Original Article

In-silico ADMET and molecular docking study of novel antihypertensive derivatives designed by bioisosteric replacement of the aminoquinazoline ring in prazosin

Sunil Sahu[1], Pankaj Minj[2], Dhansay Dewangan[3], Swarnlata Saraf[2], Rakesh Tirkey[2]*

From, [1]Sanskar City College of Pharmacy, Thakurtola, Rajnandgaon, Chhattisgarh 491441, India, [2]University Institute of Pharmacy, Pt. Ravishankar Shukla University, Raipur, Chhattisgarh 492010, India, [3]Department of Chemistry, Government Lahiri PG College, Chirimiri, District-MCB, Chhattisgarh, India

ABSTRACT

Considering the global burden of hypertension, this study aims to design and evaluate novel Prazosin analogues with enhanced pharmacokinetic properties and reduced toxicity using a bioisosteric approach. This study will help to find the prominent group for antihypertensive drug development. A bioisosteric approach was employed to generate novel Prazosin analogues using the MolOpt program. The aminoquinazoline moiety of Prazosin was systematically replaced with bioisosteric groups, and the various pharmacokinetics (absorption, distribution, metabolism, excretion, and toxicity) parameters of the newly developed analogs were calculated. Molecular docking studies were performed to assess the binding affinity of the newly designed analogues, and the top three derivatives with superior docking scores were identified. The study identified several compounds as promising analogues due to their reduced toxicity (hERG, H-HHT, DILI < 0.3), favorable drug likeness QED values (≤ 0.67), and molecular docking score compared to prazosin. Notably, analogues 038, 158, and 190. This study successfully identified novel antihypertensive derivatives with improved ADMET properties, enhanced drug-likeness, and favorable molecular docking profiles. The findings provide valuable insights for the development of next-generation antihypertensive agents with optimized pharmacological characteristics.

Key words: Prazosin, α1-Adrenoceptor antagonists, ADMET, Bioisosteric approach, Molecular Docking.

Hypertension poses a significant risk for cerebrovascular and heart diseases in developed nations, and antihypertensive medications play a significant role in improving the quality of life for patients. Despite the availability of various antihypertensive drugs, controlling all types of hypertension with a single therapy remains challenging due to the diverse origins and pathology of this condition. Moreover, each antihypertensive agent comes with unique adverse effects.

Therefore, it is necessary to design and develop new drugs with diverse chemical profiles. It is recognized that α1-adrenoceptors play a crucial role in both the central and peripheral nervous systems in maintaining normal arterial blood pressure. Antihypertensive drugs with quinazoline and quinazolidine ring systems, such as prazosin, are effective as α1-adrenoceptor antagonists [1]. Antihypertensive medicines with unique modes of action are increasingly being used to treat specific hemodynamic abnormalities without interfering with normal physiological activities [2]. Several quinazoline-based α1-adrenoceptor antagonists, including prazosin, terazosin, doxazosin, bunazosin, and alfuzosin, are clinically used for hypertension management. [3]

Prazosin is a selective competitive α1-adrenoceptor antagonist of the 2,4-diamino-6,7-dimethoxyquinazoline class that is broadly employed as a pharmacological tool for α1-adrenoceptor characterization as well as an effective agent in the treatment of hypertension [4]. Functional and molecular approaches have been used to classify three α1-adrenoceptor subtypes(α1A, α1B, and α1D). The α1L-adrenoceptor, also known as the α1A/L-adrenoceptor, is a functional phenotype of the α1A-adrenoceptor that is pharmacologically different and has a low affinity for prazosin, according to functional evidence, except for three subtype receptors [5]. The "first dose phenomenon," which can sometimes lead to syncope, is the most dangerous side effect of prazosin. Prazosin is well absorbed from the gastrointestinal system and is completely removed after significant metabolic processing. Prazosin has a limited bioavailability and a short elimination

Access this article online

Received – 07th April 2026

Initial Review – 08th April 2026

Accepted – 10th April 2026

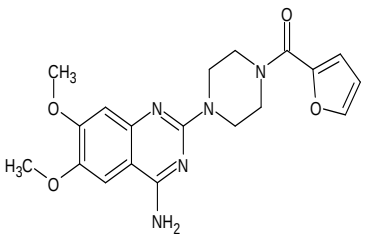
Quick Response Code

Correspondence to: Dr. Rakesh Tirkey, University Institute of Pharmacy, Pt. Ravishankar Shukla University, Raipur, Chhattisgarh 492010, India.

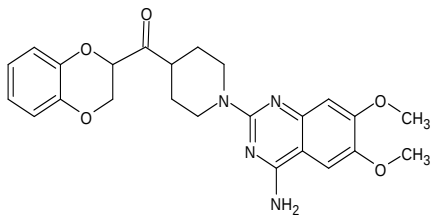
Email: rakeshtirkey99@gmail.com

half-life of roughly 2-3 hours. The easy elimination of the furoyl group from the piperazine ring is a characteristic prazosin metabolic pathway, leading to metabolites with extremely poor antihypertensive action. Enzymatic hydroxylation of the piperazine ring is likewise quite sensitive [6]. Prazosin was found to have a shorter duration and less reflex tachycardia than doxazosin and terazosin. Because quinazoline derivatives are part of the N-containing heterocyclic chemicals family [7].

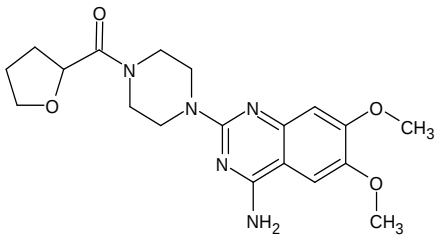
Prazosin, doxazosin, and terazosin are absorbed orally (up to 65% in the case of doxazosin) and undergo some presystemic hepatic metabolism before being primarily broken down by dealkylation and conjugation in the liver. Protein binding is high in all three medications (90% to 98%). Although the medications' half-lives differ (prazosin, 2–4 hours, doxazosin, 9–12 hours; and terazosin, 11 hours), their therapeutic activities last longer (prazosin about 10 hours; doxazosin about 30 hours). Increased intracellular Ca2+ is triggered by agonists of the α1 adrenoreceptor. The α1 agonist–receptor interaction activates phospholipase C (associated with Gq), which facilitates the hydrolysis of phosphatidylinositol bisphosphate (PIP2) and raises the synthesis of the second messengers DAG and 1,4,5-inositol triphosphate (IP3). DAG stimulates protein kinase C, whereas IP3 releases Ca2+ from the Sarcoplasmic reticulum (SR), increasing intracellular Ca2+ concentration. There's also evidence that IP3 causes contractile proteins to become more Ca2+-sensitive. IP3's phosphorylated product (IP4—1,3,4,5-inositol tetraphosphate) has been identified as the messenger responsible for vasoconstriction via increasing Ca2+ transit across the cell membrane. The α1 selective antagonists inhibit Ca2+ levels by blocking α1 receptors, resulting in smooth muscle relaxation in arterioles and venous capacitance arteries [8].



