RESEARCH PAPER

Green Synthesis of Selected Pyrazole Derivatives and In Silico Study of their Druglikeness, Pharmokinetics and Binding Affinity with Human Hypocretin Receptor 2 Gene

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ABSTRACT

Pyrazole derivatives have gained significant attention in drug discovery due to their broad pharmacological activities, including anxiolytic, anti-inflammatory, and neuroprotective effects. The human hypocretin receptor 2 (HCRTR2) gene encode a G-protein coupled receptor involved in regulating sleep-wake cycles, mood, and energy homeostasis. In this study, we have synthesized some pyrazole derivatives: 1,3-diphenyl-1H-indazole-4,7(3aH,7aH)-dione; 3-(2-hydroxyphenyl)-1-phenyl-1H-indazole-4,7(3aH,7aH)-dione; 3-(4-chlorophenyl)-1-phenyl-1H-indazole 4,7(3aH,7aH)-dione; 3-(4-hydroxyphenyl)-1-phenyl-1H-indazole-4,7(3aH,7aH)-dione and 3-(3-nitrophenyl)-1-phenyl-1H-indazole-4,7(3aH,7aH)-dione using 1,3-Dipolar Cycloaddition via green route. Their quantitative structure-activity relationship (QSAR) modeling and molecular docking were employed to evaluate the druglikeness, pharmacokinetic potential and binding affinity with the HCRTR2 gene. The QSAR model was built using multiple linear regression (MLR) and supported by molecular descriptors, while molecular docking studies provided insights into the binding modes and key interactions of the ligands with the HCRTR2 protein. The results demonstrated that selected pyrazole derivatives exhibit promising binding energies and important interactions within the active site of HCRTR2, suggesting their potential as therapeutic agents targeting the orexin system.

Keywords: Pyrazole Derivatives, Green synthesis, QSAR, Molecular docking, HCRTR2 gene, Orexin receptors, Drug discovery

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1. INTRODUCTION

From alkynes, nitriles, and titanium imido complexes, multicomponent pyrazole synthesis has been accomplished[1]. There are various methods for synthesizing pharmacologically significant pyrazoles[2]. Recent reports in the literature describe a pyrazole synthesis technique using sonication[3]. Continuous flow pyrazole synthesis catalyzed by copper is quick and clean. Thiazoyl-pyrazole derivatives' synthesis and molecular docking, as well as their anti-cancer properties, have been documented[4]. There have been reports on the synthesis and molecular docking of thiazoyl-pyrazole derivatives and their anti-cancer properties[5]. A catalyst covered with silica was used to create pyrazole derivatives[6]. Certain pyrazole derivatives were effectively produced and also had herbicidal qualities[7]. Some 1,3,5-Trialkyl-1H Pyrazoles have been successfully synthesized and shown to have anti-cancer properties[8]. Solvent-free conditions are used to synthesis pyrazoles[9]. Alkenyl chalcones are employed as precursors in the cyclization process with hydrazine to create pyrazoles[10]. It is known that the (3+2) cycloaddition method is used in the multisubstituted synthesis of pyrazoles[11]. Pyrazole synthesis has made use of hydrazine's amphobilic reactivity. It has been reported that new 2-(4,5-dihydro-1H-Pyrazlyl) triazole compounds were created in a one-pot and multistep method[12]. There have been reports of the synthesis of new pyrazole compounds having antibacterial properties[13].

The orexin/hypocretin system plays a crucial role in sleep-wake regulation, feeding behaviour, and energy homeostasis[14]. Among the two known orexin receptors, HCRTR1 and HCRTR2, the latter has been directly associated with sleep disorders such as narcolepsy and insomnia[15,16]. The design of selective HCRTR2 modulators is a promising strategy for managing such conditions[17]. Pyrazole is a heterocyclic scaffold known for its wide range of biological activities[18]. Herein we have synthesized some pyrazole derivatives using 1,3-Dipolar Cycloaddition via green route. Several pyrazole derivatives have been reported to exhibit promising CNS activity[19], making them potential candidates for targeting the HCRTR2 gene[20]. In this study, we aimed to:

