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Computational Optimization Of Purmorphamine-Derived Small Molecule Modulators Targeting The Secretin Receptor (SCTR) For Antihypertensive Therapy

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Abstract. Hypertension remains a global health problem. Although existing treatments (such as ACE inhibitors, β-blockers, etc.) are widely available, their side effects and patient compliance issues limit the therapeutic effect. Therefore, the development of new small molecule drugs is particularly important. This study targets pancreatic cholinergic receptors (SCTR), which play an important role in vasodilation and blood pressure regulation and have the potential to become a new target for antihypertensive drugs. In this study, based on the small molecule compound puromorphamine, the structure was optimized by computer-aided drug design method, combined with ADMET prediction and structure-activity relationship analysis (SAR), and the candidate compound KSD179019 was obtained. The results of virtual screening and molecular docking showed that the optimized molecule had good receptor binding ability and pharmacokinetic properties, reflecting its application prospects as a potential antihypertensive drug. Although no in vitro or in vivo experiments have been conducted, this study provides a theoretical basis for subsequent experimental verification and also demonstrates the great potential of artificial intelligence technology in new drug research and development, especially in the acceleration of G protein-coupled receptor (GPCR) target drug development.

Keywords: Hypertension; secretin receptor (SCTR); structure-based drug design.

1. Introduction

Nowadays, hypertension has become a disease of great concern in today's time. And with the problem of aging population, the incidence of hypertension is also high [1]. If not treated promptly and effectively, high blood pressure can increase the likelihood of complications and lead to heart disease and cerebrovascular disease [2]. According to the World Health Organisation's data released in 2003, the thresholds for high blood pressure, diastolic and systolic are less than or equal to 90mmHg and 140mmHg, and once they are exceeded, they are defined as high blood pressure [3].

There is a wide range of drugs available on the market, such as angiotensin-converting enzyme (ACE) inhibitors, beta-blockers, calcium channel blockers and diuretics, but the side effects need to be considered. An important aspect is the lack of adherence to medication, which leads to the possibility that some patients do not take their medication as prescribed, with a significant impact on the effectiveness of the treatment [4].

Therefore, there is a need to develop a novel small molecule drug aimed at targeting the regulation of blood pressure as well as better avoiding the shortcomings of conventional drugs to achieve therapeutic efficacy. Such small molecule drugs may provide a therapeutic approach with better availability for oral administration. The pancreatic cholinergic receptor (SCTR]. is a class B G protein-coupled receptor [5]. Due to its very important role in vasodilatation and vasomodulation, it has emerged as a novel and promising target for the treatment of hypertension. It has been demonstrated that the endogenous ligand of SCTR, glucagon, leads to the development of pulmonary hypertension and impaired cardiac function under conditions of deficiency [6].

Although SCT peptide-based therapeutics are available and can produce some therapeutic effects, they still have drawbacks. The problem of its short half-life has led to extremely strict limitations on

its therapeutic use [7]. And due to the diversity of sites of action of the glucagon receptor, other inflammatory conditions may result when using this peptide [7]. Purmorphamine is a newly synthesised small molecule compound designed to avoid the pitfalls of using peptides as therapeutics [5]. This small molecule compound is defined as an agonist of the Hedgehog signalling pathway by interacting with Smoothened (Smo]. receptors [5]. Moreover, this compound was discovered through a virtual screening approach and its pharmacological properties were successfully determined. Similar antihypertensive effects to Secretin peptides have been well demonstrated in animal studies, making it possible to use purmorphamine as a lead compound for optimisation to develop novel antihypertensive drugs [5].

Puromorphamine is an analog of puromorphamine. This study applies structure-based drug design and optimization strategies to puromorphamine. The main research method of this paper is to enhance the drug properties (solubility, metabolic stability, etc.) of this compound by using computer simulation technology combined with ADMET prediction and structure-activity relationship analysis (SAR). The study aims to optimise this compound as a viable lead candidate for the treatment of hypertension.

The significance of this research lies in the possibility of introducing a completely new therapeutic mechanism that provides an adjunct or alternative to traditional treatments. In addition, developments in AI technology such as drug design tools provide a framework for accelerated lead compound optimisation, enabling a solid theoretical foundation for future clinical studies.