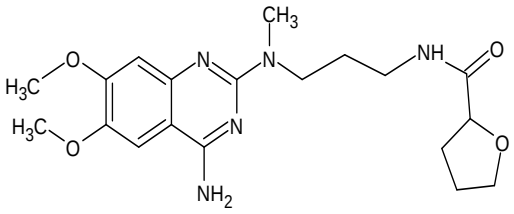
Prazosin



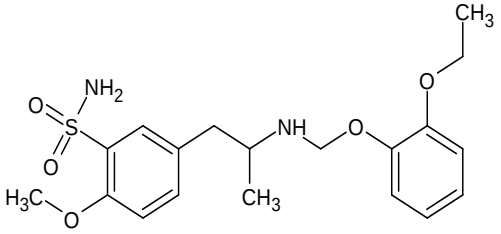
Doxazosin



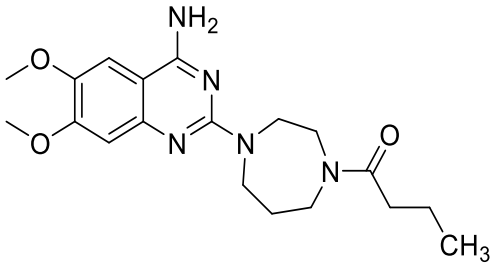
Terazosin



Alfuzosin



Tamsulosin



Bunazosin

The most serious side effect is syncope with sudden loss of consciousness (1%), which occurs after a first dose of at least 2 mg. Therefore, always begin with 1 mg of prazosin. The most common side effects of prazosin include palpitations and nausea, lack of energy, weakness, headache, drowsiness, and dizziness. Additional side effects have been documented for 1–4% of patients receiving prazosin, including constipation, vomiting, diarrhea, edema, dyspnea, vertigo, syncope, depression, anxiety, rash, nasal congestion, and increased urine frequency. [9]. In a few cases of prazosin treatment, Orthostatic hypotension and Hypothermia have been reported in some individuals [10-11]. The novelty of the present study

lies in the rational design of 190 novel prazosin analogues through bioisosteric replacement of the aminoquinazoline moiety using the MolOpt platform. Unlike previous studies focusing on limited structural modifications, this work systematically explores diverse heterocyclic substitutions and integrates comprehensive ADMET profiling, drug-likeness evaluation, and molecular docking against the α1A-adrenergic receptor (7YM8). This multi-parameter approach aims to identify safer and more potent antihypertensive candidates with improved pharmacokinetic properties.

MATERIALS AND METHODS

Prazosin, a quinazoline derivative, acts by selectively inhibiting the α1-Adrenoceptor.As shown in Figure 4, MolOpt[12]was used to design novel antihypertensive agents from modification in the prazosin structure. The molecular structures of newly designed analogues, as well as their properties, are shown in Table 1. Similarly, Figure 2depicts the novel possible derivatives designed from the replacement of the aminoquinazoline ring from prazosin. The structure of ligands was drawn using CD/ChemSketch2021.1.1 (www.acdlabs.com). [13]

ADMETLab2.0 [14] was used to study the pharmacokinetics and toxicity of newly developed analogues. Druglikeness and Drugscore were calculated using Osiris Property Explorer (PEO) [15].

2.1 Designing novel antihypertensive derivatives from the prazosin structure

The MolOpt (Bioisosteric Replacement Tool) was used for the design of novel analogues through the substitution of the aminoquinazoline core with several heterocycles. The choice of bioisosteres depended upon their structural resemblance, electronic behavior, and drug-like characteristics.

2.2 Pharmacokinetic (ADME) and Toxicity properties prediction

ADMET properties, including absorption, distribution, metabolism, excretion, and toxicity, were predicted using the ADMETlab 2.0 web server. Parameters such as human intestinal absorption (HIA), blood–brain barrier permeability (BBB), plasma protein binding (PPB), cytochrome P450 interactions, and toxicity endpoints were evaluated.

2.3 Druglikeness and Drugscore

Osiris Property Explore (PEO) was used to calculate toxicity, drug-likeness, and drug score.

2.4 In Silico study for antihypertensive activity

Molecular docking was performed using ArgusLab 4.0.1. The crystal structure of the α1A-adrenergic receptor (PDB ID: 7YM8) was retrieved from the RCSB Protein Data Bank. Protein preparation involved the removal of water molecules, the addition of hydrogen atoms, and energy minimization. Ligands were energy-minimized prior to docking using standard force field parameters. Docking was performed using the AScore scoring function with grid dimensions of 80 × 80 × 80 Å and spacing of 0.375 Å. Binding interactions were visualized using PyMOL 2.0. [16]

RESULT AND DISCUSSION

3.1 Novel antihypertensive derivatives by replacement of the Aminoquinazoline ring from the prazosin structure

A total of 190 novel antihypertensive analogues were designed using the MolOpt platform through bioisosteric replacement of the aminoquinazoline moiety, including Pyrrolidine, Quinoline, Azetidine, Benzopyrane, Quinazoline, Pyridine, Benzene 1,3-Oxazolidine, Imidazole, Cyclopenta[b]furan, Thiophene, and others (Figure 1).

Further, the ADMETLab2.0 web program was used to study these novel analogues for ADMET prediction. In drug design and development, the Lipinski rule of five is used to forecast the oral bioavailability of possible lead compounds. Predictions of several molecular parameters, including molecular weight (MW), number of hydrogen bond donors (nHD), number of hydrogen bond acceptors (nHA), and the logarithm of the n-octanol/water distribution coefficient (LogP) of recently developed analogues based on the Lipinski rule, are shown in Table No. 1

