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2D-QSAR Modeling of Quinazolinone Derivatives as Angiotensin II Type 1a Receptor Blockers

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ABSTRACT

Angiotensin receptor blockers (ARBs) are a group of drugs primarily used in the treatment of cardiovascular disease. Multiple quantitative structural activity relationship (QSAR) models were established for prediction of angiotensin II type 1a (AT-1a) receptor blocking activity of quinazolinone derivatives to investigate the structural attributes that have significant correlation with biological activity. The genetic algorithm (GA) approach was used to generate a highly predictive models using easily interpretable Py, Estate, and Padel descriptors. OECD principles have been followed to develop statistically robust QSAR models (R2tr = 0.8055 – 0.8625) with good external predictivity (CCCex = 0.7528-0.8450). The multiple QSAR models successfully identified that increase in surface area of negatively charged carbon atoms within four bonds from N atom, presence of tetrazole substituents, and sp3 N atoms govern the AT-1a receptor blocking activity. The validated QSAR models of the present study might be helpful for evaluation AT-1a receptor blocking activity to identify novel hits.

KEYWORDS

Angiotensin, Multiple QSAR, Quinazolinone, Structural Features, Validation

INTRODUCTION

Controlling hypertension is considered to be a prime objective in the management of cardiovascular diseases (“Principles of Treatment,” 2009). Neurohormonal blockade of the renin-angiotensin system through inhibiting angiotensin-converting enzyme and angiotensin II has involved the pillar of treatment therapy of hypertension (Álvarez et al., 2004; Ma et al., 2010). Renin and angiotensin-converting enzyme (ACE) are two enzymes that work together to release the linear octapeptide angiotensin II, a potent vasoconstrictor that controls blood pressure homeostasis, fluid volume, and electrolyte balance (Pacurari et al., 2014; Piqueras & Sanz, 2020). Angiotensin II also activates the AT2-receptor subtype, which has been shown in experiments to mitigate the negative effects of AT1-receptor stimulation(Timmermans et al., 1992). Selective AT1 receptor blockade thus appears to be a viable therapeutic target in hypertension and cardiovascular disease. AT1-receptor blockers have an

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advantage over ACE inhibitors in that they enable hyper-stimulation of the AT2-receptor subtype by selectively blocking angiotensin II activities at AT1-receptors (Gradman, 2002). These drugs may not only inhibit angiotensin II's harmful hemodynamic effects, but they may also enhance its beneficial cardiovascular effects (Unger, 2001).

Computer-aided drug discovery is the lynchpin in the exploration and optimization of potential lead compounds (Bajorath, 2015). CADD methodologies help to determine the association of the respective compound with its target before chemical synthesis and biological testing (Yu & MacKerell Jr, 2017). Statistical analytical methods like QSAR correlate chemical structures and biological activities is a realistic technique that can be applied in the prediction of half-maximal inhibitory concentration (IC_{50}) values of new candidates(Aykul & Martinez-Hackert, 2016; Vyas et al., 2014).

Altogether approved Angiotensin Receptor Blockers (ARBs) show the presence of biphenyl, tetrazole, benzimidazole, or non-biphenyl non-tetrazole features (Abraham et al., 2015). Previous studies show that quinazolinone ring constitutes an alternative to imidazole ring for developing novel angiotensin II type 1a (AT-1a) receptor blockers (de Laszlo et al., 1993). Quinazolinones belong to a potent category of the molecular nucleus which is reported to have potent biological importance (Al-Obaid et al., 2009). Literature study shows there have been a large number of computational studies performed and QSAR models developed by de Laszlo et al.1993 ($n_{compounds} = 41$) (de Laszlo et al., 1993), Datar et al. 2004 ($n_{compounds} = 28$)(Datar et al., 2004), Pandya et al. 2004 ($n_{compounds} = 17$) (Pandya & Chaturvedi, 2004), Sharma et al.2014 ($n_{compounds} = 19$) (Sharma & Kohli, 2014) to design novel lead as AT-1a receptor blockers. However, models were developed using a small dataset of molecules only (no. of compounds = 17 to 41) and have poor statistical performance that needs to be updated with the current knowledge and newer reported analogs.

In the current research, we aim to develop a good, rational, and statistically robust QSAR model using a larger dataset of 114 Quinazolinone derivatives using easily interpretable molecular descriptors that can correctly identify structural features, with high external predictive ability to discover novel Angiotensin II Type 1a (AT-1a) receptor blocker with more favorable clinical profiles than current generation drugs. Therefore, a better understanding of structural features of Quinazolinones as AT-1a receptor blocker that would be of great significance to any drug design scheme.

MATERIAL AND METHODS

Datasets Selection

An initial dataset of 134 substituted quinazolinone derivatives containing diverse substituents reported potential to block AT-1a receptors was selected from the ChEMBL database for the present work (Davies et al., 2015). The following criteria were adopted to refine the data sets: (1) only data tested on *Oryctolagus cuniculus* organism were collected; (2) data with binding assay performed by an *in vitro* experiment; (3) angiotensin II type 1a (AT-1a) receptor target type single protein; (4) experimental activity of each compound is expressed in IC_{50} (nM) values. We have also checked that the data we had taken for specific end-points were experimented with using similar conditions, to get the homogeneous data for reliable predictions. The reported IC_{50} (nM) values for receptor blocking activity were converted to molar units and then calculated pIC_{50} ($-\log_{10}IC_{50}$) before proceeding with QSAR model development. All chemical structures are sketched in MarvinSketch (Marvin 20.19.0, 2020) and converted into SDF format using OpenBabel considering 2D geometry optimization(O'Boyle et al., 2011). Before calculating descriptors, the dataset was further subjected to chemical curation using the Konstanz Information Miner (KNIME) workflow (https://www.knime.org/)(Berthold et al., 2009). The chemical properties of quinazolinone derivatives were read using the SDF reader node in KNIME. The steps included in KNIME workflow (available at https://sites.google.com/site/dtclabdc) includes