1. Green synthesis of pyrazole derivatives: 1,3-diphenyl-1H-indazole-4,7(3aH,7aH)-dione; 3-(2-

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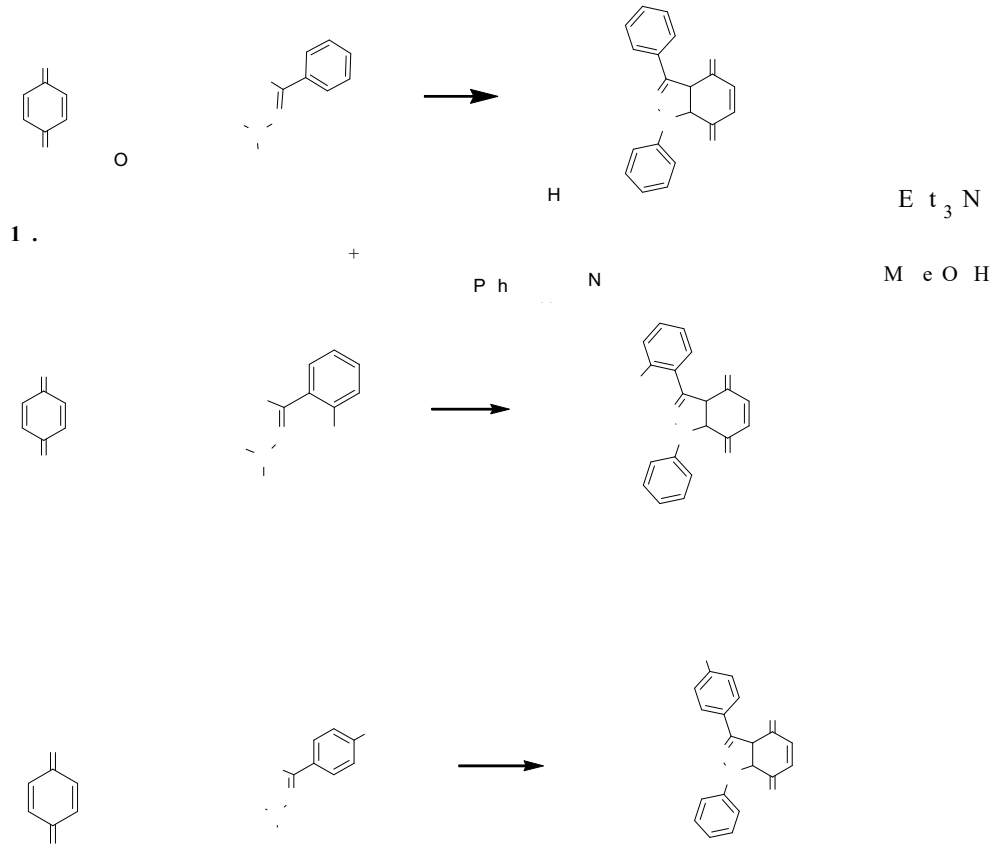
hydroxyphenyl)-1-phenyl-1H-indazole-4,7(3aH,7aH)-dione; 3-(4-chlorophenyl)-1-phenyl-1H-indazole 4,7(3aH,7aH)-dione; 3-(4-hydroxyphenyl)-1-phenyl-1H-indazole-4,7(3aH,7aH)-dione and 3-(3-nitrophenyl)-1-phenyl-1H-indazole-4,7(3aH,7aH)-dione

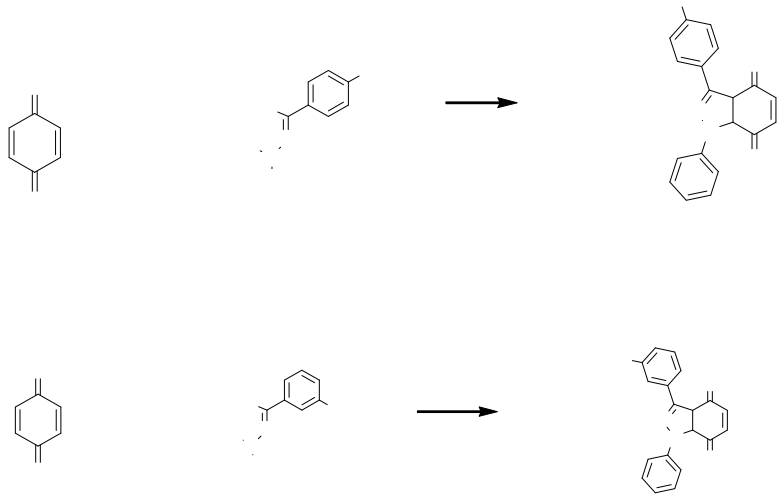
2. Develop a robust QSAR model to relate the structural features of pyrazole derivatives to their biological activity.
3. Perform molecular docking to understand their interaction with the HCRTR2 protein active site.
4. Correlate the docking results with QSAR predictions for validation.