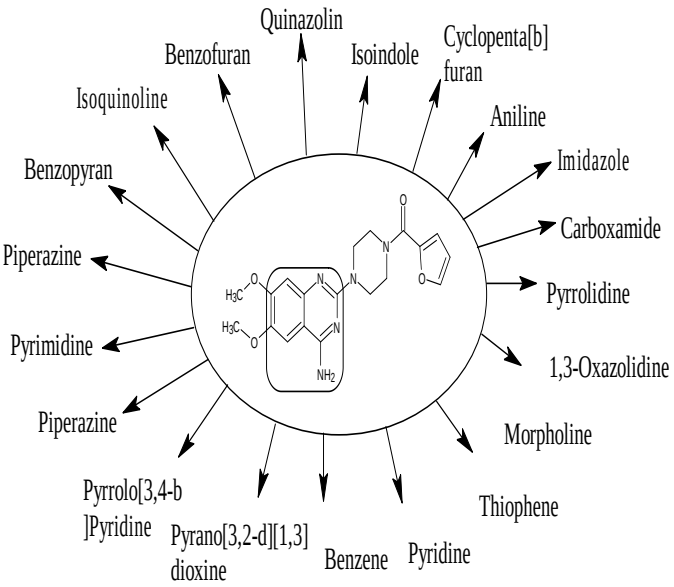
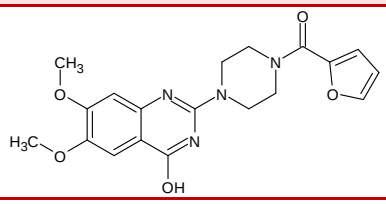
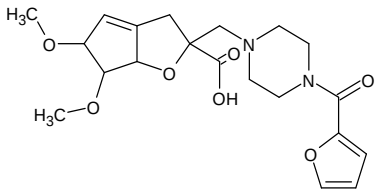
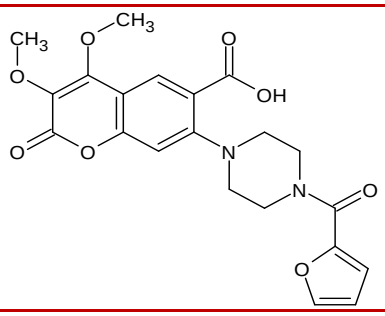
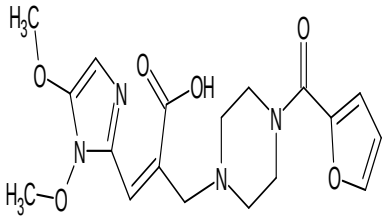
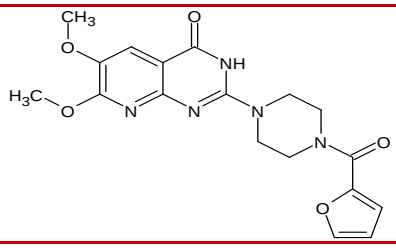
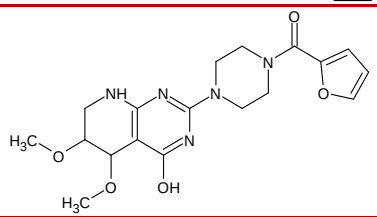
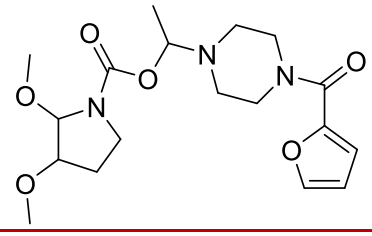
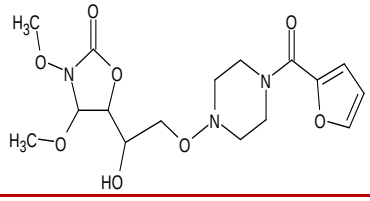
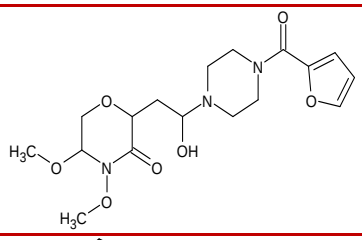
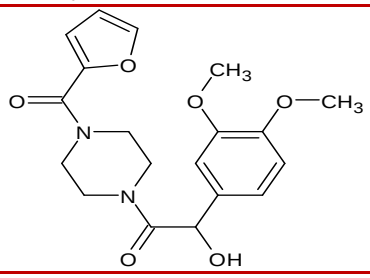
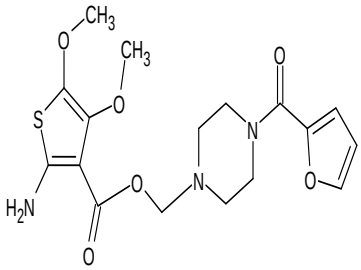
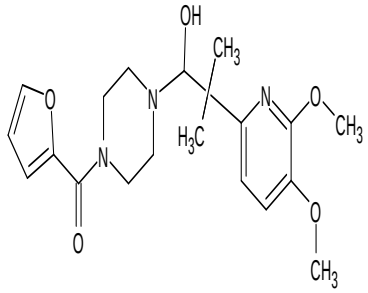
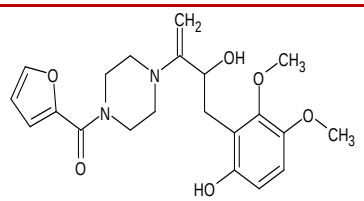
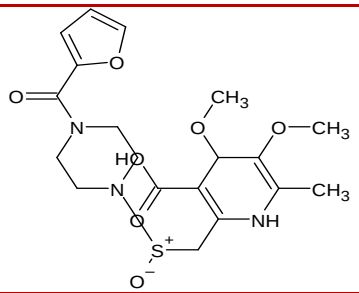
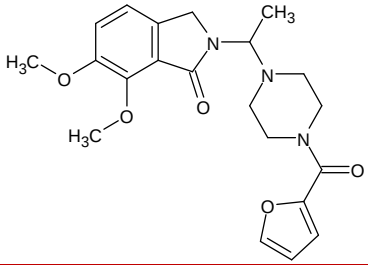
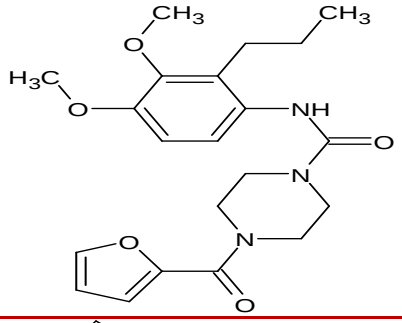
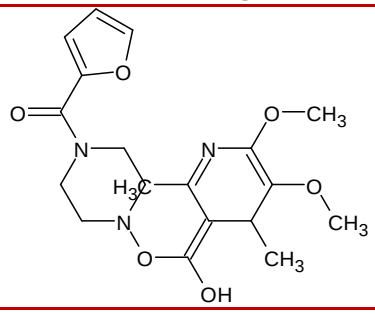
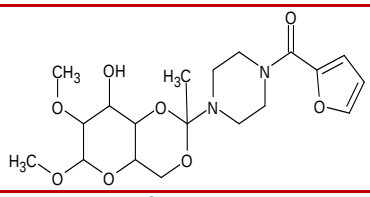
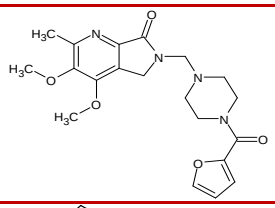
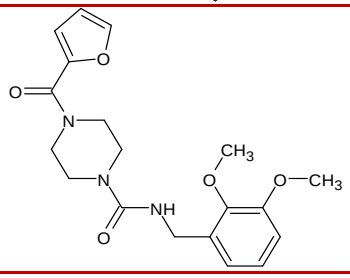
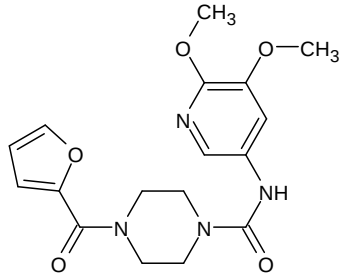
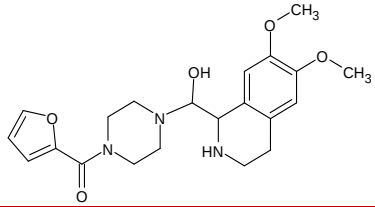


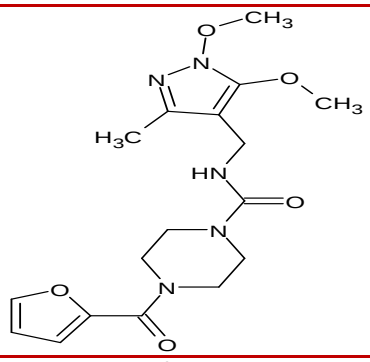
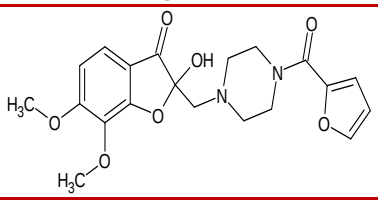
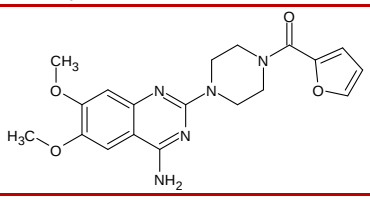
Fig 1: Bioisosteric replacement strategy used for designing novel prazosin analogues.

