Available on line www.jocpr.com

Journal of Chemical and Pharmaceutical Research

J. Chem. Pharm. Res., 2010, 2(3):544-550

ISSN No: 0975-7384
CODEN(USA): JCPRC5

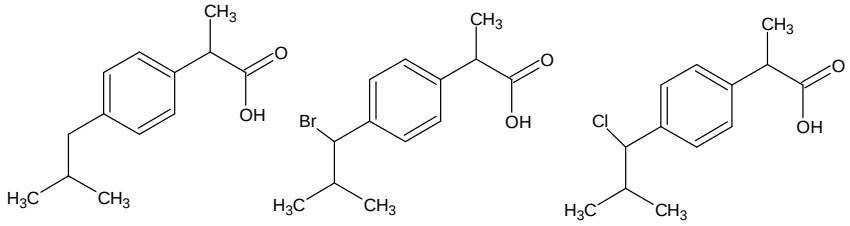
QSAR/QSPR: Designing of derivatives of α- aryl propanoic acid (NSAID) followed by selection of a good synthetic route through mathematical modeling

G. M. Nazeruddin*, S. B. Suryawanshi, Hassan A. Osman, Vijay H. Masand[≠] and Komalsingh N. Patil[≠]

Department of Chemistry, Poona College, Pune, Maharashtra, India
[≠] Department of Chemistry, Vidyabharati College, Amravati, Maharashtra, India

ABSTRACT

There are number of software such as WinMopac /Hyper chem. /Dragon etc. available commercially through which not only various derivatives of α- aryl propanoic acid can be designed but also various physical properties and number of molecular descriptor can be calculated, after comparing their physical properties and descriptors with lead compound Ibuprofen, the unknown compounds I & II are selected. A good synthetic rout can be predicted through mathematical modeling using particularly Hendrickson equation $W=\Sigma\eta iX^{li}$*, Where W=Sum of Weight, ηi- 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.*



Ibuprofen I II

Key words: Designing, Derivatives of α–aryl Propanoic acid (NSAID), Hendrickson's equation, Hypothesis

INTRODUCTION

In the early 1960s, Corwin Hansch [1] extended the concept of Linear –free energy relations (LFER) to describe the effectiveness of biologically-active molecule. This represented efforts to quantitatively relate the structure of a compound to its activity and resulting equations were aptly named quantitative structure activity relationships (QSAR). Today, these equations are also called quantitatively structure property relationship (QSPR). 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 some what replaced the traditional Hansch analysis. In the late 1980s and early 1990s combinatorial chemistry emergent diminished the importance of QSAR. Since large libraries of compounds bearing varying substitutents could be easily prepared, being able to predict activity was no longer necessary, simply by making all the compounds one can imagine and test them in high-throughput screens.

