good drug candidate with a lower molecular weight, TPSA, good lipophilicity, GIT absorption character and BBB permeability.

Molecular docking

Docking studies have been carried out and found that all the 3 derivatives have better receptor interaction compared to the standard ligand allopregnanolone. Allopregnanolone have a docking score of -8.3. This natural neurosteroid shows pi-sigma interactions and pi-alkyl interactions with the amino acids at the receptor site.

Table 3: docking scores of proposed derivatives.

Derivatives	Docking score
ZI1	-9.3
ZT1	-9.0
ZO1	-8.9

Among the proposed derivatives, ZI1 shows better interaction with the receptor. The derivative shows conventional hydrogen bonding due to the presence of hydrogen bond donors, pi- anion, pi-sigma, pi-alkyl and other interactions with various amino acids present at the receptor site (Figure 2).

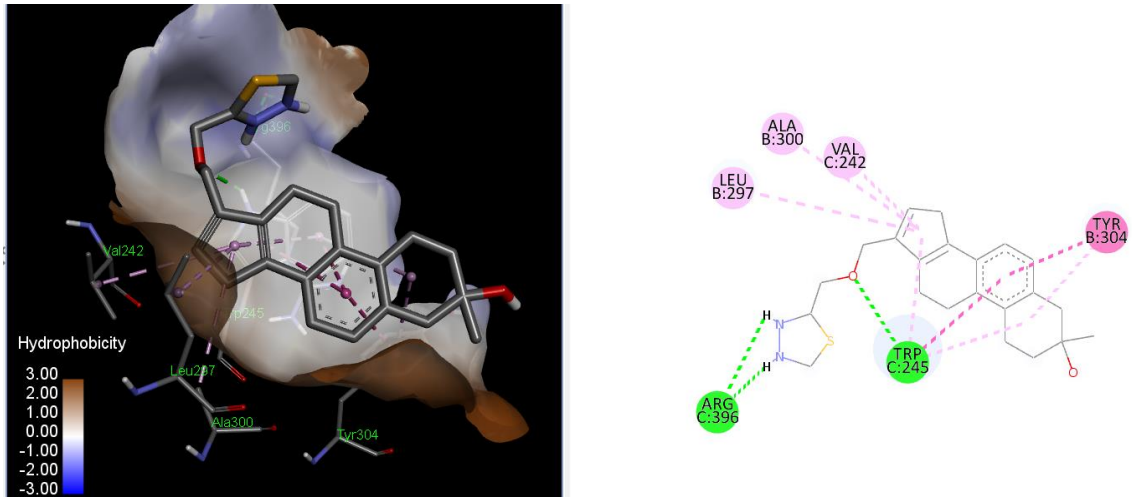


Figure 2: 3D and 2D interactions of ZI1 with the receptor site.

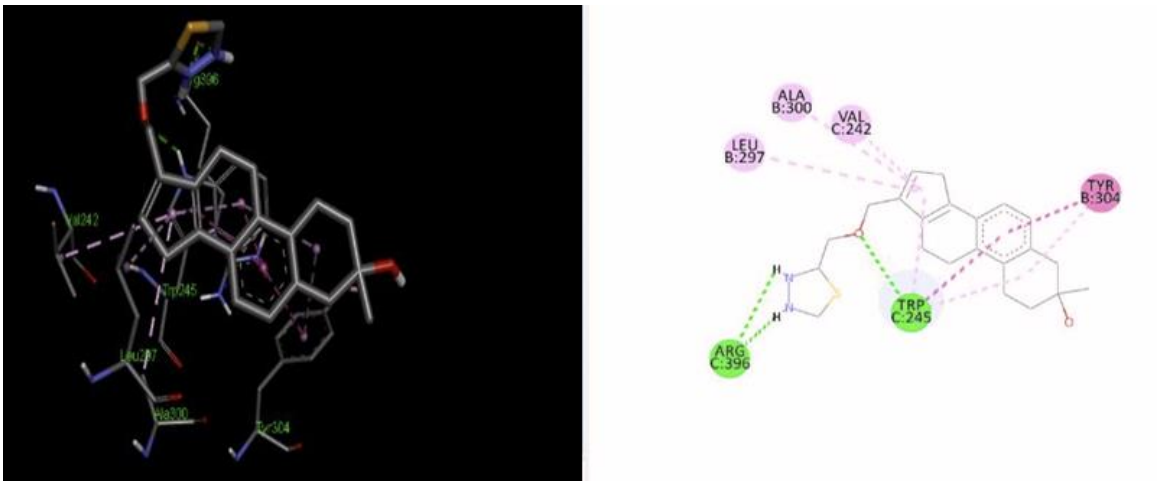


Figure 3: 3D and 2D interactions of ZT1 with the receptor sites.