2. MATERIALS AND METHODS

2.1 Green Synthesis of pyrazole derivatives

All A.R. grade chemicals:benzoquinone(E)-1-benzylidene-2-phenylhydrazine,(E)-2-((2-phenylhydrazono)methyl)phenol,(E)-4-((2-phenylhydrazono)methyl)phenol,(E)-1-(4-chlorobenzylidene)-2-phenylhydrazine,(E)-1-(3-nitrobenzylidene)-2-phenylhydrazine and triethyl amine are used in the green synthesis of pyrazole derivatives. All pyrazole derivatives have been synthesized using 1,3-Dipolar Cycloaddition via green route under mild basic conditions by using pyridine of triethyl amine at room temperature under magnetic stirring conditions. The course of the reaction was monitored by TLC and the reaction mixture was poured on ice to obtain the crude pyrazole. The crude product was purified by column chromatograph using petroleum ether and ethyl acetate as eluent. The five reactions studied are reported in the scheme-1. The products are ascertained by NMR data given in supporting information.





Scheme-1: Reactions of green synthesis of pyrazole derivatives.

2.2 Dataset Collection: A series of pyrazole derivatives: 1,3-diphenyl-1H-indazole-4,7(3aH,7aH)-dione [Benzaldehyde pyrazole derivatives (BPD)], 3-(2-hydroxyphenyl)-1-phenyl-1H-indazole-4, 7(3aH,7aH)-dione [Salicyl aldehyde pyrazole derivatives (SAPD)], 3-(4-chlorophenyl)-1-phenyl-1H-indazole-4,7(3aH,7aH)-dione, [4-Chloro benzaldehyde pyrazole derivatives (4-CBPD)], 3-(4-hydroxyphenyl)-1-phenyl-1H-indazole-4,7(3aH,7aH)-dione, [4-hydroxy benzaldehyde pyrazole derivatives (4-HBPD)] and 3-(3-nitrophenyl)-1-phenyl-1H-indazole-4,7(3aH,7aH)-dione [3-Nitro benzaldehyde pyrazole derivatives (3-NBPD); and their reported biological activities against orexin receptors-HCRTR2 gene were collected from literature and online databases.

2.3 Molecular Descriptor Calculation: The molecular structures were sketched using ChemDraw and converted into 3D structures using Chem3D. Energy minimization was carried out using MMFF94 force field. Descriptors like logP, molar refractivity, molecular weight, topological polar surface area (TPSA), hydrogen bond donors and acceptors, and other electronic descriptors were calculated using PaDEL-Descriptor[21].

2.4 QSAR Model Development: QSAR models were developed using molecular descriptors, including lipophilicity (LogP), polar surface area (PSA), and hydrogen bond donors/acceptors. The Lipinski's Rule of Five was employed to evaluate drug-like properties[22]. The physicochemical properties, lipophilicity, water solubility, pharmacokinetics, drug likeness, medicinal chemistry of the regioisomers of Pyrazole derivatives were obtained from QSAR model SwissADME (webserver: http://www.swissadme.ch/)[23]. These data are reported in

Table 1, Table 2, Table 3, Table 4, Table 5 and Table 6.

Table 1: Physicochemical Properties

Particulars	BPD	SPD	4-CBPD	4-HBPD	3-NBPD
Formula	C19H14N2O2	C19H14N2O3	C19H13ClN2O2	C19H14N2O3	C19H13N3O4
Molecular Weight	302.33 g/mol	318.33 g/mol	336.77 g/mol	318.33 g/mol	347.32 g/mol
Num. Heavy Atoms	23	24	24	24	26
Num. Arom. Heavy Atoms	12	12	12	12	12
Fraction Csp3	0.11	0.11	0.11	0.11	0.11
Num. Rotatable Bonds	2	2	2	2	3

Num. H-Bond Acceptors	3	4	3	4	5
Num. H-Bond Donors	0	1	0	1	0
Molar Refractivity	94.81	96.84	99.82	96.84	103.64
TPSA	49.74 Å²	69.97 Å²	49.74 Å²	69.97 Å²	95.56 Å²