Table 1: Novel antihypertensive analogues and their molecular properties

S. No.	Index no.	Structure of novel antihypertensive analogues	Bioisosteres	MW	nHA	nHD	TPSA	nRot	LogS	LogP
1.	005		Quinazoline	384.14	9	1	100.9	5	-3.048	1.171
2.	038		Cyclopenta[b]furan	406.17	9	1	101.68	7	-1.039	-0.221
3.	050		benzopyran	428.12	10	1	122.66	6	-3.448	1.753
4.	051		Imidazole	390.15	10	1	110.27	8	-0.954	-0.069
5.	052		Pyrimidine	385.14	10	1	113.79	5	-2.672	1.359
6.	060		Pyrimidine	389.17	10	2	112.93	5	-2.367	0.255
7.	061		Pyrrolidine	381.19	9	0	84.69	8	-0.877	0.424
8.	071		1,3-Oxazolidine	385.15	11	1	114.15	8	-1.17	-0.486

9.	099		Morpholine	383.17	10	1	104.92	7	-0.929	-0.495
10.	101		Benzene	374.15	8	1	92.45	7	-1.894	0.817
11.	105		Thiophene	395.12	9	2	107.47	8	-3.221	1.356
12.	115		Pyridine	389.2	8	1	88.27	7	-1.367	1.678
13.	125		Benzene	402.18	8	2	95.61	8	-1.246	1.05
14.	128		Pyridine	439.14	10	1	127.87	8	-0.694	-0.015
15.	130		Isoindole	399.18	8	0	75.46	6	-1.19	0.461

16.	137		Aniline	401.2	8	1	84.25	9	-3.833	2.606
17.	142		Pyridine	391.17	9	0	93.81	7	-1.239	0.41
18.	154		Pyrano[3,2-d][1,3]dioxide	412.18	10	1	103.07	5	-0.904	-0.039
19.	158		Pyrrolo[3,4-b]Pyridine	395.21	9	2	98.85	8	-0.923	-0.477
20.	161		Carboxamide	373.16	8	1	84.25	8	-1.34	0.999
21.	167		Carboxamide	360.14	9	1	97.14	7	-2.059	1.17
22.	170		Isoquinoline	401.2	8	2	87.41	6	-1.266	0.924

23.	186		Carboxamide	373.18	9	2	92.1	5	-1.957	1.284
24.	190		Benzofuran	402.14	9	1	101.68	6	-2.589	1.23
25.	PZN		Quinazolin	383.16	9	2	107.68	5	-2.573	1.247

MW(Molecular weight), nHA(Number of hydrogen bond acceptor), nHD(Number of hydrogen bond donor), nRot(Number of rotatable bonds), Logp (logarithm of the n-octanol/water distribution coefficient), Logs (The logarithm of aqueous solubility value), TPSA (Topological polar surface area), PZN(Prazosin)

3.2 Prediction of ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) features of novel antihypertensive derivatives

The pharmacokinetic characteristics, such as absorption, distribution, metabolism, excretion, and toxicity, were computed using the ADMETlab2.0 program. The medicinal properties of the analogues are listed in Table 2. Most of the designed analogues exhibited QED values above 0.67, indicating good drug-likeness, although a few compounds showed slightly lower values. All of the compounds have a synthetic accessibility of less than or equal to 6, indicating an excellent synthetic accessibility range. The findings suggest that all novel derivatives are similar to prazosin in terms of Lipinski, Pfizer, and the Golden Triangle rules. Rather than this, analogues such as 038, 125, 154, 158, 170, and 190 are rejected by GSK. All the novel derivatives mentioned in Table 2 possess natural product likeness, especially index 154. ALARM NMR and BMS showing zero value indicates an excellent compound than other values like 1,3,4, etc. Out of the designed analogues, none show any chelation.

The ADMET analysis revealed that several analogues demonstrated improved pharmacokinetic profiles compared to prazosin, particularly in terms of reduced hepatotoxicity (HHT) and drug-induced liver injury (DILI). Compounds such as 038, 115, and 170 exhibited favorable oral bioavailability and clearance values, suggesting enhanced systemic exposure. These findings highlight the potential of selected derivatives for further optimization.

Table 2: Medicinal properties of prazosin analogues

S.No.	Index No.	QED	SA score	Fsp3	MCE-18	NP score	ALARM NMR	BMS	Chelating	Lipinski	Pfizer	GSK	GT
1.	005	0.727	2.354	0.316	51.04	-1.303	3	0	0	Accepted	Accepted	Accepted	Accepted
2.	038	0.686	4.316	0.6	85.5	0.189	0	0	0	Accepted	Accepted	Rejected	Accepted
3.	050	0.608	2.573	0.286	55.111	-0.515	3	0	0	Accepted	Accepted	Rejected	Accepted
4.	051	0.68	3.104	0.389	41.76	-0.877	0	0	0	Accepted	Accepted	Accepted	Accepted
5.	052	0.704	2.69	0.333	51.333	-1.379	2	0	0	Accepted	Accepted	Accepted	Accepted
6.	060	0.775	3.748	0.5	77.407	-0.715	0	0	0	Accepted	Accepted	Accepted	Accepted

7.	061	0.758	3.808	0.667	63.6	-0.629	0	1	0	Accepted	Accepted	Accepted	Accepted
8.	071	0.675	4.263	0.625	62.308	-0.331	1	0	0	Accepted	Accepted	Accepted	Accepted
9.	099	0.702	4.126	0.647	63	-0.372	0	1	0	Accepted	Accepted	Accepted	Accepted
10.	101	0.761	2.801	0.368	59.538	-0.908	2	1	0	Accepted	Accepted	Accepted	Accepted
11.	105	0.734	2.868	0.412	42	-1.101	4	1	0	Accepted	Accepted	Accepted	Accepted
12.	115	0.805	3.201	0.5	65.333	-0.96	1	1	0	Accepted	Accepted	Accepted	Accepted
13.	125	0.73	3.167	0.381	62.241	0.049	2	0	0	Accepted	Accepted	Rejected	Accepted
14.	128	0.617	4.629	0.526	68.276	-0.33	0	0	0	Accepted	Accepted	Rejected	Accepted
15.	130	0.766	3.092	0.429	76.667	-0.711	0	1	0	Accepted	Accepted	Accepted	Accepted
16.	137	0.803	2.334	0.429	40.8	-1.076	2	0	0	Accepted	Accepted	Rejected	Accepted
17.	142	0.754	3.966	0.526	64.862	-0.638	0	0	0	Accepted	Accepted	Accepted	Accepted
18.	154	0.725	4.377	0.737	88	0.492	0	0	0	Accepted	Accepted	Rejected	Accepted
19.	158	0.749	2.809	0.45	53.931	-0.942	0	1	0	Accepted	Accepted	Rejected	Accepted
20.	161	0.866	2.121	0.368	39.231	-1.486	1	0	0	Accepted	Accepted	Accepted	Accepted
21.	167	0.891	2.274	0.353	39.913	-1.799	2	0	0	Accepted	Accepted	Accepted	Accepted
22.	170	0.78	3.391	0.476	75.935	-0.368	0	1	0	Accepted	Accepted	Rejected	Accepted
23.	186	0.831	3.707	0.444	72.692	-1.208	0	0	0	Accepted	Accepted	Accepted	Accepted
24.	190	0.791	3.245	0.4	80.571	-0.041	1	0	0	Accepted	Accepted	Rejected	Accepted
25.	PZN	0.709	2.666	0.316	51.04	-1.138	3	0	0	Accepted	Accepted	Accepted	Accepted

QED (A measure of drug likeness based on the concept of desirability), SAscore (Synthetic accessibility score), NP score (Natural Product-likeness score), Fsp3 (The number of sp3 hybridized carbons/total carbon count), MCE-18 (Medicinal chemistry evolution in 2018), GT (Golden triangle), PZN(Prazosin).

