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COMPUTATIONAL INSIGHTS INTO ANG (1-7) PEPTIDE ANALOGS: POTENTIAL ANTI-HYPERTENSIVE AGENTS THROUGH MOLECULAR DOCKING STUDIES

Biochemistry

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ABSTRACT

Hypertension remains a significant global health concern, necessitating the development of novel therapeutic strategies. Angiotensin (1-7) [Ang (1-7)], a key component of the renin-angiotensin system (RAS), exerts vasodilatory and cardioprotective effects, making it a promising candidate for hypertension management. In this study, we employed molecular docking techniques to evaluate the binding affinity and interaction profiles of manually synthesized and chemically modified Ang (1-7) peptide analogs, (ac)D-RVYIHP and DR-(me)V-YIHP, with key hypertensive regulatory targets. Docking results revealed strong and stable interactions between these synthetic Ang (1-7) analogs and the angiotensin receptors AT1R, AT2R, and MasR, suggesting a potential enhancement of antihypertensive effects. These computational insights provide a foundation for further experimental validation and drug development efforts targeting RAS modulation. Our findings highlight the potential of Ang (1-7) analogs as promising lead compounds for novel antihypertensive therapies.

KEYWORDS

Renin angiotensin system; Angiotensin II; Angiotensin (1-7); Angiotensin II Type 1 Receptor (AT1R); Mas Receptor; Synthetic Peptide Analogs; Chemical Modification

INTRODUCTION

Hypertension is a major global health challenge and a leading risk factor for cardiovascular diseases, affecting millions worldwide. Despite the availability of various antihypertensive drugs, many patients fail to achieve optimal blood pressure control, highlighting the need for novel therapeutic strategies (Savitha, Suvilesh et al. 2020). The renin-angiotensin system (RAS) plays a crucial role in blood pressure regulation, with Angiotensin (1-7) [Ang (1-7)] emerging as a key modulator due to its vasodilatory, anti-inflammatory, and cardioprotective properties. Ang (1-7) primarily exerts its effects through the Mas receptor (MasR), counteracting the hypertensive actions of Angiotensin II (Ang II) via the angiotensin type 1 receptor (AT1R) (Sherman, Day et al. 2006). Angiotensin-converting enzyme (ACE) inhibitors are widely used in the management of hypertension; however, they present several limitations. A significant drawback is their association with persistent dry cough and angioedema, both linked to elevated bradykinin levels. Additionally, ACE inhibitors can cause hyperkalemia and acute kidney injury (AKI), particularly in patients with impaired renal function or those on concomitant medications like NSAIDs and potassium-sparing diuretics. Another critical limitation is the incomplete blockade of the renin-angiotensin system (RAS). While ACE inhibitors prevent the conversion of Angiotensin I to Angiotensin II (Ang II), alternative pathways, such as chymase-mediated Ang II formation, remain active, contributing to residual hypertension. Furthermore, these drugs are contraindicated in pregnancy due to their potential teratogenic effects and are unsuitable for patients with bilateral renal artery stenosis (Savitha, Suvilesh et al. 2020, Sarkar, Jayachandra et al. 2024). Given these challenges, alternative therapeutic strategies targeting different components of the RAS have gained attention. Angiotensin (1-7) [Ang (1-7)] and its peptide analogs offer a promising approach by directly stimulating the Mas receptor (MasR), promoting vasodilation without the adverse effects associated with bradykinin accumulation. The molecular docking studies in this research suggest that the synthetic Ang (1-7) analogs, (ac)D-RVYIHP and DR-(me)V-YIHP, exhibit strong receptor binding and stability, reinforcing their potential as novel antihypertensive agents. Future studies will be essential to validate their efficacy and safety in preclinical and clinical models.

To enhance the therapeutic potential of Ang (1-7), peptide analogs with chemical modifications have been synthesized to improve stability, bioavailability, and receptor affinity (Zhang, Annan et al. 2010) (Sarkar S et al. 2024). In this study, we investigate the interaction profiles of two synthetic Ang (1-7) analogs, (ac)D-RVYIHP and DR-(me)V-YIHP, with key hypertensive regulatory receptors—AT1R, AT2R, and MasR—using molecular docking techniques. This computational approach provides crucial insights into the binding affinities and potential efficacy of these analogs as antihypertensive agents, paving the way for further experimental validation and drug development efforts.