2. Method

2.1. Lead Characterization and SAR

KSD179019 was used as a starting point for optimisation by reviewing the literature. It is used as a potential positive allosteric modulator of the secretin receptor (SCTR). The study was carried out using a chemoinformatics platform, which allows accurate characterisation of the physicochemical properties of the compounds. SwissADME was the main platform used in this study and was used to evaluate the parameters of the drug including LogP, LogS, Topological Polar Surface Area (TPSA) tested for compliance with the Lipinski and Muegge rules. Lipinski and Muegge rules, among others. [8]. In addition, data on hERG inhibition, cytochrome P450 (CYP) enzyme inhibitory potential and hepatotoxicity were evaluated using pkCSM [9].

The structure of KSD179019 and the structurally optimised compound were drawn using Chemdraw and exported to SMILES format for standardisation. The molecular structure was initially drawn using ChemDraw and standardised by canonical SMILES conversion.

2.2. Molecular Docking

The specific structure of SCTR was obtained by using PDB and molecular docking simulation experiments were carried out using Autodock dock [10]. After docking the results were analysed using Autodock tools for various conformations and the optimal conformations were filtered according to the desired docking results. Protein-Ligand Interaction Profiler was used as the main tool to predict the docking results [11]. Re-use PyMOL for visualisation [12]. The molecular docking program successfully completed the visualisation as well as the mapping, successfully demonstrating the way in which the designed small molecule lead compound interacts with key residues such as Asn289, Ser263 and Trp295.

2.3. Selectivity Prediction

The selectivity of the analogues was analysed using SwissTargetPrediction as the main platform for probing the lead compounds [13]. The likelihood of off-target effects occurring was further reduced by analysing the SMILES sequences of the analogues and ranking them based on similarity to known ligands and likelihood of targeting.

2.4. ADMET Analysis

For newly designed small molecule lead compounds, it is essential to test their pharmacological properties. The assessment of absorption, distribution, metabolism, excretion and toxicity (ADMET) of this small molecule was accomplished using various tools. Gastrointestinal absorption, logP and, P glycoprotein substrates, CYP450 inhibitory potential and other parameters were analysed using SwissADME. Clearance and hepatotoxicity predictions were provided by pkCSM [9].

2.5. Synthetic Feasibility Assessment

The evaluation of the synthetic route and ease of synthesis was also an important consideration in this study. The ease of synthesis of the compound was first assessed using SwissADME [8]. This is well illustrated by the Synthetic Accessibility Score (SAscore), the magnitude of which provides a good indication of the difficulty of synthesising the molecule under laboratory conditions. And the possibility of synthesis and the possibility of replicating the experimental process exactly in the laboratory was further verified by performing a reverse synthesis analysis using Synthia™ [14].

3. Results

3.1. Candidate Characterisation and SAR

By optimising the structure of KSD179019, the morpholine ring, the naphthalene ring and the purine-like part of the original structure of this study have been retained and linked to the substituted aromatic part by ether bonds. The candidate compounds are based on a purine-like tricyclic skeleton with hydroxymethyl substitution on the aliphatic side chain and phenolic hydroxyl substitution on the aromatic edges. The newly designed compound adds several polar functional groups to the original structure, including phenolic hydroxyl and hydroxyl groups, and the presence of multiple polar functional groups (especially hydroxyl and amide nitrogen atoms) enhances the hydrogen bonding potential. And the introduction of a small branched chain at position 2 on the purine ring can be extremely helpful for space shielding and conformational stability. The more compact structure of the candidate compounds supports their potential for oral bioavailability and selective targeting.The specific structures of the two compounds are displayed in the figure below (Figure 1).

