INVESTIGATIONS ON EFFICIENCY OF CELEBREX AND VIOXX FOR RHEUMATOID ARTHRITIS THROUGH DOCKING

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ABSTRACT

Rheumatoid Arthritis (RA) is a chronic, inflammatory, autoimmune disorder affecting the joints and sometimes other organs as well. It is by definition polyarticular; that is, it affects many joints. Scientists throughout the world are studying many promising areas of new treatment approaches for rheumatoid arthritis. The objective of this project is to uncover some of the aspects of Rheumatoid Arthritis, which will subsequently contribute to the ongoing research. Of all the drugs present for Rheumatoid Arthritis, we opted Celebrex and Vioxx which can be efficiently used for Rheumatoid Arthritis. The project work involves modification of the selected drugs. For this a deep rooted life study on these drugs was made. These modified drugs were compared with the existing one by comparing Log p value, molecular weight and by using Steepest and Polark algorithm. A QSAR study on the modified drugs were made which will be used for the treatment of the disease of interest.

KEY WORDS: Rheumatoid arthritis, Chronic, QSAR, Polark algorithm.

INTRODUCTION

Rheumatoid Arthritis (RA) being one of the major topics of concern for the modern medical science, and with an ultimate cause still unavailable, it was a challenge that we undertook by preferring to do my major project in this division of medical science. As if there's not enough outside threats to our health, our own immune system can actually turn on us and attack our joints. This leads to the disease known as Rheumatoid Arthritis. Rheumatoid arthritis is also known as an autoimmune disease. It can attack any age group even children (juvenile arthritis). It tends to attack women more than men, approximately 1 in 100 people worldwide
may have or be at risk from this disease. Those most at risk are aged between 25-50 years. Rheumatoid Arthritis (RA) is a chronic, systemic autoimmune disease, the hallmark feature of which is persistent symmetrical inflammation in the joints, especially small joints. As a systemic disease, it also may affect other tissues and organs. Current therapy is directed toward diminishing the inflammatory response and treating the uncontrolled inflammation. Although a number of different therapies are effective in RA, some patients experience disease progression that is resistant to all known therapies, and currently there is no therapy known to prevent RA. Rheumatoid arthritis affects women three times more often than men, and it can first develop at any age. The risk of first developing the disease appears to be greatest for women between 40 and 50 years of age, and for men somewhat later. RA is a chronic disease, and although a spontaneous remission may occur in a very small number of patients, the natural course is almost invariably one of persistent symptoms, waxing and waning in intensity, and a progressive deterioration of joint structures leading to deformations and disability. The small joints of the cervical spine can also be involved.

Inflammation in the joints manifests itself as a soft, "doughy" swelling, pain, tenderness to palpation and movement, local warmth, and functional impairment. Morning stiffness is often a prominent feature and may last for more than an hour. These signs help distinguish rheumatoid and other inflammatory arthritides from non-inflammatory diseases of the joints such as osteoarthritis (sometimes referred to as the "wear-and-tear" of the joints). In RA, the joints are usually affected in a fairly symmetrical fashion although the initial presentation may be asymmetrical.

Data from AERS and published case reports suggest that use of both these drugs is associated with renal effects similar to that of conventional nonselective NSAIDs. Physicians should be aware that serious or life-threatening renal failure has been reported in patients with normal or impaired renal function after short-term therapy with celecoxib and rofecoxib. Patients at greatest risk for renal injury are those with pre-existing renal impairment, heart failure, liver dysfunction, those taking diuretics and/or ACE inhibitors, and the elderly. Kidney function should be monitored closely for any signs of potential renal injuries soon after initiating treatment with these agents, especially in high-risk populations. In addition, healthcare practitioners should adequately warn patients of the signs and symptoms of serious renal toxicity, and of the need for them to see their physician promptly if they occur. Celecoxib and rofecoxib are not recommended for use in patients with advanced renal disease.\[1\]
Cyclo-oxygenase (Cox), a rate-limiting enzyme in the synthesis of prostanoids, is encoded by two genes, Cox-1 and Cox-2, which are differentially expressed and regulated. Human Cox-1 and -2 polypeptides share 61% primary sequence identity. While the expression of Cox-1 is maximal in quiescent cells. Cox-2 expression is induced by growth factors and cytokines. We have screened a human genomic library with a probe from the 5'-untranslated region (UTR) of the human Cox-2 (hCox-2) cDNA and isolated two overlapping genomic clones. We have determined the DNA sequence of 0.8 kb upstream of the transcription start site, 6 kb of protein coding region, which includes 10 exons and 9 introns, as well as 2.5 kb of the 3'-UTR. The structures of the hCox-1 and hCox-2 and the murine TIS10 (Cox-2) genes are highly conserved, with a few exceptions. The 3'-UTRs of the Cox-1 and -2 genes are distinct; for example, the largest exon in the Cox-2 gene encodes the entire 3'-UTR, containing 22 copies of the 'AUUUA' RNA instability element. Sequence analysis of the 5'-flanking region has shown several potential transcription regulatory sequences, including a TATA box, a C/EBP motif, two AP-2 sites, three SP1 sites, two NF-kappa B sites, a CRE motif and an Ets-1 site. These efforts serve as a basis for future studies on transcriptional and post-transcriptional mechanisms of Cox-2 gene regulation.[2]