MATERIALS AND METHODS

Chemicals And Reagents

Ang II, Ang (1-7), N-(tert-Butoxycarbonyl)-L-aspartic acid (Boc-Asp-OH), Nα-Fmoc-L-arginine, Nα-(9-Fluorenylmethoxycarbonyl)-L-arginine (Fmoc-Arg-OH), N-(9-Fluorenylmethoxycarbonyl)-L-valine (Fmoc-Val-OH), N-(tert-Butoxycarbonyl)-L-tyrosine (Boc-Tyr-OH), N-(9-Fluorenylmethoxycarbonyl)-L-isoleucine (Fmoc-Ile-OH), N-(9-Fluorenylmethoxycarbonyl)-L-histidine (Fmoc-His-OH), N-(tert-Butoxycarbonyl)-L-proline (Boc-Pro-OH), piperidine, rinkamide resin, trifluoroacetic acid (TFA), dimethyl formamide (DMF), and dimethyl sulfoxide (DMSO) were procured from Sigma-Aldrich (Bangalore, India). All other chemicals and reagents used in this study are analytical grade.

Peptide Synthesis

Peptides were synthesized via solid-phase peptide synthesis (SPPS) with minor modifications. The peptide analogs of Ang (1-7) (DRVYIHP), synthesized were (ac)D-RVYIHP, and DR-(me)V-YIHP. These peptides were dissolved at 1–100 µM concentrations in phosphate-buffered saline (PBS), 0.1% DMSO, 0.1% TFA, or a combination for solubility optimization.

Peptide Purification And Characterization

Peptide purity (10 µg/µL) was assessed via reversed-phase high-performance liquid chromatography (RP-HPLC) using a Shimadzu HPLC System (LC-10AD pump, SIL-10A Autoinjector, and SPD-10A UV/Vis Detector). A Bondclone 10 µm C-18 column (300 × 3.9 mm, Phenomenex, USA) was pre-equilibrated with 0.1% TFA in water and eluted with a gradient from 0.1% TFA in water (solution A) to 100% acetonitrile (solution B) over 60 minutes at a flow rate of 0.5 mL/min, monitored at 280 nm (Geenen, Guallar-Hoyas et al. 2011).

Mass Spectral Analysis

Molecular mass confirmation was performed using a Xevo G2-XS QTof Mass Spectrometer (Waters, USA) under optimal conditions in negative ion mode: capillary voltage 3.0 kV, collision energy 20 V, ramp collision energy 30–90 V, source temperature 150°C, desolvation temperature 450°C, cone gas 50 L/hour, and desolvation gas flow 800 L/hour (Geenen, Guallar-Hoyas et al. 2011).

Molecular Docking

Induced fit docking (IFD) was conducted using Schrödinger's Maestro 2014 suite following Protein Preparation Wizard protocols. The crystal structure of proteins was downloaded from PDB database for (PDB ID: 4YAY), AT2R (PDB ID: 5UNF), and Mas receptor (PDB ID: AF-P04201-F1) was obtained from the RCSB Protein Data Bank. Ligands, Ang II and Ang (1-7) along with the synthetic peptide analogs were minimized using IMPACT, generating 20 docking poses per ligand. Final poses were selected based on docking score, glide energy, and active site interactions (Behrendt, White et al. 2016).

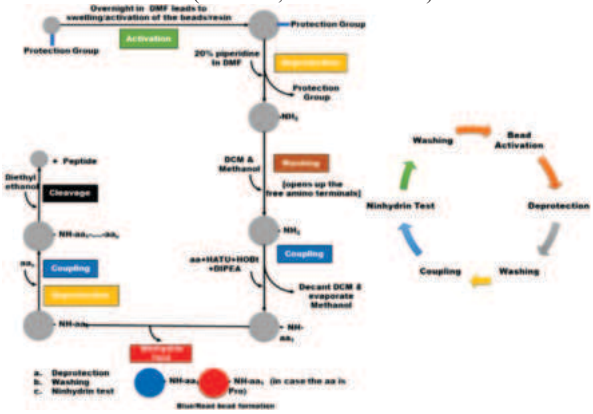

Figure 1: Schematic representation of the solid phase peptide synthesis.

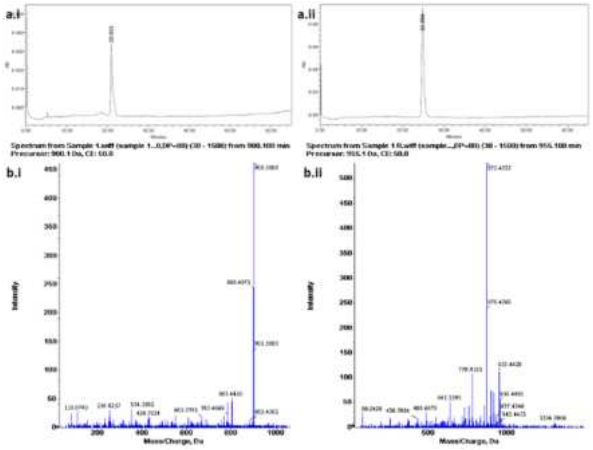

Figure 2: RP-HPLC and Mass Spectral profiles of the synthetic peptide analogs of Ang (1-7), (ac)D-RVYIHP and DR-(me)V-YIHP.