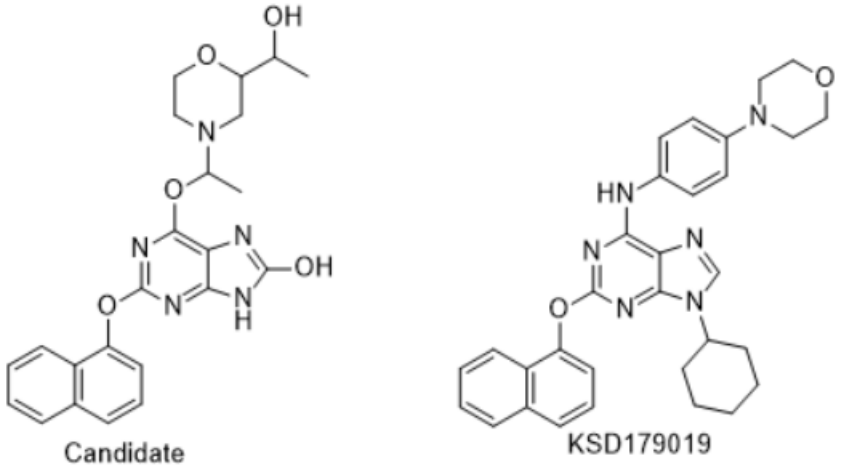

Fig. 1 The Structure of Candidate and KSD179019

3.2. Docking Results

Molecular docking technique was used to visualise the docking results of the designed candidate compounds. The docking results adequately show hydrophobic bonding contacts, hydrogen bonding interactions and interactions between π-cations. This is in agreement with the results reported in the

original article.The picture shows the interaction between the candidate compound and the protein (Figure 2.)

3.2.1. Hydrophobic Interactions

From the predicted docking results, it was shown that the hydrophobic interactions were mainly on the naphthalene ring of the candidate compounds, where the naphthalene-1-yloxy portion of the naphthalene ring had hydrophobic interactions with ALA290 (3.59 Å) and ALA292 (3.66 Å) to further stabilise the aromatic regions of the ligands. and exhibits strong hydrophobic binding between TRP295 and the hydrophobic core of the ligand (3.35 Å), which is consistent with KSD179019 in keeping with the π-π stacking interaction with TRP295. In addition, the docking results show additional hydrophobic interactions, with GLU363 exhibiting strong interactions (3.00 Å) with the candidate compounds, which may contribute to the regulation of the ligand within the metastable pocket.

3.2.2. Hydrogen Bonding Interactions

Four hydrogen bonding interactions were shown in the docking results, where hydrogen bonds were formed between Asp287 and the oxygen atoms between the ligands (H-A distance: 2.11 Å; D-A distance: 2.65 Å) and three hydrogen bonds were formed between Asn and the ligands, with bond distances of (1.64 Å, 2.15 Å, 3.05 Å).

3.2.3. π-cation Interactions

Additional π-cation interactions were found between TRP295 and the tertiary amine group on the ligand (distance: 4.19 Å), suggesting additional stabilisation through electrostatic attraction and π-system alignment.