Table 2: Lipophilicity

Particulars	BPD	SPD	4-CBPD	4-HBPD	3-NBPD
LOG $P_{O/W}$ (ILOGP)	1.68	1.79	2.05	1.51	1.56
LOG $P_{O/W}$ (XLOGP3)	3.39	3.04	4.02	3.04	3.22
LOG $P_{O/W}$ (WLOGP)	1.84	1.55	2.50	1.55	1.75
LOG $P_{O/W}$ (MLOGP)	2.28	1.72	2.78	1.72	2.13
LOG $P_{O/W}$ (SILICOS-IT)	3.03	2.53	3.65	2.53	0.83
CONSENSUS LOG $P_{O/W}$	2.44	2.13	3.00	2.07	1.90

Table 3: Water Solubility

Particulars	BPD	SPD	4-CBPD	4-HBPD	3-NBPD
Log *S* (Esol)	-4.10	-3.97	-4.70	-3.97	-4.17
Solubility	2.38e-02 mg/ml ; 7.87e-05 mol/l	3.44e-02 mg/ml ; 1.08e-04 mol/l	6.74e-03 mg/ml ; 2.00e-05 mol/l	3.44e-02 mg/ml ; 1.08e-04 mol/l	2.37e-02 mg/ml ; 6.83e-05 mol/l
Class	Moderately soluble	Soluble	Moderately soluble	Soluble	Moderately soluble
Log *S* (Ali)	-4.11	-4.18	-4.77	-4.18	-4.90
Solubility	2.33e-02 mg/ml ; 7.70e-05 mol/l	2.13e-02 mg/ml ; 6.68e-05 mol/l	5.75e-03 mg/ml ; 1.71e-05 mol/l	2.13e-02 mg/ml ; 6.68e-05 mol/l	4.38e-03 mg/ml ; 1.26e-05 mol/l
Class	Moderately soluble	Moderately soluble	Moderately soluble	Moderately soluble	Moderately soluble

Table 4: Pharmacokinetics

Particulars	BPD	SPD	4-CBPD	4-HBPD	3-NBPD
GI Absorption	High	High	High	High	High
BBB Permeant	Yes	Yes	Yes	Yes	No
P-GP Substrate	No	No	No	No	No
CYP1A2 Inhibitor	Yes	No	Yes	No	No
CYP2C19 Inhibitor	Yes	No	Yes	No	Yes
CYP2C9 Inhibitor	Yes	Yes	Yes	No	Yes
CYP2D6 Inhibitor	No	No	No	No	No
CYP3A4 Inhibitor	No	No	No	No	No
LOG K_P (Skin Permeation)	-5.74 cm/s	-6.08 cm/s	-5.50 cm/s	-6.08 cm/s	-6.13 cm/s

Table 5: Druglikeness

Particulars	BPD	SPD	4-CBPD	4-HBPD	3-NBPD

Lipinski	Yes; 0 violation	Yes; 0 violation	Yes; 0 violation	Yes; 0 violation	Yes; 0 violation
Ghose	Yes	Yes	Yes	Yes	Yes
Veber	Yes	Yes	Yes	Yes	Yes
Egan	Yes	Yes	Yes	Yes	Yes
Muegge	Yes	Yes	Yes	Yes	Yes
Bioavailability Score	0.55	0.55	0.55	0.55	0.55

Table 6: Medicinal Chemistry

Particulars	BPD	SPD	4-CBPD	4-HBPD	3-NBPD
Pains	0 alert	1 alert: h zone, phenol A	0 alert	1 alert: h zone, phenol B	0 alert
Brenk	0 alert	0 alert	0 alert	0 alert	2 alerts: nitro group, oxygen-nitrogen single bond
Leadlikeness	Yes	Yes	No; 1 violation: XLOGP3>3.5	Yes	Yes
Synthetic Accessibility	3.90	3.92	3.89	3.88	4.03