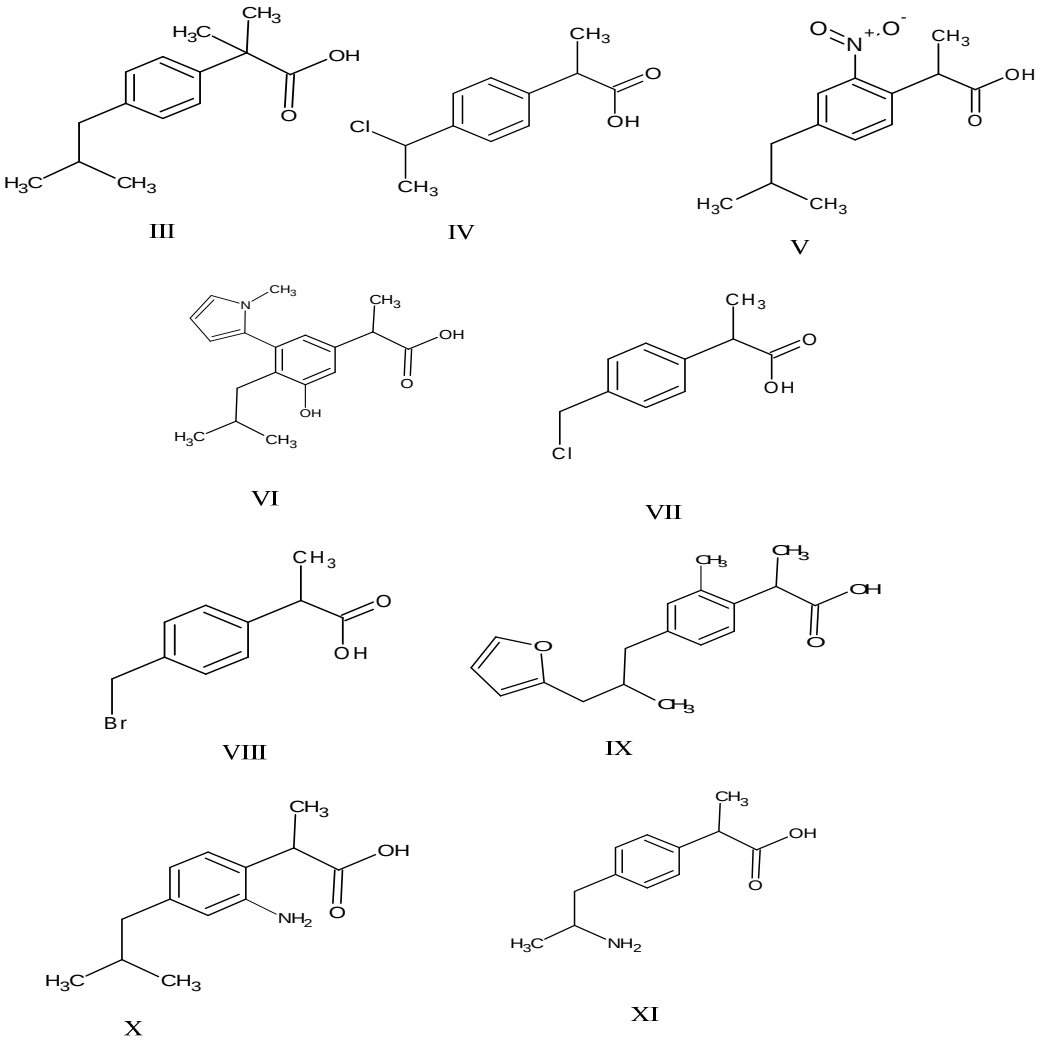
Since the middle 1990s, a technique called comparative molecular field Analysis (COMFA) [2] has emerged. This method uses highly complicated statistical analysis with large number of variable to correlate practical molecular properties to activity. However, Drug designing is still a big challenge. We wish to report here a simple hypothesis, in which certain physical properties such as Heat of formation, Dipole moment , Ionization potential Weiner index and log P should be calculated for newly design α–aryl propanoic acid derivatives and compared with the lead compound Ibuprofen .The derivatives which are having comparable properties are selected. By applying Hendrickson equation [3] $\Sigma \eta i X^{li}$. Even best synthetic route also can be predicted.

Computational Work and Calculation

There are number of software such as Winmopac /Hyper chem. /Dragon etc. are available in the market through them not only various new derivatives of α–aryl propanoic acid can be designed but also various physical properties and molecular descriptors [4] can be calculated. Similarly the same calculation can be done for the lead compound Ibuprofen followed by comparison of these values. New derivatives of α–aryl propanoic acid I & II are selected. For illustration, we have selected ten examples for calculation which are as under and results are given in table 1:

Table 1: Calculated values of various physical properties such as HOF, I.P., DM and log P of various derivatives of α aryl propanoic acid

Derivative	HOF	I.P	DM	Log P	Derivative	HOF	I.P	DM	Log P
Ibuprofen	-98.259	-9.691	-4.850	3.72	VI	-96.7	-8.86	-6.6	3.88
I	-94.186	-9.977	-3.617	3.35	VII	-86.9746	-10.0314	-3.190	2.12
II	-103.220	- 9.993	- 3.698	3.78	VIII	-76.3237	-9.9977	-2.942	2.55
III	-103.27	-9.330	-1.84	4.07	IX	-92.47	-9.12	4.7	4.69
IV	-93.297	-10.009	-3.232	2.47	X	-101.82	-8.70	-5.36	2.44
V	-96.286	-10.144	-4.05	3.45	XI	-96.53	-9.470	-0.567	1.44



Log P which is considered as very important to predict the drug likeness of any compound. The comparison of log P values shows that compound no. I and II are very similar to ibuprofen. More over Heat of formation (H.O.F) and other parameters are also close to Ibuprofen; hence these may act as very good anti-inflammatory drugs like Ibuprofen. To get better results we have carried out Quantum Mechanical calculations also. The ESP contour diagram for Ibuprofen and its derivatives I and II are shown in figure 1, 2 and 3 respectively.

