Combinatorial Library Generation of Tumor Necrosis Factor Inhibitor using Vlife MDs 3.5

R.DEVIKA and M.ALEKYA

Abstract – Tumor Necrosis Factor-alpa (TNF-A) is a cytokine critical for effective immune surveillance wherein cytokines are usually associated with inflammatory process which in turn causes many clinical problems associated with autoimmune disorders. The present investigation was aimed to generate a combinatorial library with eight TNF inhibitors in terms of creation, physico chemical characterization, alignment, 2D QSAR analysis and bar graph visual pattern for chemical diversity among the molecule using Vlife MDS3.5.

Key Words: Cytokines, Inhibitor, QSAR, Tumor Necrosis Factor (TNF), Vlife,

I. Introduction

It has been widely accepted that combinatorial chemistry was born in the early 1980s when Mario Geysen, Melbourne, Australia invented the pin method in which simultaneous synthesis of diversified peptides gave rise to the first combinatorial libraries [1]. Combinatorial library methods were first applied to peptides, synthetic oligomers, small molecules and oligosaccharides. The method of library preparation depends on the type of library desired and involves three main steps such as (a) Preparation of the library (b) Screening of library components (c) Determination of the chemical structures of active compounds [2]. The main objective of library design is to reduce the number of molecules without decreasing the diversity of the library,

Tumor necrosis factor – alpha (TNF-A) is a pleiotrophic inflammatory cytokine which was isolated by Carswell, responsible for necrosis of the Sarcoma Meth A [3]. TNF – A is an acute phase protein which initiates a cascade of cytokines and increases vascular permeability thereby recruiting macrophage and neutrophils to the site of infection, TNF-A participates in both inflammatory disorders and non inflammatory origin. Exogenous and parasites factors from bacteria, viruses and other cytokines [4].

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When the cytokine production increases, infection enters the bloodstream and ensures systematic edema which result in low blood volume, hypo protein anaemia, neutropenia resulting in organ failure and ultimate death[5]. Tumor Necrosis Factor (TNF) promotes inflammatory responses which in turn causes many of the clinical problems associated with autoimmune disorders such as rheumatoid arthritis, ankylosing spondylitis, Crohn's discase, Proriasis, Hidradenitis suppurativa and Refractory asthma[6].

The investigation was aimed to recognize inhibitors of TNF-A and create a combinatorial library using Vlife MDS 3.5. There are many evidences for suppression of TNF –A production. Remission induction after pentoxifylline treatment in a patient with rheumatoid arthritis showed suppression of TNF – A production by activated macrophages, Th-1 responses of T cells and fibroblast proliferation and metalloproteinase production [7].

II. Materials And Methods

Fasta format of TNF of Arthritis was retrieved from Swissprot database.

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>sp|P01375|TNFA_HUMAN Tumor necrosis factor OS=Homo sapiens
GN=TNF PE=1 SV=1
MSTESMIRDVELAEEALPKKTGGPQGSRRCLFLSLFSFLIVAGATTLFCLLHFGVIGPQR
EEFPRDLSLISPLAQAVRSSSRTPSDKPVAHVVANPQAEGQLQWLNRRANALLANGVELR
DNQLVVPSEGLYLIYSQVLFKGQGCPSTHVLLTHTISRIAVSYQTKVNLLSAIKSPCQRE
TPEGAEAKPWYEPIYLGGVFQLEKGDRLSAEINRPDYLDFAESGQVYFGIIAL
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Eight natural inhibitors such as Apoptasis, Angiotensin, Lipoxygenase, Motapione, Pentoxifylline, Rolipram, Talidomide, Zardaverine were selected for Tumor necrosis factor A protein using KEGG and Literature database and the template molecule were identified using V-life MDS 3.5 software.

Combinatorial library was generated using V-life LeadGrow module and various descriptors were identified for the template molecule using QSAR.

A worksheet was developed for training and testing set with descriptors as independent variables.

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III Results And Discussion

Tumor Necrosis Factor (TNF) promotes inflammatory responses which in turn causes many of the clinical problems associated with autoimmune disorders such as rheumatoid arthritis, ankylosing spondylitis, Crohn's disease, Psoriasis, Hidradenitis suppurativa and Refractory asthma[6]. The inhibition can be achieved with a monoclonal antibody such as infliximab (Remicade)[8], adalimumab (Humira), Certolizumab pegol (Cimzia) and golimumab (Simponi) or with a circulating receptor fusion protein such as etanercept (Enbrel)[9].

In the present study, eight natural inhibitors such as Apoptasis, Angiotensin, Lipoxygenase, Motapione, Pentoxifylline, Rolipram, Talidomide, Zardaverine were selected for Tumor necrosis factor A protein using KEGG and Literature database. The template molecule were identified using V-life MDS 3.5 software (Fig.1). Clinical application of anti TNF drugs/inhibitors for rheumatoid arthritis was demonstrated by Marc and Ravinder[10] and won the 2003 Lasker Award and proved that these eliminate abnormal B cell activities.