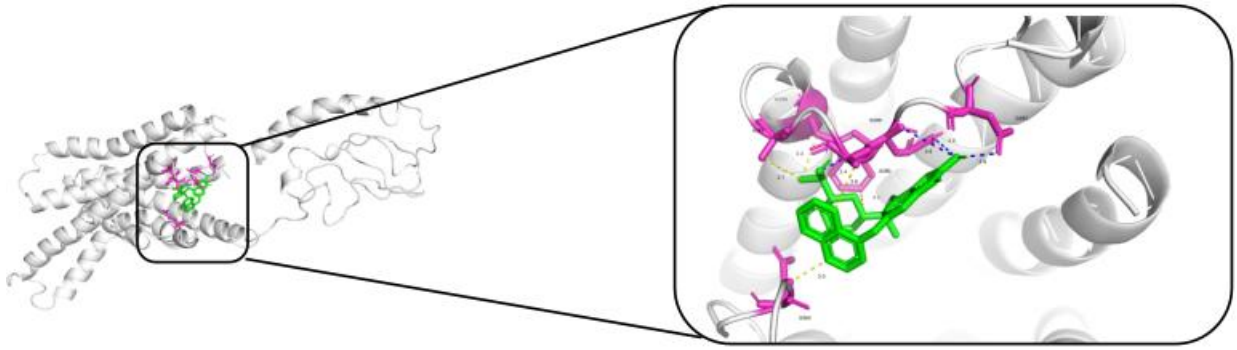

Fig. 2 The docking result

3.3. Selective forecasting

This study used SwissTargetPrediction as the primary platform for the assay [13]. The analyses showed that the compound has the potential to interact with a variety of human protein kinases, of which PIK3CA is one of the most important targets. Other kinases such as CDK1, CDK2, CDK9, mTOR and MAPK1 showed similar activity, indicating a significant affinity for the structural domain of ATP-binding kinases. Acetylcholinesterase (ACHE) and butyrylcholinesterase (BCHE) also had moderate probability of hits, suggesting a possible cholinergic interference. Metalloesterases such as MMP1, MMP2 also appeared in the data, suggesting a risk of off-target effects. Although a low off-target probability of GPCR was indicated, additional binding experiments are still required to validate the interaction between the drug candidate and SCTR. Therefore, the drug candidate still has a certain probability of off-target effects, and therefore very stringent tests and observations are still required for the future use of this drug candidate in the treatment of hypertension and some chronic diseases (Figure 3 and Figure 4).