Absorption properties (Caco-2, MDCK, and HIA) and distribution properties (Plasma protein binding (PPB), Volume of distribution, Blood blood-brain barrier, and Fu) are displayed in Table 3. All of the novel derivatives exhibited excellent Caco-P and MDCK values. HIA of analogues 061, 105, 115, 125, 158, and 190 have good oral absorption in humans, similar to Prazosin, suggesting that these compounds may be orally active. The BBB (Blood Brain Barrier) value of analogue 071, 099, 125, 154is moderate. Additionally, all of the novel derivatives showed considerable PPB (less than90%), as compared to prazosin, which has a PPB (greater than 90%). All of the analogues, like prazosin, have a good volume of distribution. All of the derivatives exhibit outstanding Fu (The fraction unbound in plasma). A 0-0.3 value is required for an excellent Pgp (P-glycoprotein) inhibitor and Pgp (P-glycoprotein) substrate molecule. All analogues have excellent Pgpinh and Pgp sub-values, with the exception of061,115,159, and 170 for Pgp sub.F(20%) and F(30%) is the indicator of the efficiency of the drug delivery to the systemic circulation. Analogue 105, 115, and 125 have excellent F(20%) and F(30%) values.

Table 3: Absorption and distribution properties of the designed antihypertensive analogues

S.No.	Index No.	Caco-2	MDCK	BBB	PPB (%)	VDss	Fu (%)	Pgp-inh	Pgp-sub	HIA	F 20%	F 30%
1.	005	-4.811	Ex.	0.239	91.50%	0.967	6.10%	0.046	0.996	0.019	0.026	0.008
2.	038	-5.505	Ex.	0.737	42.57	0.541	53.87	0.001	0.029	0.969	0.81	0.84
3.	050	-4.933	Ex.	0.174	71.92%	0.754	28.25%	0.002	0.801	0.118	0.724	0.014
4.	051	-5.142	Ex.	0.693	46.87	1.147	51.73	0.001	0.006	0.934	0.991	0.983
5.	052	-4.678	Ex.	0.037	92.02%	0.491	3.05%	0.014	0.984	0.075	0.024	0.009
6.	060	-5.168	Ex.	0.569	79.95%	1.011	23.79%	0.009	0.998	0.5	0.085	0.022
7.	061	-4.44	Ex.	0.637	33.75	1.134	62.69	0.011	0.605	0.01	0.826	0.145
8.	071	-4.663	Ex.	0.525	20.13	0.428	82.53	0.008	0.298	0.932	0.946	0.923
9.	099	-4.749	Ex.	0.459	22.91	0.652	77.10	0.003	0.582	0.889	0.892	0.318
10.	101	-4.71	Ex.	0.933	52.95%	1.388	32.54%	0.064	0.924	0.555	0.824	0.162
11.	105	-4.629	Ex.	0.922	42.94	1.345	57.44	0.002	0.004	0.007	0.189	0.026
12.	115	-4.622	Ex.	0.977	67.80	1.243	29.18	0.38	0.864	0.013	0.217	0.079
13.	125	-4.779	Ex.	0.48	69.45	1.039	31.24	0.008	0.042	0.254	0.017	0.01
14.	128	-5.72	Ex.	0.357	72.12%	0.502	33.53%	0.004	0.976	0.903	0.762	0.922
15.	130	-4.779	Ex.	0.974	51.40%	1.598	41.00%	0.001	0.005	0.133	0.984	0.885
16.	137	-4.646	Ex.	0.541	88.31%	0.852	9.22%	0.298	0.979	0.006	0.034	0.055
17.	142	-4.675	Ex.	0.77	49.20%	1.563	60.11%	0.867	0.006	0.01	0.592	0.969
18.	154	-4.824	Ex.	0.502	27.46	0.906	61.83	0.036	0.101	0.871	0.902	0.888
19.	158	-5.32	Ex.	0.952	71.38	1.698	30.04	0.001	0.008	0.033	0.919	0.84
20.	161	-4.948	Ex.	0.968	76.97%	1.031	18.75%	0.003	0.827	0.055	0.47	0.687
21.	167	-4.793	Ex.	0.896	83.38%	0.809	21.90%	0.005	0.895	0.025	0.059	0.786
22.	170	-5.15	Ex.	0.924	55.21	1.727	39.98	0.006	0.882	0.888	0.689	0.163
23.	186	-5.214	Ex.	0.503	73.33%	1.339	39.18%	0.003	0.993	0.734	0.114	0.078
24.	190	-4.613	Ex.	0.968	57.53	1.433	27.46	0.01	0.038	0.044	0.592	0.016
25.	PZN	-5.097	Ex.	0.364	90.22	0.822	8.45	0.005	0.998	0.099	0.025	0.003

Caco-2(The human colon adenocarcinoma cell line), MDCK(Madin-Darby Canine Kidney cells), and >2x 10-6cm/s indicates excellent, HIA (Human Intestinal Absorption), PPB (Plasma protein binding), BBB (Blood Brain Barrier), VD (Volume of Distribution), Fu (The fraction unbound in plasma), Pgpinh.(The inhibitor of P-glycoprotein),Pgp sub. (The substrate of P-glycoprotein),F(20%) The human oral bioavailability 20%, F(30%) The human oral bioavailability 30%,), Ex. (Excellent), PZN(Prazosin).

Metabolism properties of cytochrome P450 isozymes (1A2, 2C19, 2C9, 2D6, and 3A) are described in Table 4. Excretion properties like CL and $T_{1/2}$ were calculated. A clearance value of more than 5 is indicated as excellent. The analogues 105, 115, 125, and 170 have a higher clearance than prazosin. The $T_{1/2}$ value of most of the analogues is better than that of prazosin.

Table 4: Metabolism and excretion properties of novel antihypertensive derivatives

S No.	IndexNo.	CYP1A2	CYPC19	CYP2C9	CYP2D6	CYP3A4	CL	T12
1.	005	+	-	-	+	+	4.369	0.719
2.	038	+	+	+	+	+	1.811	0.128
3.	050	+	-	-	+	+	2.007	0.812
4.	051	-	+/-	+	+	+	4.263	0.804
5.	052	+	+/-	+	+	+	4.263	0.804
6.	060	+	+	+	+	+	2.852	0.831
7.	061	+	+	+	+	+	3.93	0.485
8.	071	+	+	+	+	+	4.411	0.223
9.	099	+	+	+	+	+	3.524	0.481
10.	101	+	-	-	+	-	4.114	0.63
11.	105	-	+	+	+	+	5.727	0.126
12.	115	+	+	+	+	+	5.14	0.655
13.	125	+	+	+	+	+	5.187	0.893
14.	128	+	+	+	+	+	3.148	0.769
15.	130	+	+	+	+	+	3.409	0.739
16.	137	+	+	+	+	+	4.784	0.865
17.	142	+	+	+	+	+	6.732	0.605
18.	154	+	+	+	+	+	2.562	0.203
19.	158	+	+	+	+	+	4.003	0.539
20.	161	+	+	+	+	-	5.173	0.918
21.	167	+	+	+	+	+	5.246	0.882
22.	170	+	+	+	+	+	5.683	0.738
23.	186	+	+	+	+	+	3.559	0.387
24.	190	+	+	+	+	+	4.32	0.309
25.	PZN	+	-	+	+	+	4.407	0.797

S No. – Serial Number, I No. – Index Number, (-) sign indicates inhibitor and (+) indicates substrate, human cytochrome P450 isozymes-1A2, 2C19, 2C9, 2D6 and 3A4, CL (The clearanace of a drug), $T_{1/2}$ (The half life of a drug), PZN(Prazosin).