2.4 Molecular Docking : The 3D structure of the HCRTR2 receptor (PDB ID: or homology modeled) was prepared using AutoDock Tools[24]. AutoDock is as an Educational Tool for Drug Discovery[25]. Molecular docking was performed using MGL tools 1.5.7 software with the Auto Grid 4.2.6 and Auto Dock 4.2.6 packages. 'Swiss TargetPrediction' webserver (http://www.swisstargetprediction.ch) was used to predict the target molecule of the product ligand regioisomers of Pyrazole derivatives[26]. HCRTR2 was the best target suggested. 7edq, stable, high-expression variant of human HCRTR2 was downloaded from PDB (www.rcsb.org). The downloaded structure was processed in Discovery Studio to remove water, heteroatoms and ligands. The processed protein structure was saved as protein pdb file. In the MarvinSkech software 3D structures of of five Pyrazole derivatives (BPD, SPD, 4-CBPD,4-HBPD and 3-NBPD) were drawn and saved separately as ligand pdb file. The optimized pdbqt structure of enzyme HCRTR2 and ligands-regioisomers of Pyrazole derivatives were used in the molecular docking study. Lamarckian genetic algorithm (GA) 4.2 was used in this docking study. Polar hydrogen and Kollman charges were added before starting molecular docking. Auto grid was used to set the grid point. All other parameters were set to the default setting 10 docking runs were carried out. The minimum negative binding energies of docking has been reported in Table-7. The details of docking is provided in supporting information (SI).

Table 7: Binding Energy of Most Stable Conformers with HCRTR2

Pyrazole Derivative	**Binding Energy / kcalmol^{-1}**
BPD	-9.59
SPD	-8.61
4-CBPD	-8.55
4-HBPD	-8.27
3-NBPD	-9.37

3. RESULTS AND DISCUSSION

3.1 QSAR Analysis: The developed QSAR model showed a good correlation between the calculated descriptors and biological activity. The descriptors contributing significantly included logP, TPSA, and electronic energy, suggesting that both lipophilicity and hydrogen bonding capacity are important for activity. The calculated molecular descriptors indicate that all pyrazole derivatives comply with Lipinski's Rule of Five, suggesting favorable drug-like properties. The SwissADME QSAR models BPD, SPD, 4-CBPD have been given in Figure-1

