

Multifactorial Thiophenyl Pyrazolourea derivatives as excellent JNK3 Inhibitors for Alzheimer's Disease: In-silico approach.

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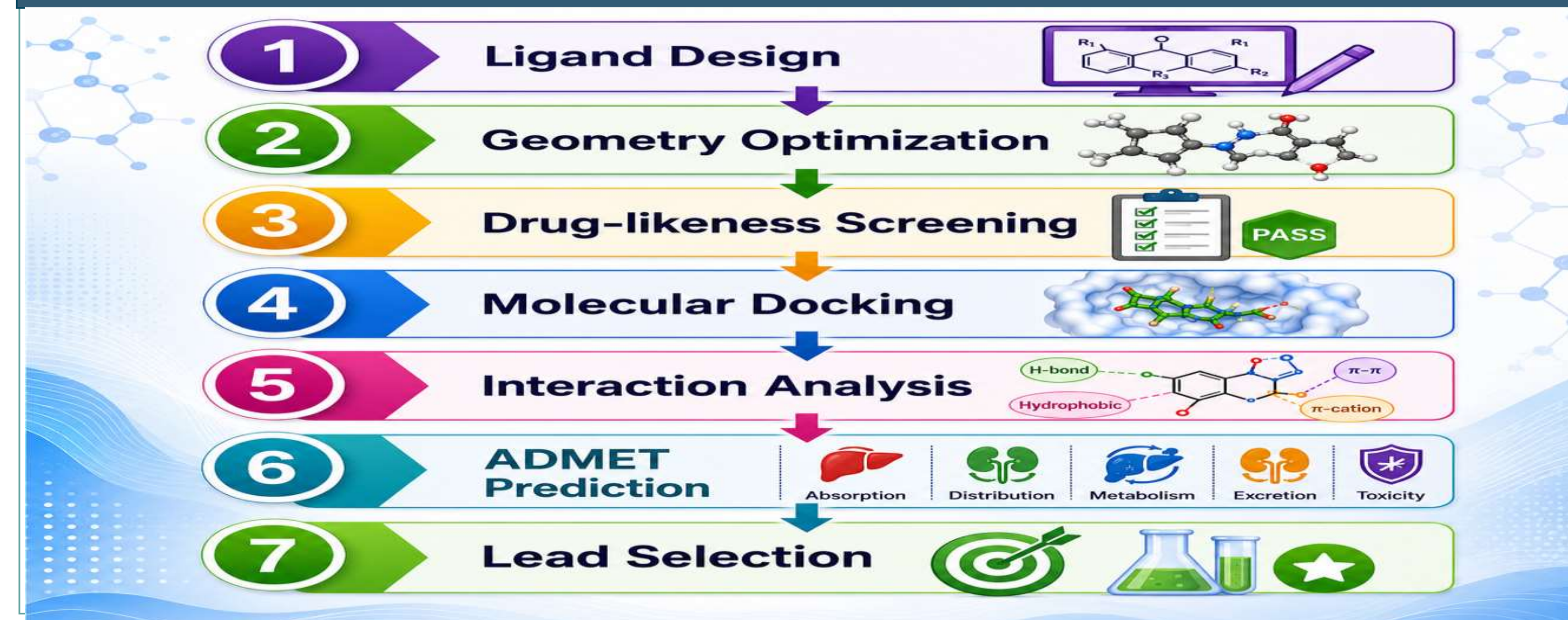
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INTRODUCTION:

Alzheimer's disease (AD) is a multifactorial neurodegenerative disorder marked by progressive cognitive impairment and neuronal degeneration, with limited availability of effective disease-modifying therapies. c-Jun N-terminal kinase 3 (JNK3), a neuron-specific kinase involved in amyloid- β -mediated neurotoxicity, tau hyperphosphorylation, oxidative stress, and neuroinflammation, has emerged as a promising therapeutic target for AD management. Therefore, an effective inhibition of JNK3 in AD promotes neuroprotection by reducing neuronal apoptosis, tau hyperphosphorylation, and neuroinflammation, while slowing cognitive decline