The toxicity properties, such as hERG, HHT, DILI, AMES, and NR-AR, are shown in Table 5. The human ether-a-go-go-related gene is known as hERG. The regulation of the interchange of the resting potential and cardiac action potential during cardiac depolarisation and repolarisation is mostly dependent on a voltage-gated potassium channel that is encoded by hERG.A 90% compound has an excellent hERG value(hERG value less than 0.3), whereas prazosin has a high hERG Toxicity value. All analogues have lower human hepatotoxicity (HHT) than the standard drug prazosin. Drug-induced liver damage (DILI) is lower in all analogues compared to the standard drug. All Compounds have no or less AMES toxicity, which is less than 0.3, except 071. 50% of derivatives exhibited a lower carcinogenicity value, and in Approximately 65% of novel derivatives have no or minimal respiratory toxicity. The NR-AR value of the maximum analogues is excellent.

Table 5: Toxicity profile of novel antihypertensive analogues

S No.	Index	hERG	H-HT	DILI	Ames	Carc.	Res.	NR-AR	NR-AR-LBD
1.	005	0.527	0.525	0.95	0.194	0.734	0.195	0.08	0.059
2.	038	0.029	0.092	0.291	0.039	0.536	0.799	0.017	0.172
3.	050	0.336	0.488	0.984	0.028	0.366	0.049	0.811	0.215
4.	051	0.084	0.634	0.205	0.061	0.827	0.979	0.021	0.154
5.	052	0.394	0.392	0.981	0.293	0.711	0.289	0.01	0.033

6.	060	0.692	0.168	0.874	0.105	0.806	0.252	0.01	0.006
7.	061	0.139	0.68	0.251	0.044	0.911	0.069	0.501	0.027
8.	071	0.239	0.656	0.49	0.937	0.949	0.033	0.222	0.264
9.	099	0.167	0.427	0.155	0.604	0.946	0.121	0.095	0.046
10.	101	0.731	0.093	0.17	0.016	0.179	0.809	0.536	0.039
11.	105	0.934	0.068	0.235	0.559	0.441	0.742	0.287	0.023
12.	115	0.396	0.178	0.216	0.012	0.121	0.982	0.639	0.011
13.	125	0.421	0.413	0.104	0.03	0.847	0.961	0.727	0.522
14.	128	0.027	0.945	0.965	0.082	0.399	0.442	0.011	0.11
15.	130	0.789	0.422	0.449	0.016	0.107	0.344	0.802	0.004
16.	137	0.937	0.273	0.332	0.015	0.41	0.543	0.802	0.041
17.	142	0.075	0.977	0.609	0.649	0.555	0.889	0.066	0.039
18.	154	0.398	0.173	0.17	0.306	0.908	0.964	0.002	0.016
19.	158	0.337	0.442	0.258	0.069	0.248	0.917	0.606	0.026
20.	161	0.823	0.174	0.075	0.034	0.176	0.035	0.777	0.065
21.	167	0.583	0.183	0.909	0.037	0.247	0.181	0.666	0.034
22.	170	0.204	0.635	0.29	0.014	0.119	0.958	0.522	0.004
23.	186	0.385	0.613	0.788	0.103	0.853	0.958	0.077	0.024
24.	190	0.446	0.129	0.216	0.087	0.482	0.285	0.215	0.189
25.	PZN	0.873	0.95	0.953	0.358	0.704	0.932	0.03	0.057

hERG (The Human ether-a-go-go related gene), H-HT (The human hepatotoxicity), DILI drug induced liver injury, Ames (Test for mutagenicity), Carc. (carcinogenic), Res. (Respiration), NR-AR (Androgen receptor-a-nuclear hormone receptor), NR-AR-LBD (Molecule bind with LBD of Andogen receptor bind),PZN(Prazosin)

3.3 Drug likeness and Drug score prediction

In drug discovery, Drug-likeness assesses a molecule's potential as an oral drug based on its physicochemical, structural, and bioavailability characteristics [17]. The drug score integrates drug-likeness, cLogP, logS, molecular weight, and toxicity risk to evaluate overall drug potential [15]. Most compounds in this study, particularly compounds 101, 190, and 167, have the highest DL and DS, as presented in Table 6. These parameters were assessed using Osiris Property Explorer (OPE).

Table 6: Drug likeness and Drug score

S No.	Index	Toxicity Risk				DL	DS
		M	T	I	R		
1.	005	-	-	-	-	7.18	0.8
2.	038	-	-	-	-	7.14	0.79
3.	050	-	-	-	-	5.32	0.79
4.	051	-	-	-	-	9.3	0.85
5.	052	-	-	-	-	7.62	0.84
6.	060	-	-	-	-	7.87	0.86
7.	061	-	-	-	-	-3.59	0.45
8.	071	+	-	-	-	3.22	0.52
9.	099	+	-	-	-	8.41	0.54
10.	101	-	-	-	-	9.36	0.89
11.	105	-	-	-	-	7.06	0.84
12.	115	-	-	-	-	5.84	0.85
13.	125	-	-	-	-	5.17	0.82
14.	128	-	-	-	-	6.09	0.89
15.	130	-	-	-	-	7.87	0.85
16.	137	-	-	-	-	5.44	0.76
17.	142	-	-	-	-	6.56	0.72

18.	154	-	-	-	-	4.77	0.86
19.	158	-	-	-	-	6.09	0.87
20.	161	-	-	-	-	6.66	0.87
21.	167	-	-	-	-	7.09	0.88
22.	170	-	+	+	-	8.57	0.31
23.	186	+	-	-	+	9.93	0.41
24.	190	-	-	+	-	9.66	0.68
25.	PZN	-	-	-	-	7.97	0.78

M (Mutagenic), T (Tumorigenic), I (irritant), R (reproductive), G (No toxicity risk), O (toxicity risk), R (High toxicity risk), DL (Drug Likeness), DS (Drug Score), PZN(Prazosin).

Drug-likeness (DL) values were calculated using Osiris Property Explorer, where positive values indicate favorable structural features for drug development.

3.4 In Silico study for antihypertensive activity

The 3D schematics of prazosin, novel α-1A adrenergic antagonist derivatives(038, 158, and 190), and the α1A adrenergic (7ym8) protein's inhibitory binding sites are shown in Figure 2. Novel derivatives linked to the protein binding sites (amino acids) of α1A adrenergic (7ym8) protein include p-alkyl, hydrogen, p-donor hydrogen, van der Waals, p-sulfur, p-cation, carbon-hydrogen link, p-anion, and p-sigma. Remarkably, the same 240GLY residue forms an H-bond with prazosin and its derivatives (Table 7-10).