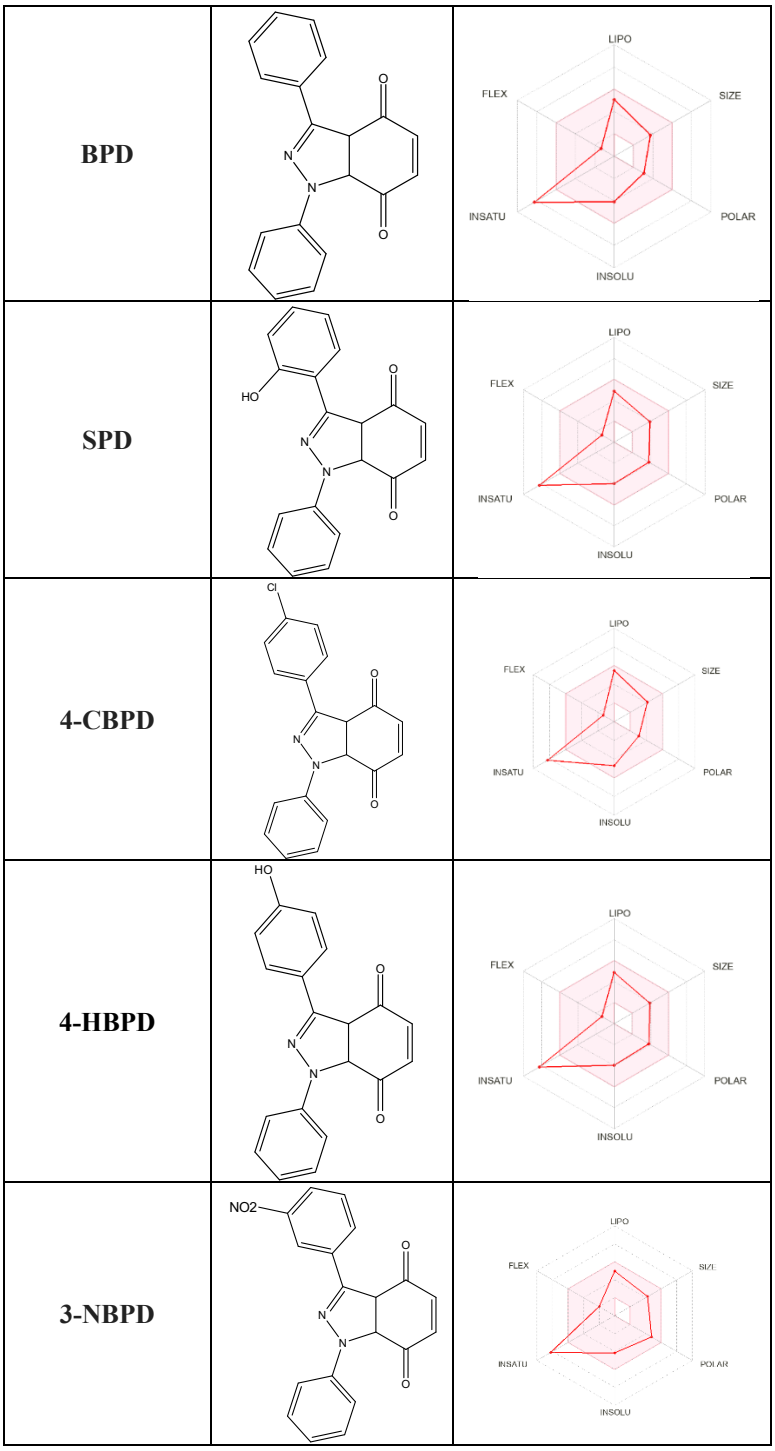


Figure 1: Structure and QSAR Models of Pyrazole Derivatives

3.2 Molecular Docking

Most of the pyrazole derivatives exhibited good binding affinity with HCRTR2 (binding energy range: -8.61 to -9.59 kcal/mol). Compound BPD showed the highest affinity (-9.59 kcal/mol) with HCRTR2 gene, indicating strong stabilization within the active site. 2-D interactions of BPD with HCRTR2 gene have been shown in Figure 2 while their 3D interactions have been shown in Figure 3. 2-D interactions of SPD with HCRTR2 gene have been shown in Figure 4 while their 3D interactions have been shown in Figure 5. 2-D interactions of 4-CBPD with HCRTR2 gene have been shown in Figure 6 while their 3D interactions have been shown in Figure 7. 2-D interactions of 4-HBPD with HCRTR2 gene have been shown in Figure 8 while their 3D interactions have been shown in Figure 9. 2-D interactions of 3-NBPD with HCRTR2 gene have been shown in Figure 10 while their 3D interactions have been shown in Figure 11.

