Computational Biology and Chemistry 58 (2015) 158–166

Contents lists available at ScienceDirect

Computational Biology and Chemistry

journal homepage: www.elsevier.com/locate/compbiolchem

In silico identification of novel IL-1β inhibitors to target protein–protein interfaces

Sobia Ahsan Halim*, Muhammad Jawad, Muhammad Ilyas, Zulfiqar Mir, Atif Anwar Mirza, Tayyab Husnain

National Center of Excellence in Molecular Biology, University of the Punjab, Lahore 53700, Pakistan

ARTICLE INFO

Article history:
Received 27 October 2014
Received in revised form 6 June 2015
Accepted 11 June 2015
Available online 30 June 2015

Keywords:
IL-1β
Virtual screening
QSAR
Pharmacophore modeling
Molecular docking

ABSTRACT

Interleukin-1β is a drug target in rheumatoid arthritis and several auto-immune disorders. In this study, a set of 48 compounds with the determined IC_{50} values were used for QSAR analysis by MOE. The QSAR model was developed by using training set of 41 compounds, based on 12 unique descriptors. Model was validated by predicting the IC_{50} values for a test set of 7 compounds. A correlation analysis was carried out comparing the statistics of the measured IC_{50} values with predicted ones. Subsequently, model was used for the screening of a large data set of 7,397,957 compounds obtained from "Drugs Now" category of ZINC database. The activities of those compounds were predicted by developed model. 708,960 compounds that showed best predicted activities were chosen for further studies. Additionally this set of 708,960 compounds was screened by pharmacophore modeling that led to the retrieval of 1809 molecules. Finally docking of 1809 molecules was conducted at the IL-1β receptor binding site using MOE and FRED docking program. Several new compounds were predicted as IL-1β inhibitors *in silico*. This study provides valuable insight for designing more potent and selective inhibitors for the treatment of inflammatory diseases.

1. Introduction

The cytokine interleukin-1 (IL-1) has a predominant role in inducing IL-2 release, B-cell maturation and proliferation, and fibroblast growth factor activity that stimulates thymocyte proliferation. IL-1 gene family is involved in inflammatory response. They are identified as endogenous pyrogens and play role in the release of collagenase and prostaglandin from synovial cells. IL-1 has two subtypes IL-1α, and IL-1β. IL-1α and β are pro-inflammatory cytokines that put forth pleiotropic effects on various cells and play crucial role in severe inflammatory and autoimmune disorders. IL-1β has a size of 17.3 kDa, mainly produced by macrophages cells and stimulates osteoclastogensis. The inflammatory response induced by IL-1β involves the association of TRAF6 with IRAK1 (Dinarello, 1997a,b; Braddock and Quinn, 2004).

There are two receptors for IL-1, IL-1 type 1 receptor (IL-1RI) and IL-1 type 2 receptor (IL-1RII). IL-1α and IL-1β signal *via* IL-1RI. IL-1RII is known as decoy receptor, as binding to this receptor does not excites cell signaling. The binding of IL-1 to IL-1RI in the presence of IL1 receptor accessory protein (IL-1RAcP) produces a high-affinity-binding-receptor-complex responsible for intracellular signaling. Another IL-1 family member known as IL-1 receptor antagonist (IL-1ra) binds to IL-1 receptors and avoids the interaction of IL-1 with the receptors, therefore, acts as a natural IL-1 inhibitor (Dinarello, 1997a,b; Braddock and Quinn, 2004).

Pain and inflammatory process involves a cytokine cascade, which is complex as it involves glial, immune and neural cell interactions. Pro-inflammatory cytokines IL-1, produced under immunological and psychological response, exerts neuro-endocrine and stress responses. IL-1 is primarily involved in stress-induced activation of the hypothalamus–pituitary–adrenal axis and secretion of glucocorticoids leading to effects of stress on memory functioning and neural plasticity. Thus, IL-1 signaling and in result production of glucocorticoid secretion intercede the development of gloomy symptoms, that is why the blockage of IL-1 signaling will prove as preventive and therapeutic mechanism

Abbreviations: CADD, computer aided drug design; FRED, fast rigid exhaustive docking; IL-1β, interleukin-1 beta; IL-1R, interleukin-1 receptor; MOE, molecular operating environment; PDB, protein data bank; PLIF, protein ligand interaction fingerprints; QSAR, quantitative structure activity relationship; VS, virtual screening; ZINC, zinc is not commercial.

* Corresponding author at: National Center for Excellence in Molecular Biology, University of the Punjab, 87 West Canal Bank Canal Bank Rd., Lahore 53700, Pakistan.

E-mail addresses: sobia.halim@cemb.edu.pk, sobiahal@gmail.com (S.A. Halim).

http://dx.doi.org/10.1016/j.compbiolchem.2015.06.004
1476-9271/

for curing stressed associated neuropathology and psychology (Goshen and Yirmiya, 2009).

IL-1β is known to influence memory consolidation during sickness. It helps in impairing the memories that are dependent on hippocampal-formation (Rachal et al., 2001). IL-1β has vital homeostatic roles in the normal organism, such as regulation of feeding, sleep, and temperature (Dinarello, 1997a,b). However, overproduction of IL-1β is connected with the patho-physiological vicissitudes that occur during different disease situations, such as rheumatoid arthritis, inflammatory bowel disease, osteoarthritis, vascular disease, multiple sclerosis, neuropathic pain, and Alzheimer's disease (Dinarello, 1997b, 2002; Braddock and Quinn, 2004). IL-1β can be released from keratinocytes, fibroblasts, synoviocytes, endothelial, neuronal, immune cells such as macrophages and mast cells, and glial cells such as Schwann cells, microglia and astrocytes (Watkins et al., 1995; Copray et al., 2003; Shamash et al., 2002; Sommer and Kress, 2004; Perrin et al., 2005; Clark et al., 2006; Guo et al., 2007). The processing of IL-1β by caspase-1 *via* the inflammasome is one of research area that has shed new light into IL-1β's role in inflammation and pain during disease state.

