QSAR/QSPR: Designing of New Non-Steroidal Anti-inflammatory Drugs (NSAIDs) considering Diclofenac as a lead compound followed by Suggestion of a good Synthetic Route through Mathematical Modelling

Hassan.A. Osman, Sampatrao B. Suryaawanshi, Nazeruddin N. Gulam Mohammed *

Department of Chemistry (Post-Graduate & Research Centre) 
Poona College of Arts, Science and Commerce, Camp, Pune-411 001, India

ABSTRACT

Quantitative structure–activity relationship/Quantitative structure property relationship (QSAR/QSPR) methods represent an attempt to correlate structural and/or physical properties and descriptors of compounds with biological activities. We have designed various new non steroidal anti-inflammatory drugs (NSAIDs) and calculated various physical properties and molecular descriptors like log P, Dipole moment, Heat of formation, Ionization Potential, Wiener’s index, HOMO (Highest occupied molecular orbital) and LUMO (lowest unoccupied molecular orbital) energies and pKa by using different software such as Vega zz, Mopac, ADME and ChemDraw etc. and compared them with the lead compound, Diclofenac. The newly designed compounds, which are having the comparable properties with the lead compound, are selected for their synthesis. A good synthetic route can be predicted through mathematical modeling using particularly Hendrickson equation $W = \sum W_i X^{-1}$, Where $W=$Sum of Weight, $W_i$ is number of skeletal carbons in each piece and $X$ is reciprocal of the average yield for each step. With the help of this hypothesis, not only the activity of Non Steroidal Anti-Inflammatory Drugs (NASID) can be predicted especially for the new compounds but through mathematical modeling a good synthetic route can also be suggested.

Key words: Designing, Derivatives of –aryl ethanoic acid (NSAID), Hendrickson’s equation, Hypothesis
INTRODUCTION

Use of computational techniques in drug discovery and development process is rapidly gaining popularity, implementation and appreciation. Term Computer-Aided Drug Discovery and Development (CADDD) [1] will be employed to cover the entire process. Both computational and experimental techniques have important roles in drug discovery and development and CADDD is being utilized to identify hits (active drug candidates), select leads (most likely candidates for further evaluation), and optimize leads i.e. transform biologically active compounds into suitable drugs by improving their physicochemical, pharmaceutical, ADMET/PK (pharmacokinetic) properties. Virtual screening is used to discover new drug candidates from different chemical scaffolds by searching commercial, public, or private 3-dimensional chemical structure databases. It is intended to reduce the size of chemical space and thereby allow focus on more promising candidates for lead discovery and optimization. The goal is to enrich set of molecules with desirable properties (active, drug-like, lead-like) and eliminate compounds with undesirable properties (inactive, reactive, toxic, poor ADMET/PK). In another words, in silico modeling is used to significantly minimize time and resource requirements of chemical synthesis and biological testing [2]. Role of computational models is to increase prediction based on existing knowledge [3]. Computational methods are playing increasingly larger and more important role in drug discovery and development. In early 1960s, Corwin Hansch [4] extended the concept of Linear –free energy relationship (LFER) to describe the effectiveness of biologically-active molecule. Generating useful Hansch equation can be very challenging and even a good Hansch equation will not give perfect predication of activity. For this reason new methods have somewhat replaced the traditional Hansch analysis. In the late 1980s and early 1990s combinatorial chemistry emergent diminished the importance of QSAR. Since the middle 1990s, a technique called comparative molecular field Analysis (COMFA)[5] has emerged. This method uses highly complicated statistical analysis with large number of variable to correlate practical molecular properties to activity. However, Drug designing is still a big challenge. This is in continuation of our earlier work[6]. We wish to report here a simple hypothesis, in which, physical properties such as Heat of formation, Dipole moment, Ionization potential, HOMO, LUMO energies, Weiner index should be calculated for newly design α-aryl ethanoic acid derivatives and compared with the lead compound Diclofenac. The derivatives which are having comparable properties are selected. By applying Hendrickson equation [7] $\Sigma \eta_i x_i$, even best synthetic route can be predicted.

Computational Work and Calculation

There are number of software such as Vega zz, Mopac, ADME and Chem Draw etc. Which are available in the market through them not only various new derivatives of α-aryl ethanoic acid can be designed but also various molecular descriptors [8] can be calculated. It is observed that compound I compound II do have quite good comparable physical properties with the lead compound Diclofenac. For illustration, ten compounds were selected as mentioned below and various physical properties, molecular descriptors were calculated by using above said software as depicted in table 1.
Table 1: Calculated values of various physical properties such as HOF, LP, DM and log P of several α-aryl ethanoic acid derivatives.