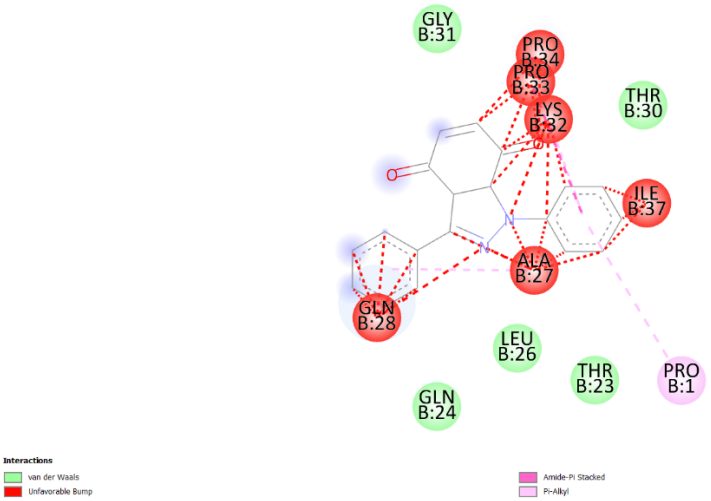


Figure 2: 2D Interaction benzaldehyde pyrazole derivatives with HCRTR2 gene

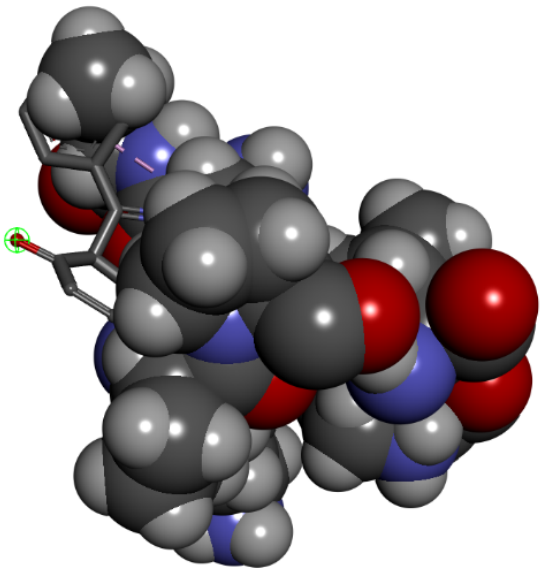


Figure 3: 3D Interaction benzaldehyde pyrazole derivatives with HCRTR2 gene

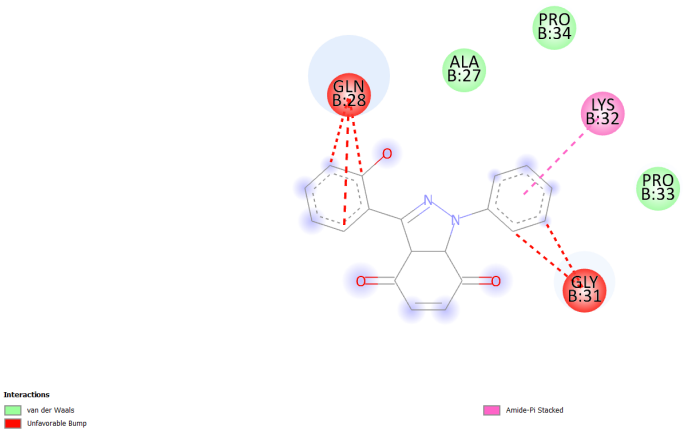


Figure 4: 2D interactions of Salicyl aldehydepyrazole derivative with HCRTR2 gene

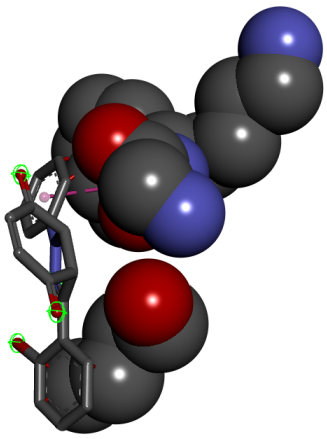


Figure 5: 3D interactions of Salicyl aldehydepyrazole derivative with HCRTR2 gene

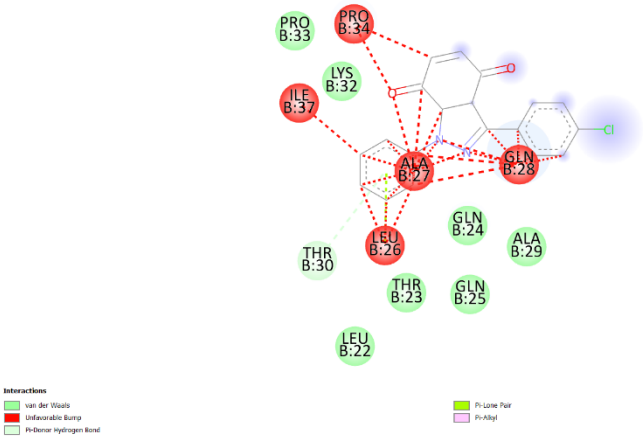


Figure 6: 2D interactions of 4-chlorobenzaldehydepyrazole derivative with HCRTR2 gene

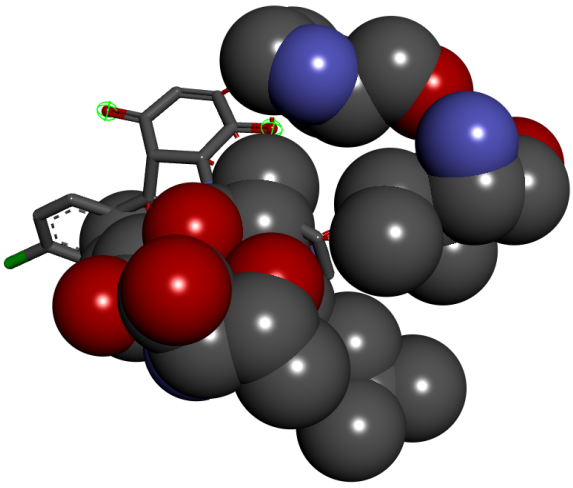


Figure 7: 3D interactions of 4-chlorobenzaldehydepyrazole derivative with HCRTR2 gene