PyMOL 2.0 and ArgusLab 4.0.1 results show that prazosin and derivative 038 both bind with 240GLY (ALPHA HELIX) and 321ILE (COIL). Similarly, 38LEU (ALPHA HELIX), 317LEU (COIL), and 39PHE (ALPHA HELIX) are bound with derivatives 158 and 190. When compared to the reference drug prazosin, Derivative 038 exhibited the highest binding affinity (−9.10 kcal/mol), significantly stronger than prazosin (−6.50 kcal/mol), indicating enhanced receptor interaction. This suggests that the derivatives have a strong affinity for the α1A adrenergic receptor binding site (Table 7-10). Compared to the standard drug prazosin (−6.50 kcal/mol), derivative 038 exhibited a significantly better binding affinity (−9.10 kcal/mol), indicating stronger receptor interaction. The presence of multiple hydrogen bonds and hydrophobic interactions further supports its potential as a lead compound.

Table 7: In Silico Docking Data used in Argus Lab 4.0.1

Derivatives	Constant term	vdW coefficient	H-bond coefficient neutral-neutral	Rotors coefficient	Hydrophobic coefficient
038 (a)	2.510	0.00081	0.29	-0.2	0.0415
158 (b)	2.510	0.00081	0.29	-0.2	0.0415
190 (c)	2.510	0.00081	0.29	-0.2	0.0415
Prazosin	2.510	0.00081	0.29	-0.2	0.0415

Grid Parameters: Spacing 0.375 Å and Grid size 80X Å, 80Y Å and 80Z Å

Table 8: Properties of novel antihypertensive derivatives(Iigand) as per Molecular Structure

Derivatives	Molecular Parameters*							
	Stretch	Bend	Stretch-Bend	Torsion	Non-1,4 VDW	1,4 VDW	Dipole/Dipole	Total Energy (kcal/mol)
038 (a)	3.7776	33.69	0.8773	10.343	05.0525	21.24	-2.8415	62.04
158 (b)	2.1117	32.1527	0.2584	2.8007	-4.2672	23.4751	-12.9806	43.5507
190 (c)	2.3406	30.6981	0.3318	6.7110	-5.0403	22.7116	-2.6356	55.1172
Prazosin	1.9508	25.7762	0.2912	6.8427	-1.6744	27.4764	-7.1124	53.5503

Table 9: Chemical data of selected Ligands

Derivatives	Molecular Formula	Molecular Mass (g/mol)	CLogP values*	CMR	Gibbs Energy: [kJ/mol]
038 (a)	$C_{20}H_{26}N_20_7$	406.17	-2.25	10.18	-268.36
158 (b)	$C_{20}H_{24}N_4O_5$	395.21	0.46	10.4333	284.64
190 (c)	$C_{20}H_{22}N_2O_7$	402.14	0.63	10.1181	-141.8
Prazosin	$C_{19}H_{21}N_5O_4$	383.16	2.02752	10.1967	457.62
* Data generated using ChemBioDraw 13 software.					

Table 10: Docking results of novel antihypertensive compounds(ligands) and standard drug against 7YM8 receptor protein

Derivatives	Binding Energy (kcal/mol)	No. Of Hydrogen Bonds	Bond Length of H-Bonds in Å	H-Bond with Receptor residue	Protein's Binding Site residue
038 (a)	-9.10804	3	2.90	347SER	**Chain A** 160GLY(COIL), 164GLY(COIL), 157ILE(COIL), 153LEU(ALPHA HELIX), 240GLY(ALPHA HELIX), 346PHE(ALPHA HELIX), 347SER(ALPHA HELIX), 165TRP(COIL), 321ILE(COIL), 156VAL(COIL),
			2.70	165TRP	
			2.78	240GLY	
158 (b)	-7.13053	3	2.52	321PRO	**Chain A** 317GLY(Coil), 321PRO(Coil), 325PRO(Coil), 249SER(Coil), 251THR(ALPHA HELIX), 324TYR(COIL), 250VAL(ALPHA HELIX) **Chain B** 221ASN(ALPHA HELIX), 84ASP(COIL), 224GLU(COIL), 16HIS(BETA STRAND), 216 ILE(ALPHA HELIX), 217ILE(COIL), 220MET(ALPHA HELIX), 86THR(COIL), 225TYR(COIL), 85VAL(COIL)
			2.25	240GLY	
			2.13	86THR	
190 (c)	-7.26573	4	2.90	240GLY	**Chain A** 392CYS(ALPHA HELIX), 440CYS(COIL), 450GLN(COIL), 388ILE(COIL), 433ILE(COIL), 436ILE(COIL), 437ILE(COIL), 446LYS(COIL) **Chain B** 226ASN(Coil)
			2.52	446LYS	
			2.59	446LYS	
			2.74	450GLN	
Prazocin	-6.50216	2	2.89	240GLY	**Chain A** 280CYS (ALPHA HELIX), 240GLY(ALPHA HELIX), 321ILE(COIL), 324ILE(COIL), 325ILE(COIL), 36LEU(ALPHA HELIX), 38LEU (ALPHA HELIX), 317LEU(COIL), 39PHE (ALPHA HELIX)
			2.70	392CYS	

Grid Parameters (Argus Lab.): Spacing 0.375 Å and Grid size 80X Å, 80Y Å and 80Z Å