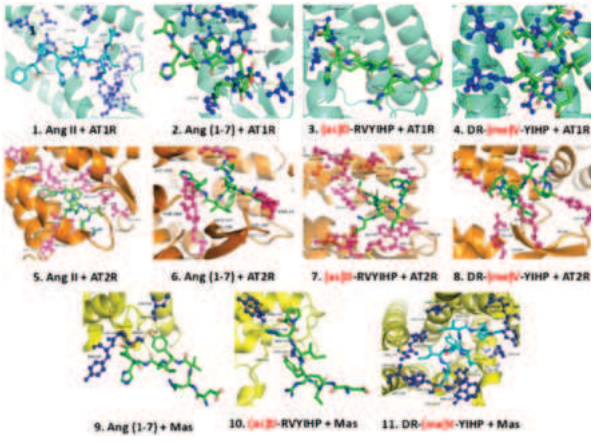

Figure 3: Induced fit molecular docking of the synthetic peptide analogs of Ang (1-7), (ac)D-RVYIHP, and DR-(me)V-YIHP.

Table 1. The binding energies of individual ligands with the specific receptors.

S.no	Peptide docking	Docking score	Confidence score	H -bond interactions	Hydrophobic
1	Ang II - AT1R	-219.76	0.8288	C66,L69,T70,P73	F28,C66,L68,L69,L71,P72,L73,V76,F86,97
2	Ang(1-7) - AT1R	-199.95	0.7309	F67,L68,T70,L74,V76,S97	L71,P72,L73,V76,F86,97
3	-RVYIHP - AT1R	-183.25	0.6604	C66,S97	F28,C66,L68,L69,L71,P72,L73,V76,F86,97
4	DR- -YIHP - AT1R	-188.41	0.6831	A181,F1259,T1292	F28,C66,L68,L69,L71,P72,L73,V76,F86,97
5	Ang II- AT2R	-263.17	0.9058	Y108,M179,I187,V189,M198,S208,K215,D297,P301	I187,L190,C195,I196,M197,F199,S208,I211,F272,D279,W283,L300,P301
6	Ang(1-7) - AT2R	-215.20	0.7859	Y108,R182, Y189,D297,K215	L190,C195,I196,M197,F199,S208,I211,F272,D279,W283,L300,P301
7	-RVYIHP - AT2R	-230.70	0.834	Y108,R182,Y189,K215,D297	I187,L190,C195,I196,M197,F199,S208,I211,F272,D279,W283,L300,P301
8	DR- -YIHP - AT2R	-256.8	0.8945	R182,Y189,K215	Y108,I187,L190,C195,I196,Y204,S208,T276,D279,L300,P301,I304
9	Ang [1-7) - Mas	-226.46	0.8219	C142,K146	Y140,R141,H143,R144,P145,Q148,S149,A150
10	-RVYIHP - Mas	-232.9	0.8401	H143,P145,K146,Y147	Y140,R141,H143,R144,P145,Q148,S149,A150
11	DR- -YIHP - Mas	-220.28	0.8031	S109,R181 Y251,Y248	N64,Y140,R141,H143,R144,P145

RESULTS AND DISCUSSION

Figure 1 illustrates the schematic representation of the peptide synthesis process using the solid-phase peptide synthesis (SPPS) pathway. This method involves the activation of the resin bead, deprotection of blocked reactive functional groups, and sequential coupling of the required amino acids. As a result, the peptide analogs of Ang (1-7), (ac)D-RVYIHP, and DR-(me)V-YIHP were successfully synthesized and subsequently analyzed for purity and authenticity using reverse-phase high-performance liquid chromatography (RP-HPLC) and mass spectrometry (Figure 2).

HPLC profiles revealed that both peptide analogs eluted at 31-32 minutes, displaying single peaks, which confirm their high purity. Mass spectrometric analysis further validated their synthesis by confirming the expected molecular weights.

Molecular docking analysis demonstrated that the chemically modified peptide analogs, (ac)D-RVYIHP and DR-(me)V-YIHP, exhibit comparable or superior glide energy compared to the endogenous ligands Ang II and Ang (1-7). Induced fit docking (IFD) studies further highlighted the binding sites and hydrogen bond interactions, confirming the high-affinity binding of these analogs to the specific angiotensin receptors. These findings suggest that the structural modifications in the peptide analogs enhance their stability and receptor interactions, potentially improving their antihypertensive efficacy.

These findings lay a strong foundation for further experimental validation. Future in vitro and in vivo studies will be crucial to confirming the efficacy, stability, and clinical potential of these analogs as next-generation antihypertensive therapeutics.

CONCLUSIONS

This study successfully synthesized and characterized the Ang (1-7) peptide analogs (ac)D-RVYIHP and DR-(me)V-YIHP, confirming their purity through RP-HPLC and mass spectrometry. Molecular docking revealed strong and stable interactions with AT1R, AT2R, and MasR, suggesting their potential as antihypertensive agents. These findings provide a foundation for further experimental validation and drug development.

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