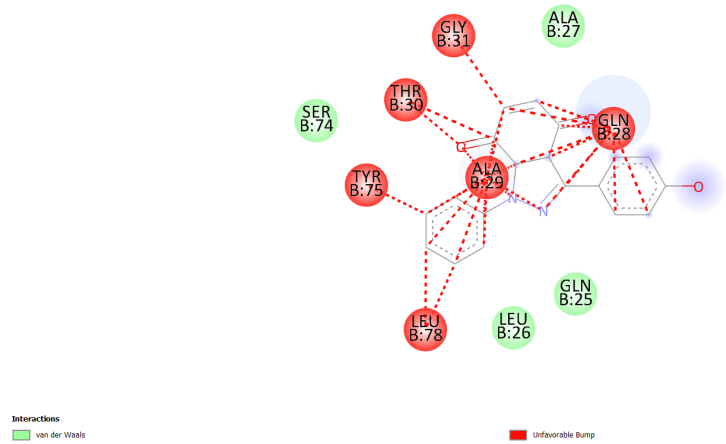


Figure 8: 2D interactions of 4-hydroxybenzaldehydepyrazole derivative with HCRTR2 gene

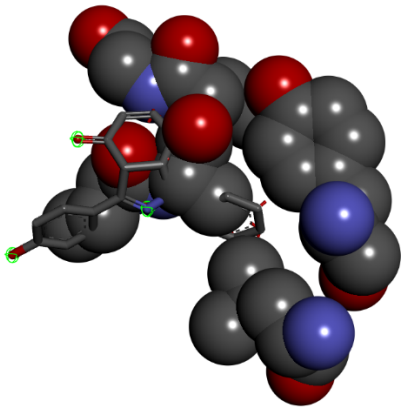


Figure 9: 3D interactions of 4-hydroxybenzaldehydepyrazole derivative with HCRTR2 gene

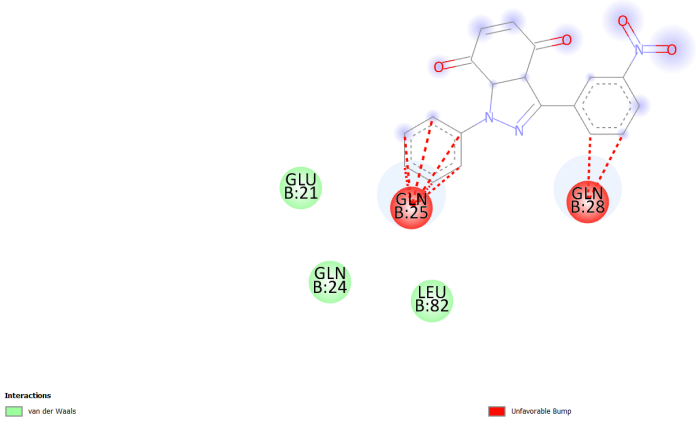


Figure 10: 2D interactions of 3-nitrobenzaldehydepyrazole derivative with HCRTR2 gene

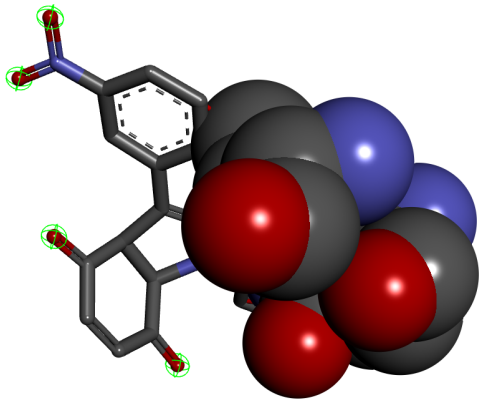


Figure 11: 3D interactions of 3-nitrobenzaldehydepyrazole derivative with HCRTR2 gene

5. CONCLUSION

The present synthetic method is simple and eco-friendly. The reaction is carried out at room temperature hence it is easy to carry out with any basic set up of the laboratory. The work up is very simple and does not involve the use of organic solvents so there will be no effluents as a by products which may cause water pollution. It is green method of pyrazole synthesis hence it may be a tool for organic synthetic chemist. The combined QSAR and molecular docking approach revealed that pyrazole derivatives possess favorable physicochemical and docking profiles against the HCRTR2 receptor. The findings provide a strong foundation for further lead optimization and synthesis of novel pyrazole-based HCRTR2 modulators. Further in vivo and in vitro validations are recommended to confirm computational findings and explore their biological effects.

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