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Discovery of potent adenosine A2a antagonists as potential anti-Parkinson disease agents. Non-linear QSAR analyses integrated with pharmacophore modeling

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ABSTRACT

Adenosine A_{2A} receptor antagonists are of great interest in the treatment for Parkinson's disease. In this study, we combined extensive pharmacophore modeling and quantitative structure-activity relationship (QSAR) analysis to explore the structural requirements for potent Adenosine A_{2A} antagonists. Genetic function algorithm (GFA) joined with k nearest neighbor (kNN) analyses were applied to build predictive QSAR models. Successful pharmacophores were complemented with exclusion spheres to improve their receiver operating characteristic curve (ROC) profiles. Best QSAR models and their associated pharmacophore hypotheses were validated by identification of several novel Adenosine A_{2A} antagonist leads retrieved from the National Cancer Institute (NCI) structural database. The most potent hit illustrated IC_{50} value of 545.7 nM.

1. Introduction

Adenosine receptors (AR) are four seven transmembrane G protein-coupled receptors; A_1, A_{2A}, A_{2B} and A_3 [1]. Adenosine A_{2A} receptors are primarily expressed in the dopamine rich areas of the CNS, e.g. the striatum [2]. AR antagonists have been studied for the treatment of heart failure with related renal impairment, cystic-fibrosis and asthma [3]. Currently, the connections between A_{2A} and D_2 receptors are of great interest in the treatment for Parkinson's disease (PD), which involves a decrease in dopamine levels [4]. The A_{2A} receptors interact tonically and antagonistically with the D_2 receptors, causing a decrease in affinity of the D_2 receptors for dopamine upon stimulation [5]. Therefore, an A_{2A} receptor antagonist may be beneficial as a monotherapy for the treatment of PD. On the other hand, A_{2A} receptor antagonists are capable of augmenting the effect of clinically used dopamine receptor agonists by increasing the duration of dopaminergic drug response [6].

There has been a significant effort over the past decade to synthesize novel and selective A_{2A} receptor antagonists, and recently istradefylline (KW-6002) was launched under the name Nouriast® as the first antiparkinsonian agent based on A_{2A} receptor antagonism [6].

The prominent current interest in developing new Adenosine A_{2A} antagonists as potential agents for treatment of PD, encouraged us to examine the possibility of developing ligand-based pharmacophore(s) combined within predictive QSAR model(s). Genetic function algorithm (GFA) coupled k nearest neighbor (kNN) analysis was employed to search for optimal QSAR models that combined high-quality pharmacophores with other physicochemical molecular descriptors capable of explaining bioactivity variation across a collection of diverse Adenosine A_{2A} antagonists. The successful pharmacophore model(s) can be applied as 3D search query(ies) to search molecular libraries for new Adenosine A_{2A} antagonists, while the associated QSAR model(s) can be used to prioritize the bioactivities of captured hits for *in vitro* evaluation. This innovative approach was applied towards the discovery of new leads for mTOR inhibitors [7] and

Abbreviations: GFA, genetic function algorithm; kNN, k nearest neighbor; NCI, National Cancer Institute; PD, Parkinson's disease; QSAR, quantitative structure-activity relationship; ROC, operating characteristic curve.

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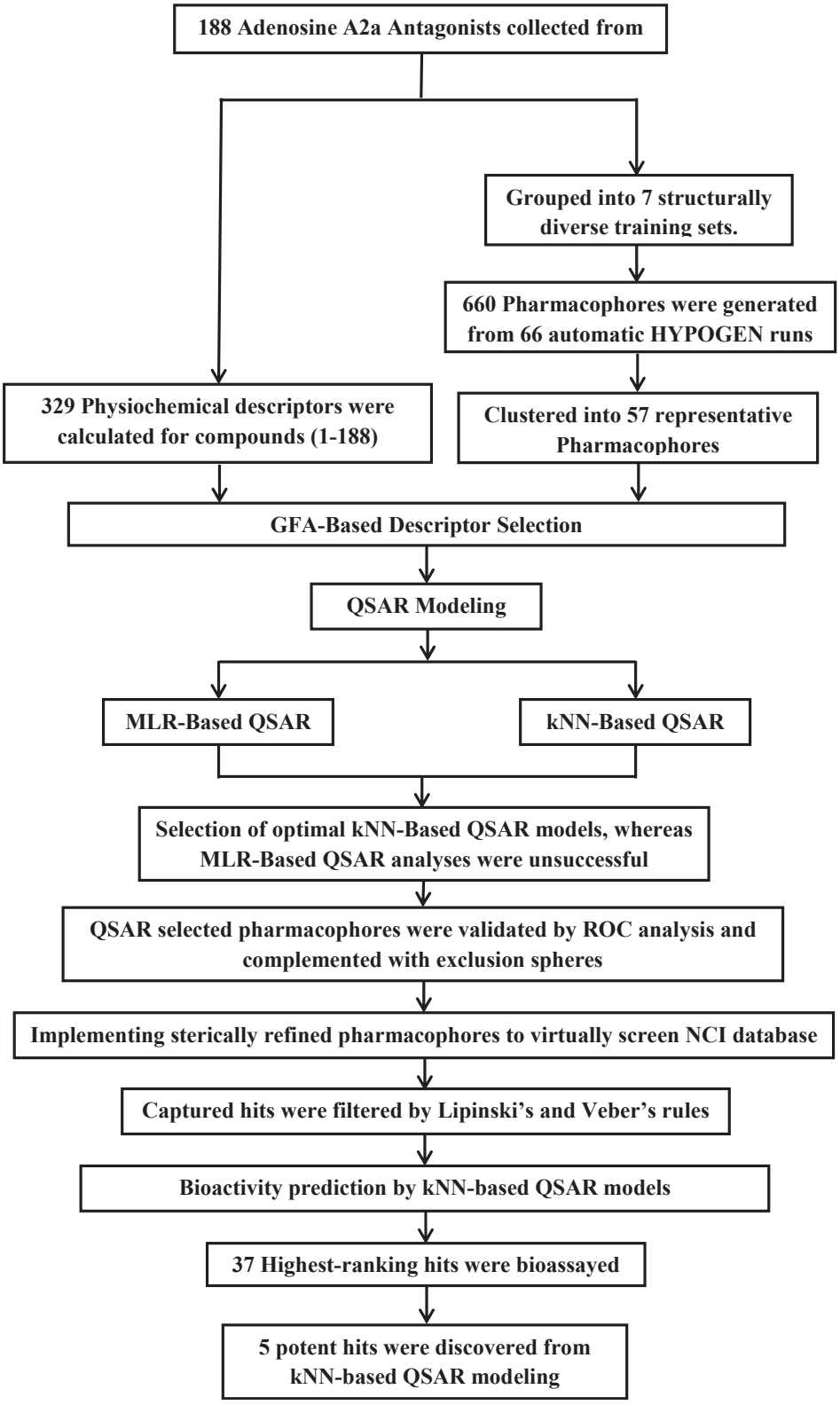

Fig. 1. General computational workflow implemented for discovering novel Adenosine A2a Antagonists. Acronyms: GFA: genetic function approximation; MLR: multiple linear regression; kNN: k nearest neighbor; and ROC: receiver operating characteristic.