Hence, IL-1β holds substantial potential as a therapeutic target for the treatment of autoimmune diseases. For the development of new immune-modulators, current therapies target IL-1β production or the IL-1β signaling pathway. The use of monoclonal antibodies as therapeutics has a promising solution for diluting the effect of IL-1β (Cignarella, 2011). However, therapeutic antibodies have several disadvantages including high cost and nonexistence of oral bioavailability. A small molecule inhibitor of the IL-1β/IL-1R1 interaction could offer a significant development in immunosuppressive therapy. Until now, small molecule inhibitors of IL-1β have been difficult to identify (Wu et al., 2009). In contrast, computational drug design tactics can be effectively carried out resulting in lower cost and less screening time (Dasgupta et al., 2009).

The use of computational practices in drug discovery and development has become routine in the pharmaceutical industry, and recently gained momentum in academia with the availability of compound libraries. To-date computer aided drug design (CADD) is based on the knowledge of the structure, either of the receptor, or that of the ligand. The former is described as structure-based design, while the latter as ligand-based drug design (Halim et al., 2013; Khan et al., 2014; Haq et al., 2015).

In order to search novel chemical space as putative IL-1β inhibitors, three computational strategies were adopted to screen the ZINC database: (i) 2D-QSAR modeling, (ii) pharmacophore modeling and (iii) molecular docking simulations. For QSAR modeling a dataset of 48 compounds were retrieved from literature (Matsuda et al., 2001a,b). The best QSAR model with q^2 value of >0.5 was used to predict the activity of molecules taken from ZINC database comprising 7.5 million compounds. This approach screened the molecules and squeezed the database size from 7.5 million to 0.7 million. Furthermore, pharmacophore models were established to reduce the size of library containing 0.7 million compounds. Subsequently 1809 molecules were filtered according to pharmacophore query. Hence the dataset of 1809 molecules were subjected to structure based virtual screening protocol in order to find molecules that specifically binds at the interface of IL-1β/IL-1RI.

The structure based virtual screening was performed using two docking protocols *i.e.*, MOE and FRED to identify new ligands for IL-1β. A set of 1809 drug-like compounds obtained from previous two strategies served as screening library. After docking, 500 top ranked docked compounds were selected and their binding modes were visually analyzed. The ranking analysis revealed 284 compounds that were common in both MOE and FRED docking results. Out of 284 compounds, 7 compounds showed the maximum common interaction at the surface of IL-1β/IL-1RI interface, suggested to be the putative IL-1β inhibitors. The whole computational strategy is shown in Fig. S1 in Supporting information.

2. Material and methods

2.1. Data set for QSAR studies

Data for this QSAR studies were retrieved from literature reported by Matsuda et al. (2001a,b). 2D-QSAR analysis was performed on a structurally diverse set of 48 (1–48, Table 1) compounds covering a good range of IL-1β production inhibitory activity. Matsuda et al. (2001a,b) reported a series of fifty five novel pyradizine derivatives that inhibits the production of IL-1β. Out of 55 compounds, 28 compounds are the analogues of 3,4-bis(4-methoxyphenyl)-pyr-idazine and 27 compounds are 5,6-bis(4-methoxyphenyl)-2H-pyr-idazin-3-one analogues. Only compounds that possess defined IC_{50} (*i.e.*, $IC_{50} \leq 1$ 00 uM) was considered in this study. *Kennard Stone* (Kennard and Stone, 1969), a statistical method for data distribution, was used for initial data distribution into training and test sets. By using this application approximate 80% data set was distributed as training and rest as test set. Hence 48 compounds were segregated in training and test set comprising 41 and 7 molecules, respectively. The compounds in the test set evenly spanned the biological activity range and the chemical diversity of the database. The IC_{50} values were transformed into negative logarithmic scale ($pIC_{50} = -\log IC_{50}$) which cover an interval of 4 log units. The biological activity and chemical structures of compounds are shown in Table 1.

The 2D coordinates of molecules was sketched on ChemDraw software version 8.0.3 (http://dtclab.webs.com/software-tools) and saved in mol2. The structures of all the compounds were imported into MOE database file using MOE-DB option. The coordinates of all the compounds were converted into 3D-structures by MOE wash module (MOE, 2013.08). The ring nitrogens of the nitrogen bearing compounds were deprotonated according to their physiological pH. Using MOE wash command partial charges were applied on the compounds and their energy was minimized using MMFF94 force field (Darian and Gannett, 2005). Relative pIC_{50} value of each compound was entered in database manually opposite to molecules.

2.2. Molecular descriptors

This study presents a descriptor based QSAR analysis. MOE offers several 2D, and 3D molecular descriptors to calculate molecular properties of compounds. Initially all 2D descriptor (total 192) present in MOE was calculated for all the compounds (both training and test set). Subsequently "QuaSAR-Contingency", a statistical application in MOE was used for the selection of appropriate descriptors for QSAR modeling. The contingency analysis suggested 12 2D (Table S1) descriptors for further experimentation. These descriptors are of two type belonging to the same category SlogP_VSA and SMR_VSA. These VSA descriptors have wide applicability to both biological activity and ADME property prediction (MOE, 2013.08). Usually QSAR models developed by using these descriptors are able to screen only ADMET fit molecules.

2.3. Fitting the experimental data

QSAR model was constructed choosing the IL-1β inhibitory activities (as dependent variable) and the descriptors as model