Rofecoxib and naproxen had similar efficacy against rheumatoid arthritis. During a median follow-up of 9.0 months, 2.1 confirmed gastrointestinal events per 100 patient-years occurred with rofecoxib, as compared with 4.5 per 100 patient-years with naproxen (relative risk, 0.5; 95 percent confidence interval, 0.3 to 0.6; P<0.001). The respective rates of complicated confirmed events (perforation, obstruction, and severe upper gastrointestinal bleeding) were 0.6 per 100 patient-years and 1.4 per 100 patient-years (relative risk, 0.4; 95 percent confidence interval, 0.2 to 0.8; P=0.005). The incidence of myocardial infarction was lower among patients in the naproxen group than among those in the rofecoxib group (0.1 percent vs. 0.4 percent; relative risk, 0.2; 95 percent confidence interval, 0.1 to 0.7); the overall mortality rate and the rate of death from cardiovascular causes were similar in the two groups. In patients with rheumatoid arthritis, treatment with rofecoxib, a selective inhibitor of cyclooxygenase-2, is associated with significantly fewer clinically important upper gastrointestinal events than treatment with naproxen, a nonselective inhibitor.[3-10]

Present study aims at the study of cyclooxygenase-2 (COX-2) protein, which is responsible for the disease Rheumatoid Arthritis and also find the potential drugs to inhibit the activity of this protein.
2. MATERIALS AND METHODS
A Deep literature review was done to find all the genes and proteins involved in Rheumatoid Arthritis, and also all the available drugs for treating Rheumatoid Arthritis was identified.

3. RESULTS AND DISCUSSION
The information’s about Rheumatoid Arthritis have taken from pubmed. We have listed some genes and proteins which are responsible for Rheumatoid Arthritis and the drugs which are using for it.

Table 1: List of genes, proteins & drugs for Rheumatoid Arthritis

<table>
<thead>
<tr>
<th>GENES</th>
<th>PROTEINS</th>
<th>DRUGS</th>
</tr>
</thead>
<tbody>
<tr>
<td>HLA-B27</td>
<td>PTGS2</td>
<td>Methotrexate</td>
</tr>
<tr>
<td>HLA-DR4</td>
<td>DCR3</td>
<td>Sulfasalazine</td>
</tr>
<tr>
<td>IRF5</td>
<td>Thrombin</td>
<td>celebrex</td>
</tr>
<tr>
<td>M-CSF</td>
<td>Fibronectin</td>
<td>Vioxx</td>
</tr>
<tr>
<td>CD 14</td>
<td>NF Kappa B</td>
<td>Enbrel</td>
</tr>
<tr>
<td>TRAF1-C5</td>
<td>S100A4</td>
<td>Arava</td>
</tr>
<tr>
<td>PT PN-22</td>
<td>IL</td>
<td>Abatacept</td>
</tr>
<tr>
<td>PAD-2</td>
<td>HSP-22</td>
<td>Rituximab</td>
</tr>
<tr>
<td>MMP-3</td>
<td>VEGF</td>
<td>Minocycline</td>
</tr>
<tr>
<td>HOX</td>
<td>SUMO-1</td>
<td>Cyclosporine</td>
</tr>
</tbody>
</table>

4.2. DRUG MODIFICATION
We modified the drugs (celebrex, vioxx) according to the Lipinski five rule by using chemsketch. The modified structures are

CELEBREX A

![CELEBREX A](https://via.placeholder.com/150)

\[
O=S(=O)(c1ccc(cc1)n2nc(cc2c3ccc(C)cc3)C(Br)(Cl)Cl)N
\]

4-{3-[bromo(dichloro)methyl]-5-(4-methylphenyl)-1H-pyrazol-1-yl}benzenesulfonamide
Molecular Formula = C₁₇H₁₄BrCl₂N₃O₂S
Formula Weight = 475.18696
Composition = C(42.97%)H(2.97%)Br(16.82%)Cl(14.92%)N(8.84%)O(6.73%)S(6.75%)
Molar Refractivity = 109.02 ± 0.5 cm³
Molar Volume = 288.9 ± 7.0 cm³
Parachor = 797.1 ± 8.0 cm³
Index of Refraction = 1.678 ± 0.05
Surface Tension = 57.9 ± 7.0 dyne/cm
Density = 1.64 ± 0.1 g/cm³
Dielectric Constant = Not available
Polarizability = 43.22 ± 0.5 10⁻²⁴ cm³
Monoisotopic Mass = 472.936707 Da
Nominal Mass = 473 Da
Average Mass = 475.191457 Da