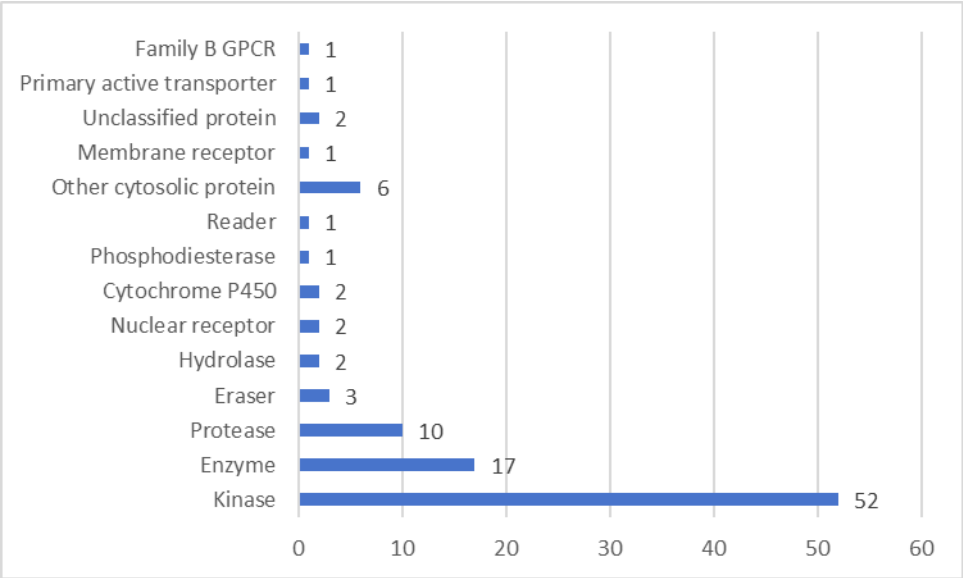

Fig. 3 Off-Target Classes

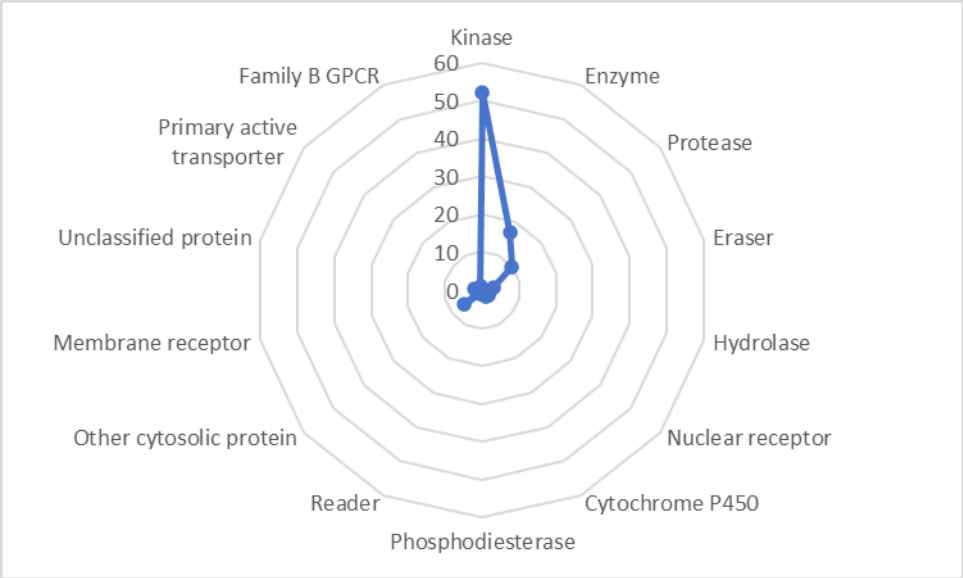

Fig. 4 Off-target Classes by using Target radar map

3.4. ADMET Properties

The drug candidates showed better potential as well as pharmacokinetic profiles compared to earlier reference structures. SwissADME and pkCSM were used as the main platform for prediction. Under the ADMET parameter display, the drug candidate showed a Caco-2 permeability of 0.099 log Papp and a predicted intestinal absorption of 76.60%, which was slightly lower than the reference compound's 1.147 log Papp and 89.13%, still demonstrating good oral bioavailability. And the water solubility of the drug candidates was - 2.898, which was not significantly different from the reference compound (log S = -2.922). Although both compounds acted as P-gp substrates, the drug candidates were not inhibitors of P-gp I or II, effectively reducing the risk of drug-drug interactions due to transporter proteins.

In terms of the distribution level of the compounds, the log VDss was 0.015 for both compounds, and the candidate compound had a higher free plasma fraction (0.345 vs. 0.241). In addition, the blood-brain barrier permeability (-1.936 vs. -0.286) and CNS permeability (-4.706 vs. -1.814) of the candidate drug showed a significant decrease compared to the reference drug. This provides a better safety profile for the treatment of hypertension, a disease that requires effect in peripheral tissues. The metabolic profiles of the two drugs showed that the drug candidate was not an inhibitor of any

cytochrome or a substrate of CYP450 enzymes, whereas the reference drug exhibited some inhibition of CYP (CYP3A4, CYP2C9 and CYP2C19), suggesting a higher probability of drug-drug interactions with the reference drug. In addition, the clearance of the candidate drug was significantly lower compared to the reference drug (log CL = 0.460 vs. 0.867), suggesting a longer residence time in plasma.

Both compounds were non-mutagenic, non-hepatotoxic and non-hERG I inhibitors, although both compounds were hERG II inhibitors. However, the new candidate compounds demonstrated a better safety threshold (LOAEL = 2.99 log mg/kg/day and a higher maximum tolerated dose (0.442 vs. 0.072 log mg/kg/day).

In conclusion, the new candidate compounds have enhanced metabolic safety, better tolerability and reduced off-target liability, supporting their suitability as promising oral agents for the treatment of hypertension.

3.5. Synthetic Accessibility

Synthesis accessibility The candidate showed the property of easy synthesis.The synthesis likelihood of the candidate was shown to be 4.84 in SwissADME indicating moderate difficulty in synthesis and there were no PAIINS or structural alerts further proving the synthesizability of the candidate. Therefore, SYNTHIA™ was used as a tool to simulate the synthetic pathway to be used. The synthia dataset: A large collection of synthetic images for semantic segmentation of urban scenes. in Proceedings of the IEEE conference on computer vision and pattern recognition (pp. 3234-3243). The synthetic pathway includes a number of transformation reactions such as phosphoramidation. These reaction reagents are commercially available, indicating that the synthetic pathway can be performed under laboratory conditions. Figure 5 shows the specific reaction flow.