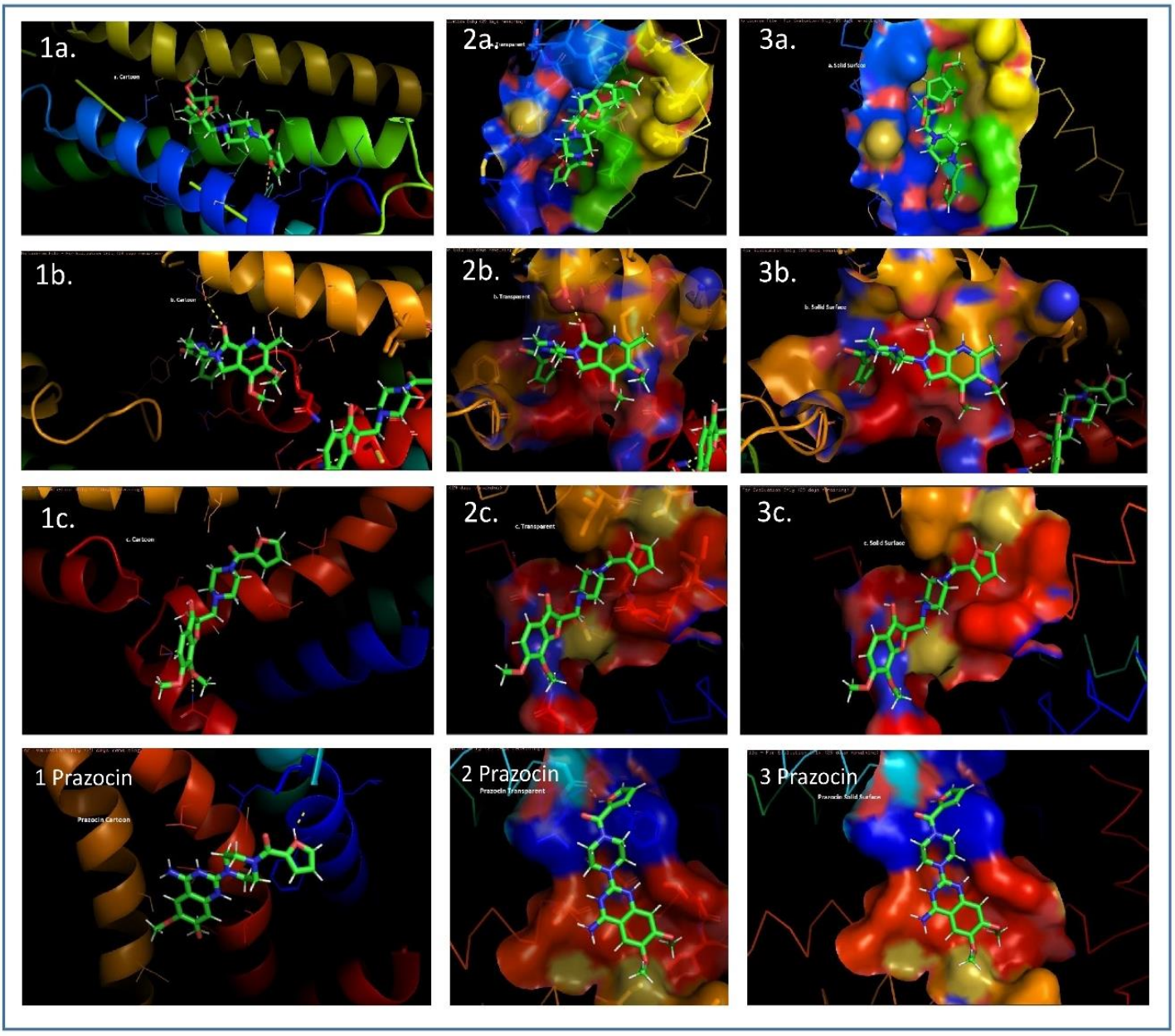


Figure 2: 3D representation of docking interactions of prazosin and selected derivatives (038, 158, 190) with the α1A-adrenergic receptor (PDB ID: 7YM8).

CONCLUSION

In the present study, a series of 190 novel prazosin analogues were successfully designed using a bioisosteric replacement approach. Comprehensive in silico evaluation, including ADMET prediction, drug-likeness assessment, and molecular docking, identified several promising candidates. Among them, derivatives 038, 158, and 190 demonstrated improved binding affinity and favorable pharmacokinetic properties compared to prazosin. Notably, derivative 038 exhibited the highest binding energy (−9.10 kcal/mol), suggesting strong interaction with the α1A-adrenergic receptor. These findings indicate that the designed analogues may serve as potential leads for antihypertensive drug development. However, further in vitro and in vivo studies are required to validate their efficacy and safety.

Author contributions

SS: Data Collection, Formulating Concepts, Curating Data, Developing Methodology, Validating Results, Drafting Original Manuscript, Software Handling, Writing & Editing, RT: resources, writing review & editing, DD: Molecular Docking.

REFERENCE

1. Orallo F, Garcia-Ferreiro T, Enguix M J et al. In vivo and in vitro pharmacological studies of a new hypotensive compound (QF0301B) in rat: comparison with prazosin, a known α1-adrenoceptor antagonist. Curr Vasc Pharmacol 2003;40(2);97-108. https://doi.org/10.1016/S1537-1891(02)00337-3
2. Campbell SF, Davey MJ, Hardstone JD et al. 2, 4-Diamino-6, 7-dimethoxyquinazolines. 1. 2-[4-(1, 4-Benzodioxan-2-ylcarbonyl) piperazin-1-yl] derivatives as. alpha. 1-adrenoceptor antagonists and antihypertensive agents. J Med Chem 1987;30(1);49-57. DOI: 10.1021/jm00384a009
3. Pathak SR, Malhotra V, Nath R et al. Synthesis and antihypertensive activity of novel quinazolin-4 (3H)-one derivatives. Cent Nerv Syst Agents Med Chem 2014;14(1);34-38. DOI: 10.2174/1871524914666140825144729
4. Giardinà D, Crucianelli M, Gulini U et al. Synthesis and α1-antagonist activity of new prazosin-and benextramine-related tetraamine disulfides. Eur J Med Chem 1997;32(1); 9-20. https://doi.org/10.1016/S0223-5234(97)84357-7
5. Davis BJ, Chapple CR, Sellers DJ et al. α1L-adrenoceptors mediate contraction of human erectile tissue. J Pharmacol Sci 2018;137(4);366-671. DOI: 10.1016/j.jphs.2018.08.003
6. Honkanen E, Pippuri A, Kairisalo P et al. Synthesis and antihypertensive activity of some new quinazoline derivatives. J Med Chem 1983;26(10);1433-1438. DOI: 10.1021/jm00364a014
7. Rahman MU, Rathore A, Siddiqui AA et al. Synthesis and antihypertensive screening of new derivatives of quinazolines linked with isoxazole. BioMed Res Int 2014;(1);1-13. http://dx.doi.org/10.1155/2014/739056
8. Sear JW, Antihypertensive Drugs and Vasodilators. 2nd ed.; Elsevier: London, 2019. https://doi.org/10.1016/B978-0-323-48110-6.00026-0
9. Koola MM, Varghese SP, Fawcett JA, High-dose prazosin for the treatment of post-traumatic stress disorder. TherAdvPsychopharmacol, 2014;4(1);43-47. https://doi.org/10.1177/2045125313500982
10. Take H, Shibata K, Awaji T et al. α1-adrenoceptor subtype selectivity and α1-blocker-induced orthostatic hypotension. Jpn J Pharmacol 1998;77(1);61-70. DOI: 10.1254/jjp.77.61
11. De Leeuw PW, Birkenhäger WH, Hypothermia: a possible side effect of prazosin. Brit Med J 1980;281(6249);1181. PMID: 7427628
12. MolOpt software (In silicoBioisostericment System). Available: https://xundrug.cn/molopt, (Accessed November 16, 2022).
13. ACD/ChemSketch, version 2021.1.1; Advanced Chemistry Development, Inc., Toronto, ON, Canada, 2021. Available at: www.acdlab.com, (Accessed March 12, 2023).
14. Xiong G, Wu Z, Yi J et al. ADMETlab 2.0: an integrated online platform for accurate and comprehensive predictions of ADMET properties. Nucleic Acids Res 2021;49(W1);W5-W14.
15. OSIRIS Property Explorer.available:https://openmolecules.org/propertyexplorer/applet.html, (Accessed May 08, 2024).
16. Thompson MA, Molecular docking using ArgusLab, an efficient shape-based search algorithm and the AScore scoring function.InACS meeting, Philadelphia 2004 Aug 21 (Vol. 172, p. 42).
17. Antoine D, Michielin O, Zoete V, SwissADME: a free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules. *Scientific reports* 7, no. 1 2017;42717. DOI: 10.1038/srep42717.

How to cite this article: Sahu S, Minj P, Dewangan D, Saraf S, Tirkey R. Development and Validation of a UHPLC Method for the Simultaneous Estimation of Hydrochlorothiazide and Amlodipine in Solid Dosage Forms. Indian J Pharm Drug Studies. 2026; 5(2):72-86.

Funding: None; *Conflicts of Interest: None Stated*