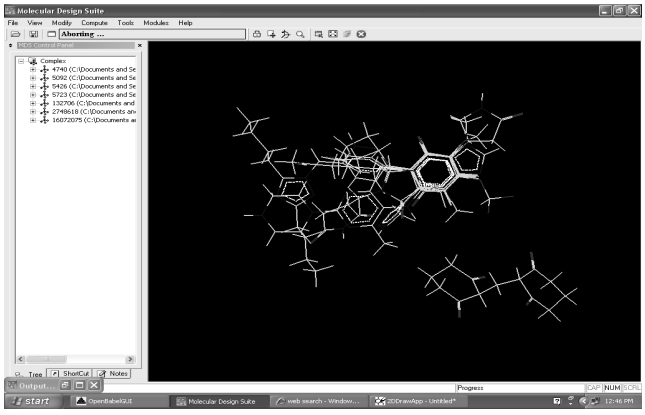

Fig – 1: Template Molecule

A combinatorial library was generated with substitution groups such as alkyl, alkene, acid, ester, aromatic ring etc, and group was allocated with substitution site such as 8x, 9x, 10x, 11x, 12x, etc., shown in fig – 2

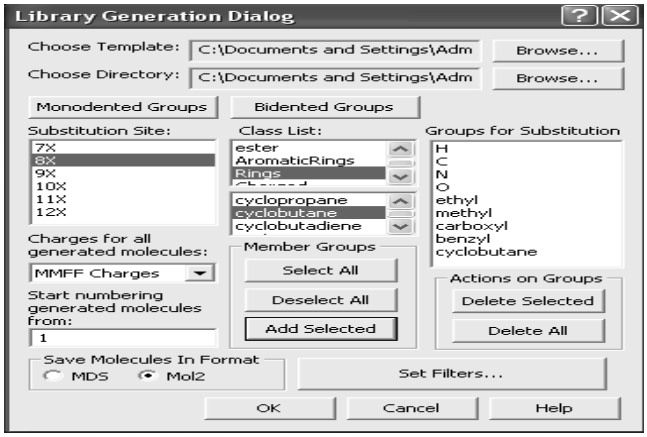

Fig – 2: Library Generation Dialog

An attempt was made to calculate the physico chemical properties of the descriptors and the alignment with the independent descriptor are shown in the Fig - 3

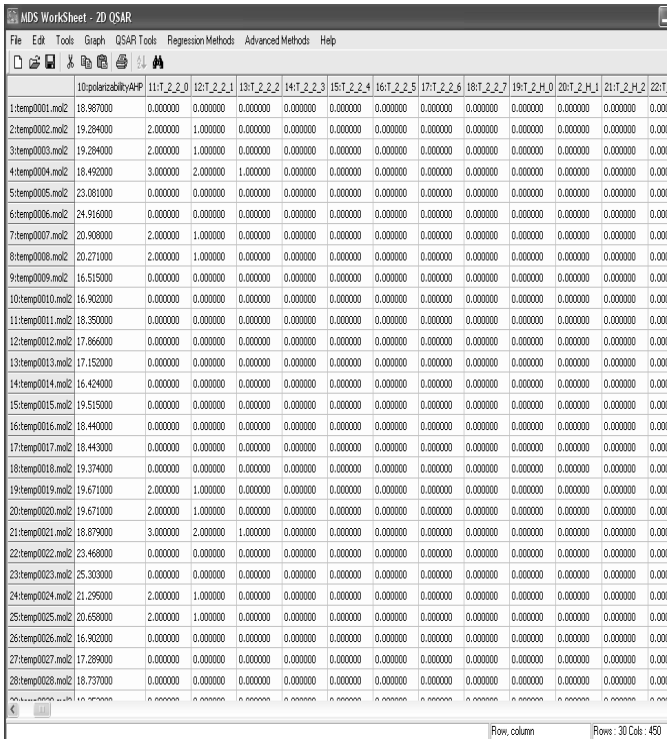

Fig – 3: Alignment Independent Descriptor Result

The main objective of the present investigation is to develop a training and testing set made with dependent variables and descriptors as independent variables wherein a worksheet of 2D QSAR gave a detailed list and created a work region with the resulted data in the form of bar graph to visualize the chemical diversity for the entire set of LeadGrow generated molecules with reference molecule in red and other compounds in the blue colour (Fig - 4).

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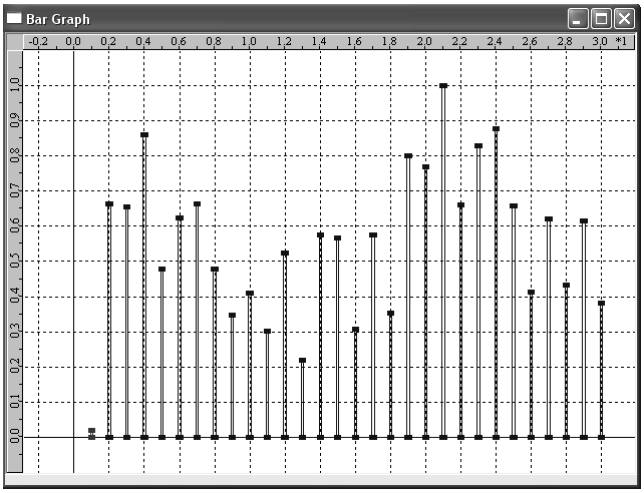

Fig – 4: Bar Graph

IV Conclusion

From the above methodology and result it is very easy to compare and elucidate the chemical compounds of various molecules and create a combinatorial library with common features among the molecules.

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