VIOXX A

![VIOXX A](image)

O=C₂O\C(=C\(=\c1ccccc1)c3ccc(cc3)S(F)(=O)=O
4-(5-oxo-4-phenyl-2,5-dihydrofuran-3-yl)benzenesulfonyl fluoride

Molecular Formula = C₁₆H₁₁FO₄S
Formula Weight = 318.3195432
Composition = C(60.37%) H(3.48%) F(5.97%) O(20.10%) S(10.07%)
Molar Refractivity = 78.18 ± 0.4 cm³
Molar Volume = 224.6 ± 3.0 cm³
Parachor = 600.9 ± 6.0 cm³
Index of Refraction = 1.613 ± 0.02
Surface Tension = 51.2 ± 3.0 dyne/cm
Density = 1.417 ± 0.06 g/cm³
Dielectric Constant = Not available
Polarizability = 30.99 ± 0.5 \times 10^{-24} \text{ cm}³
Monoisotopic Mass = 318.036207 \text{ Da}
Nominal Mass = 318 \text{ Da}
Average Mass = 318.324336 \text{ Da}

4.3. 3D STRUCTURES OF DRUGS
We converted the modified structures from 2d to 3d by the help of corina. The structures are,

Fig :D STRUCTURE OF CELEBREX A

3D STRUCTURE OF VIOXX A
4.4. PROPERTIES OF DRUGS- ADME TOX
The property of the modified structures was taken from ADME TOX.

<table>
<thead>
<tr>
<th>STRUCTURE</th>
<th>LOG P</th>
<th>H DONOR</th>
<th>H ACCEPTOR</th>
<th>MOLECULAR WEIGHT</th>
</tr>
</thead>
<tbody>
<tr>
<td>CELEBREX</td>
<td>2.960000</td>
<td>1</td>
<td>5</td>
<td>381.3</td>
</tr>
<tr>
<td>CELEBREX 1</td>
<td>2.960000</td>
<td>1</td>
<td>5</td>
<td>414.2</td>
</tr>
<tr>
<td>VIOXX</td>
<td>1.480000</td>
<td>0</td>
<td>4</td>
<td>299.2</td>
</tr>
<tr>
<td>VIOXX 1</td>
<td>3.060000</td>
<td>0</td>
<td>4</td>
<td>318.2</td>
</tr>
</tbody>
</table>

RESULT OF ADME TOX.

4.5. DOCKING OF MODIFIED STRUCTURES WITH PTGS2
The docking results between PTGS2 with the original drug and our modified structures are,

CELEBREX DOCKED WITH PTGS2

5. SUMMARY AND CONCLUSION

SUMMARY
The target protein PTGS1 is identified and retrieved from Protein data Bank. The PDB id of the PTGS1) is 6COX. The Protein structure is visualized and active site amino acids are analysed by RasMol tool. The wire frame model structure of PTGS1 is shown in the (Figure 1). Celebrex and Vioxx are important PTGS1 inhibitors. The structure of PTGS1 inhibitors has found in the pubchem compound database. The 2D structure of celebrex and Vioxx drug is retrieved from NCBI pubchem compound database. The physiochemical parameters of these two inhibitors are analysed.
By using chemsketch molecular drawing tool, we have done three modifications in cellebrex and Vioxx drug and they are named as cellebrex A and Vioxx A. In cellebrex A ammonia is replaced by bromin, in Vioxx A flurin is added.

3 dimensional structure predictions of all the drugs have done in corina 3D conversion tool. 3D structures of all the drugs are analysed and visualised in rasmol tool then they are saved in pdb file format.

Docking steps are done in VegaZZ software. drug celebrex is docked with PTGS1 -2 to form protein ligand complex. The docking score of celebrex with PTGS1 -2 is 258 (Figure 13) and binding energy score of celebrex is230 .All the modified drugs are docked with its target protein PTGS1, Docking score and interaction energy value is calculated.

Interaction energy calculation of all the four drugs is done in Escher NG automatics docking system. Comparison of interaction energy value and docking score of all the five drugs are done.

Physiochemical properties of cellebrex, Vioxx, cellebrex A and Vioxx A was predicted using ADME Boxes and ADME Toxes Tools. Molecular weight of all the five drugs are predicted and values are predicted. Number of Hydrogen bond donors and H bond acceptors are calculated. Partation coefficient value (Log P) of all the four drugs are also predicted.

Comparisons of all physiochemical properties of all the four drugs are done. Based on the lipinski’s rule of 5 the drug must have the hydrogen bond donors below 5, hydrogen bond acceptors below 12 and partition coefficient( log P) value is below 5. From graphical result all the drugs are passed lipinski’s 5 rule

6. REFERENCE