METHODS



RESULTS

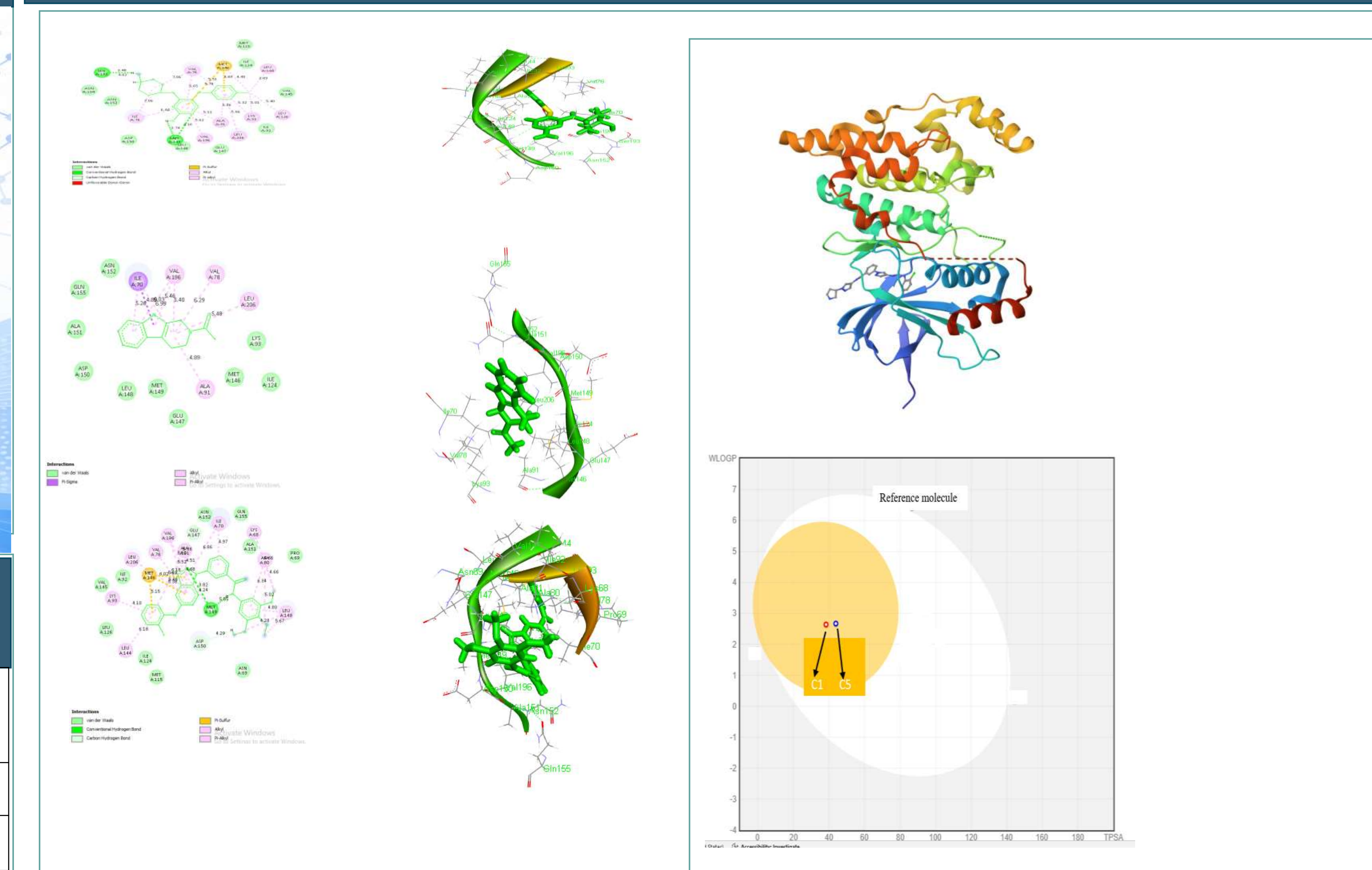
S/No	Docking score (kcal/mol)	MMGBSA
1	-10.23	-62.02
5	-9.38	-60.12
Reference	-9.30	-52.68

MOLECULE	Lipinski	MW	RB	HBA	HBD	MR	TPSA	Log P
1	PASSED	334.8	4	4	3	90.35	93.29	2.44
5	PASSED	214.26	1	1	1	67.55	36.1	1.52
REFERENCE		512.53	9	6	2	144.26	86.64	4.71

Pharmacokinetic Studies
Demonstrated favourable blood-brain barrier permeability, supporting CNS-targeting potential. Exhibited optimal gastrointestinal absorption, indicating strong oral bioavailability. Predicted good aqueous solubility, consistent with acceptable pharmacokinetic behaviour. Identified as P-glycoprotein substrates, suggesting active efflux regulation across biological membranes. Showed no Ames toxicity liability, indicating a non-mutagenic safety profile

❖ MDS Studies

❖ Molecular dynamics simulations confirmed the stability of the protein-ligand complexes, with minimal structural fluctuations



CONCLUSION

- ❖ Lead compounds exhibited stronger JNK3 binding than the reference inhibitor.
- ❖ Molecular dynamics confirmed stable protein-ligand complexes.
- ❖ ADMET profiles indicated favourable oral bioavailability and CNS penetration.
- ❖ Compounds satisfy major drug-likeness criteria.
- ❖ These leads warrant further in vitro and in vivo validation

REFERENCES

- Bhujbal, S. P., & Hah, J.-M. (2025). Advances in JNK inhibitor development: therapeutic prospects in neurodegenerative diseases and fibrosis: SP Bhujbal, JM Hah. *Archives of Pharmacol Research*, 48(9), 858-886

Alzheimer's Disease Mechanisms: Amyloid- β and Tau Pathology & JNK3 Therapeutic Targeting