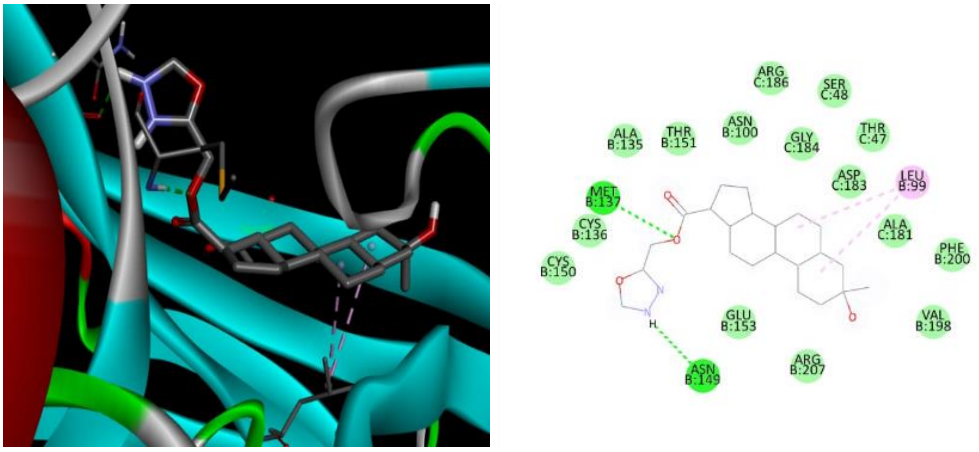


Figure 4: 3D and 2D interactions of ZO1 with the receptor sites.

All three derivatives show better interactions with the receptor. The interactions are mainly hydrogen bonding, pi-pi stacking, and pi-alkyl interactions. The favourable interactions are

more. So the designed molecules have good receptor interaction and binding affinity.

DISCUSSION

This study focuses on the rational design and *in-silico* evaluation of novel Zuranolone derivatives (ZI1, ZT1, ZO1) as potential therapeutic agents for postpartum depression (PPD). The reasoning behind this exploration is based on the neurosteroid hypothesis of PPD, which suggests that the significant drop in allopregnanolone levels after childbirth disrupts GABA-A receptor modulation, resulting in mood instability. Zuranolone, a synthetic neurosteroid, has shown rapid symptom relief in comparison to traditional antidepressants. However, its pharmacokinetic limitations require structural modifications to enhance efficacy and stability.

The bioisosteric replacement of the pyrazole ring with imidazole, thiadiazole, and oxadiazole rings aimed to improve receptor binding and physicochemical properties. Among these, ZI1 (an imidazole derivative) showed excellent drug-likeness, with lower molecular weight, optimal lipophilicity (logP of 3.24), high gastrointestinal absorption, and favorable blood-brain barrier (BBB) permeability.

Docking studies supported ZI1's potential, yielding a docking score of -9.3 compared to -8.3 for the natural ligand, allopregnanolone. This increased binding affinity is due to stabilizing interactions like hydrogen bonding and pi contacts with receptor residues. Although ZT1 and ZO1 showed strong interactions, their higher topological polar surface area (TPSA) may limit their BBB permeability compared to ZI1.

The findings suggest that bioisosteric modifications of Zuranolone can lead to derivatives with better pharmacological properties. The imidazole substitution is particularly promising, balancing physicochemical properties and receptor affinity. This aligns with current trends in neurosteroid drug design, where heterocyclic modifications often enhance CNS penetration and metabolic stability.

CONCLUSION

This study employed bioisosteric modification of Zuranolone to design three novel derivatives (ZI1, ZT1, ZO1) and evaluated them through in-silico physicochemical profiling and molecular docking. All derivatives demonstrated favourable drug-like properties and stronger receptor interactions compared to allopregnanolone, with ZI1 (imidazole derivative) showing comparatively better drug-likeness and docking affinity. These findings suggest that

structural modification of neurosteroids may enhance therapeutic potential in postpartum depression.

However, this study designed and evaluated novel Zuranolone derivatives through computational methods, with ZI1 showing comparatively better drug-likeness and receptor affinity. These findings are preliminary, as they rely solely on in-silico predictions. Laboratory synthesis is required to confirm chemical feasibility and stability, while experimental studies are essential to establish activity, safety, and toxicity before any clinical relevance can be determined.

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