<table>
<thead>
<tr>
<th>Derivative</th>
<th>HOF (kJ/mol)</th>
<th>DM (debye)</th>
<th>LP (kcal/mol)</th>
<th>Log P</th>
<th>HOMO (eV)</th>
<th>LUMO (eV)</th>
<th>P ka</th>
<th>W.I</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diclofenac</td>
<td>-221.92</td>
<td>3.952</td>
<td>8.9326</td>
<td>4.12</td>
<td>9.348</td>
<td>4.413</td>
<td>4.30</td>
<td>527</td>
</tr>
<tr>
<td>I</td>
<td>-200.87</td>
<td>4.994</td>
<td>9.272</td>
<td>4.81</td>
<td>3.390</td>
<td>1.366</td>
<td>2.20</td>
<td>793</td>
</tr>
<tr>
<td>II</td>
<td>-242.94</td>
<td>4.753</td>
<td>9.282</td>
<td>4.69</td>
<td>4.710</td>
<td>1.399</td>
<td>2.20</td>
<td>793</td>
</tr>
<tr>
<td>III</td>
<td>-249.14</td>
<td>5.521</td>
<td>8.857</td>
<td>4.69</td>
<td>-8.914</td>
<td>-0.850</td>
<td>4.30</td>
<td>870</td>
</tr>
<tr>
<td>IV</td>
<td>-226.82</td>
<td>14.93</td>
<td>4.435</td>
<td>4.3</td>
<td>1.440</td>
<td>1.038</td>
<td>4.30</td>
<td>545</td>
</tr>
<tr>
<td>V</td>
<td>-115.53</td>
<td>17.7</td>
<td>4.381</td>
<td>4.4</td>
<td>9.436</td>
<td>1.325</td>
<td>4.30</td>
<td>704</td>
</tr>
<tr>
<td>VI</td>
<td>-238.64</td>
<td>17.61</td>
<td>4.42</td>
<td>4.0</td>
<td>1.06</td>
<td>4.30</td>
<td>4.30</td>
<td>601</td>
</tr>
<tr>
<td>VII</td>
<td>-61.60</td>
<td>15.69</td>
<td>4.45</td>
<td>4.29</td>
<td>9.315</td>
<td>4.37</td>
<td>4.30</td>
<td>527</td>
</tr>
<tr>
<td>VIII</td>
<td>-242.87</td>
<td>16.93</td>
<td>4.35</td>
<td>3.7</td>
<td>3.25</td>
<td>1.08</td>
<td>4.30</td>
<td>608</td>
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<tr>
<td>IX</td>
<td>-91.76</td>
<td>14.75</td>
<td>4.67</td>
<td>4.9</td>
<td>1.95</td>
<td>4.75</td>
<td>4.30</td>
<td>542</td>
</tr>
<tr>
<td>X</td>
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<td>15.34</td>
<td>4.6</td>
<td>4.9</td>
<td>1.32</td>
<td>2.90</td>
<td>4.30</td>
<td>549</td>
</tr>
</tbody>
</table>

The comparison of log P values shows that compound no. I and II are very similar to Diclofenac. Moreover H.O.F. and other parameters are also close to Diclofenac; hence these may act as very good anti-inflammatory drugs.

**Retroynthetic Analysis:**
Prediction of good synthetic route is another task. To select a good synthetic route various approaches like SYNGEN, CAOS, CAMEO etc. are available in literature [9]. All the approaches have their own advantages & limitations. Three retroynthetic approach of target molecules are depicted in scheme 1,2,3. [10, 11, 12, 13]

**Scheme 1**

**Scheme 2**
Scheme: 3

\[
\begin{align*}
&\text{NH} \quad \text{N} \quad \text{Cl} \\
&\text{Cl} \quad \text{Cl} \quad \text{COOH} \\
&\text{Cl} \quad \text{Cl} \\
&\text{N}=14 \\
\end{align*}
\]

\[
\begin{align*}
&\text{N}=14 \\
\end{align*}
\]

\[
\begin{align*}
&\text{NH} \quad \text{N} \quad \text{Cl} \\
&\text{Cl} \quad \text{Cl} \\
&\text{N}=12 \\
\end{align*}
\]

\[
\begin{align*}
&\text{Br} \quad + \\
&\text{N}=12 \\
\end{align*}
\]

\[W = 17.50 + 21.84 + 23.40 = 62.74\]

The SYNGEN approach first proposed by Hendrickson has the major focus on the skeletal rather than functional disconnection. The approach was based on the following equation:

\[W = \sum \eta_i X_i\]

Where \(W\) = Sum of Weight, \(\eta_i\) is no. of skeletal carbons in each piece, and \(X\) is reciprocal of the average yield for each step. The whole quantity \(X_i\) is related to no. of steps 1. For each step yield is presumed 80%.

To illustrate the equation let us take scheme 1

\(\eta_1\) is no. of skeletal carbons in first step is 13. Reciprocal of the yield in this first step will be 100/80 i.e. 1.25. Therefore, \(w = 14 \times 1.25 = 17.50\)

Similarly, in the second step no. of skeletal carbons is 13 and reciprocal of yield will be 100/64 i.e. 1.56. So, \(w = 14 \times 1.56 = 21.84\)

RESULTS AND DISCUSSIONS

Two target molecules were selected by comparing the physical properties such as Heat of formation; Dipole moment & ionization potential etc. followed by calculation of \(W\) using Hendrickson’s equation for three Retro synthetic approaches. The \(W\) value was found to be lowest for the approach depicted in scheme 3. Therefore, this may be selected as a synthetic strategy for compound I & II.

CONCLUSIONS

This is very Simple hypothesis based on molecular descriptor, physico-chemical parameters and Hendrickson equation, not only to predict an active derivative of \(\text{—aryl ethanoic acid}\) but also to select a good synthetic route.

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REFERENCES.


