QSAR and QAAR Studies on Mixtures of 3-(Benzyldiene)Indolin-2-One Isomers as Leads to Develop PET Radiotracers for Detection of Parkinson’s Disease

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ABSTRACT
Deposition of α–synuclein, tau and β–amyloid protein plaques in brain leads to neurodegeneration. A series of indolin derivatives, which can bind to α–synuclein and detect Parkinson’s disease (PD), were used for development of QSAR and QAAR models. It is the first attempt of QSAR for any radiotracer agents used for detection of PD. The binding affinity against α–synuclein was used as dependent variable while independent variables, such as structural, topological, E-state keys, electronic, molecular shape analysis and spatial molecular descriptors were used for QSAR modeling. For QAAR modeling, the binding affinities of molecules for tau and β–amyloid along with different molecular descriptors were used as independent variables. All models were successfully developed using multiple linear regression method, and validated internally and externally, based on different standard criteria. This article describes how the derived models postulate that conformation of molecules and presence of unsaturated hydrocarbon chains, nitro, methoxy and amine functionalities play an important role in determining binding affinity.

KEYWORDS
α – synuclein,, Multiple Linear Regression, Parkinson’s Disease, PET Radio Tracer Agent, QAAR, QSAR

INTRODUCTION
Parkinson’s disease (PD) is second most common incurable and progressive neurodegenerative disorder after Alzheimer’s disease (AD) which gradually takes control of motor function in body (Dexter & Jenner, 2013). The PD has been diagnosed in 1% of the population with age more than 65 years and considered as sporadic or idiopathic disease. The characteristic features of PD are degeneration and loss of dopaminergic neurons in substantia nigra of brain due to development of protein plaques from accumulation of insoluble misfolded protein (Skovronsky, Lee, & Trojanowski, 2006). The α-synuclein protein is responsible for forming insoluble aggregates like Lewy bodies (LB) and Lewy neurites (LN) (Lee & Trojanowski, 2006; Kim, Kågedal, & Halliday, 2014). Both protein aggregates are morphologically different. The α-synuclein protein regulates release of neurotransmitters, synaptic vesicle recycling and synthesis as well as vesicular storage in central nervous system (CNS) (Bendor, Logan, & Edwards, 2013). Apart from PD, these protein aggregates are also found in other synucleinopathies such as dementia with Lewy bodies (DLB), multiple system atrophy (MSA) and Pick’s disease (Marques & Outeiro, 2012). Another protein aggregates, called neurofibrillary tangles

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which are common in AD are also found in PD patients along with β-amyloid (Ho, Troncoso, Knox, Stark, & Eberhart, 2014). Neurofibrillary tangles are aggregates of tau proteins.

As PD is a sporadic disease, there is an urgent need of detecting the disease in an early stage. Studies have shown that protein aggregates start forming way before development of motor symptoms in PD patients. Therefore, detecting LB and LN in PD is more sensible than relying on changes in dopaminergic neuronal cells (Dauer & Przedborski, 2003). In addition, dopaminergic biomarkers have failed to correlate with clinical status PD patients (Sharma et al., 2013; Brooks et al., 2003). These protein aggregates can be detected by radiotracer imaging agents using techniques such as positron emission tomography (PET). Good tracer imaging agents for α-synuclein should be selective towards α-synuclein, able to cross blood brain barrier (BBB), able to locate and distinguish LB for different synucleinopathies producing minimum radioactive metabolite and able to identify post translational modified α-synuclein (Eberling, Dave, & Frasier, 2013). Several α-synuclein radiotracer ligands, such as tricyclic phenothiazine derivatives SIL5, SIL23 and SIL 26, benzoxazole analogue BF-227 and a benzothiazole analogue PIB (Pittsburgh compound B), fluorescent dyes LDS 798 and LDS 730, and indolinone 5 have been successfully utilized for detecting LB in PD affected patients (Bagchi et al., 2013; Zhang et al., 2014; Neal et al., 2013; Yu et al., 2012). Although these compounds have shown reasonable ability to detect insoluble protein aggregates, in vitro instability and inadequate selectivity towards α-synuclein among tau and β-amyloid make them meager radiotracer imagining agents. In order to overcome these limitations, Chu et al. introduced indolinone-diene derivatives which serve as second generation radiotracer imaging agents for α-synuclein (Chu et al., 2015). In the present study, quantitative structure-activity relationship (QSAR) modeling on a set of indolinone-diene derivatives has been performed to identify structural features contributing to the binding affinity towards α-synuclein in comparison to that against tau and β-amyloid proteins (Chu et al., 2015). The QSAR models were developed using the binding affinity of molecules against α-synuclein as the dependent variable while quantitative structure activity-activity relationship (QAAR) models were developed using the binding affinity of molecules against α-synuclein as the dependent variable while additionally using binding affinities against tau and β-amyloid proteins among the independent variables.

The QSAR study helps to establish relationship between the end point activity of compounds and their physical and chemical properties, while QAAR study assists to find relationship between different end point activities for the same target or different targets provided that the compounds used for the study remain same (Sangion & Gramatica, 2016; Roy & Roy, 2009).

MATERIALS AND METHODS

Dataset Preparation

A molecular dataset of 48 data points (Chu et al., 2015) with activity data provided as binding affinities (Ki) in nano molar (nM) range towards α-synuclein, tau and β-amyloid proteins as shown in Table 1 was selected for this study. Out of the 48 data points, Ki values of 28 cases are available as a mixture of either E and Z or EE and ZE isomers in various proportions, Ki values for 17 cases were for E, Z, EE or ZE isomers and remaining 3 data points correspond to tricyclic phenothiazine derivatives. As usual in QSAR analysis, the dependent variable values (Ki) were converted into negative logarithmic values (pKi = -log Ki).

Structural, topological, E-state keys, electronic (Dipole-mag, HOMO, LUMO and Superdelocalizability), spatial and molecular shape analysis descriptors for the molecules in the dataset were calculated using Cerius2 version 4.16 (Cerius2, 2005). Computation of 3D descriptors based on molecular shape analysis involves energy minimization and conformational analysis of dataset compounds, hypothesizing an active conformer based on biological activity and selecting reference compound for pairwise shape alignment to measure shape similarity is important here (Leonard &
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