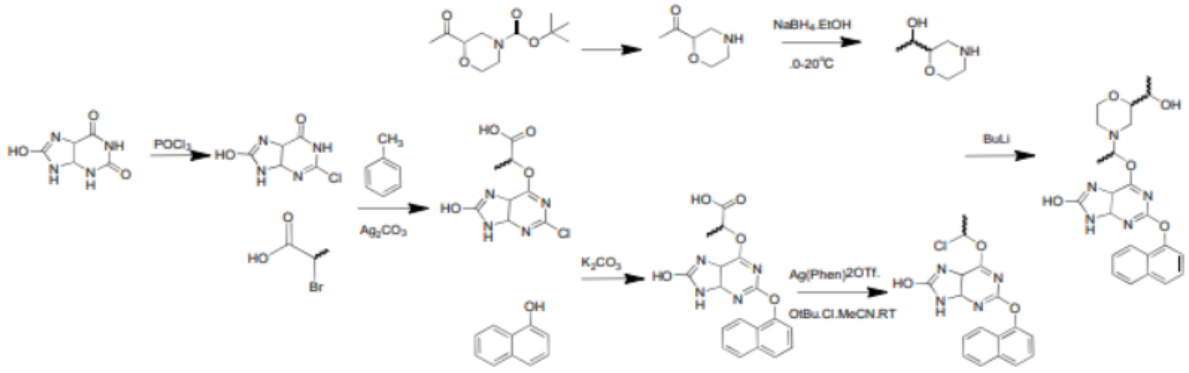

Fig 5. The route of synthesis

4. Discussion

In this paper, a structure-based drug design strategy with computer technology and an online prediction tool as an aid for the optimisation of laughing compounds was mainly employed to successfully optimise KSD179019 as a novel small molecule modulator targeting the SCTR for anti-hypertensive therapy. The main functional groups of KSD179019 were retained during the optimisation process with some degree of structural modification and optimisation. Molecular docking results indicated that the optimised candidate compounds fully retained the key interbinding interactions, with the hydrophobic interactions with ALA290, ALA292 and TRP295 remaining consistent with those in existing studies, and these findings fully justify the rationale for retaining these structural features in the development of SCTR. SAR analyses indicate that hydroxylation and modification of the naphthalene ring can increase the number of hydrogen bonds and simultaneously decrease lipophilicity.

The prediction of ADMET properties further supports the possibility of this candidate compound as a possible oral drug for the treatment of hypertension. The candidate compound exhibits good gastrointestinal absorption and reduced blood-brain barrier clearance and is not subject to CYP450 enzyme inhibition. These properties fully support the potential of this compound for the treatment of hypertension, a chronic disease. Moreover, this candidate compound also exhibits a low clearance and half-life, making its efficacy potentially more effective.

Selective analyses showed moderate off-target interactions of the optimised candidate compounds with protein kinases such as PIK3CA and CDK, as well as cholinesterases (ACHE and BCHE). Although no potential off-target effects of class B GPCRs were detected, further analyses are necessary to ensure receptor specificity. By evaluating the possible synthetic pathways, the compound is moderately difficult to synthesise and can be completed in the laboratory.

However, there are some flaws in this study. The experimental data in this study were obtained from computer techniques or online prediction tools, and were not validated in the laboratory in the next step of experiments, so the simulated data need to be validated more to ensure the validity of the experimental data. In addition, this study did not validate additional analogues and was not supported by a quantitative constitutive effectiveness relationship (QSAR) model, which may have led to omissions in the data or overlooked possible safety risks. Future analyses should include molecular dynamics simulations to further assess the binding stability between ligand and receptor under physiological conditions. In vitro experimental analyses are also needed to assess in vitro toxicity analyses. The construction of more complete conformational relationships and models can be more effective in optimising pharmacokinetic properties.

Overall, this study provides a rational framework for computer optimisation of SCTR modulators and proposes among others novel candidate compounds with therapeutic potential for hypertension. These findings provide a theoretical basis for future experimental validation and demonstrate the potential of computer and AI technologies in drug development.

5. Conclusion

The present study presents a computational framework and rational optimisation of KSD179019 as a potential small molecule modulator of the sensitin receptor (SCTR), a non-traditional therapeutic target for hypertension. An analogue was designed by retaining the major functional groups and structural modification, and its pharmacological properties were effectively improved. The docking results and ADMET predictions excellently demonstrate the potential of computer applications and development in the field of drug discovery.

Although no wet-lab experiments were performed, this study lays a clear foundation for future preclinical validation. Most importantly, it reinforces the feasibility of non-peptide backbone modulation of SCTR - an under-explored avenue in anti-hypertensive research. Thus, this study not only contributes a promising drug candidate, but also exemplifies how computational design can accelerate the identification and optimisation of lead compounds in the GPCR-targeted drug development process.

Although this study relied entirely on computer simulations, it still lays the foundation for future research. Thus, this study not only designed a small molecule compound that may be therapeutically effective for hypertension, but also demonstrated the potential of how computer technology can accelerate drug optimisation.

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