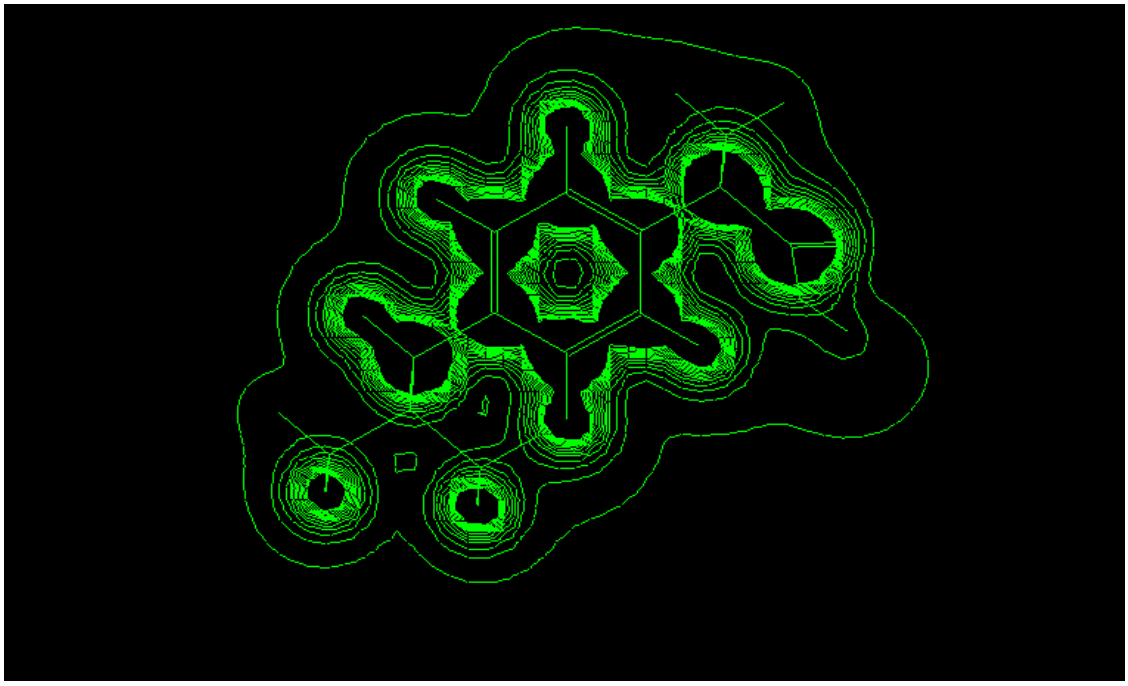


Fig 1: Ibuprofen Method: PM3 single point ESP and Log P = 4.07, W = 465

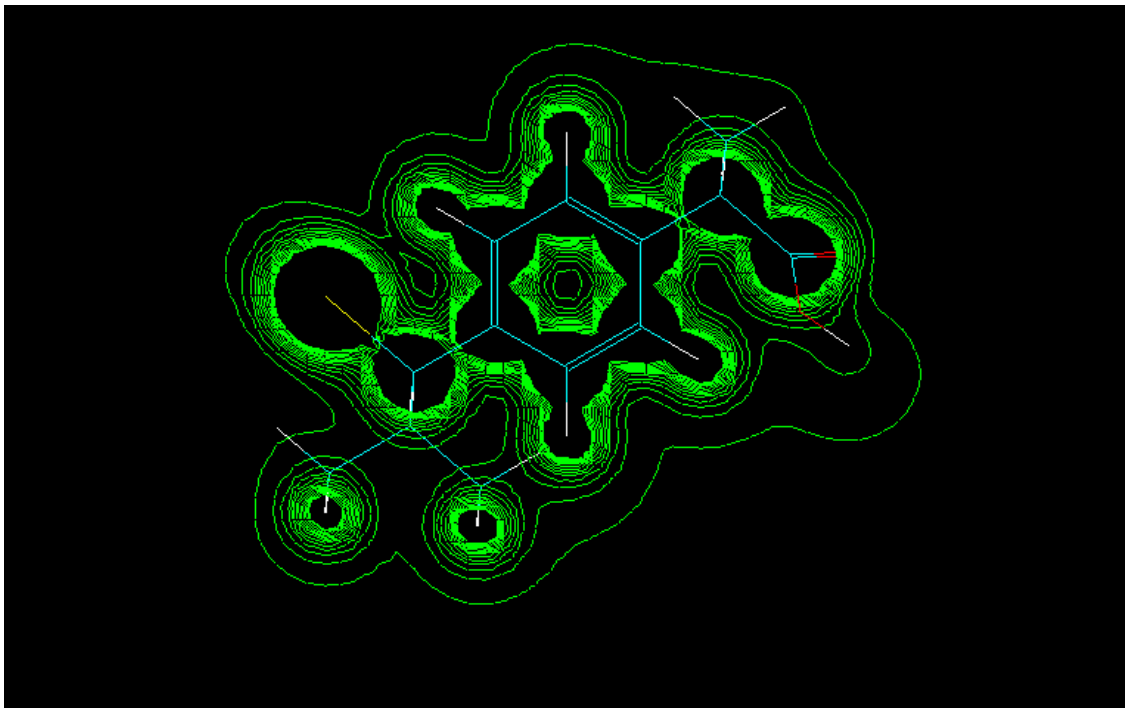


Fig 2: Derivative-II Method: PM3 single point ESP and Log P = 3.35, W = 470

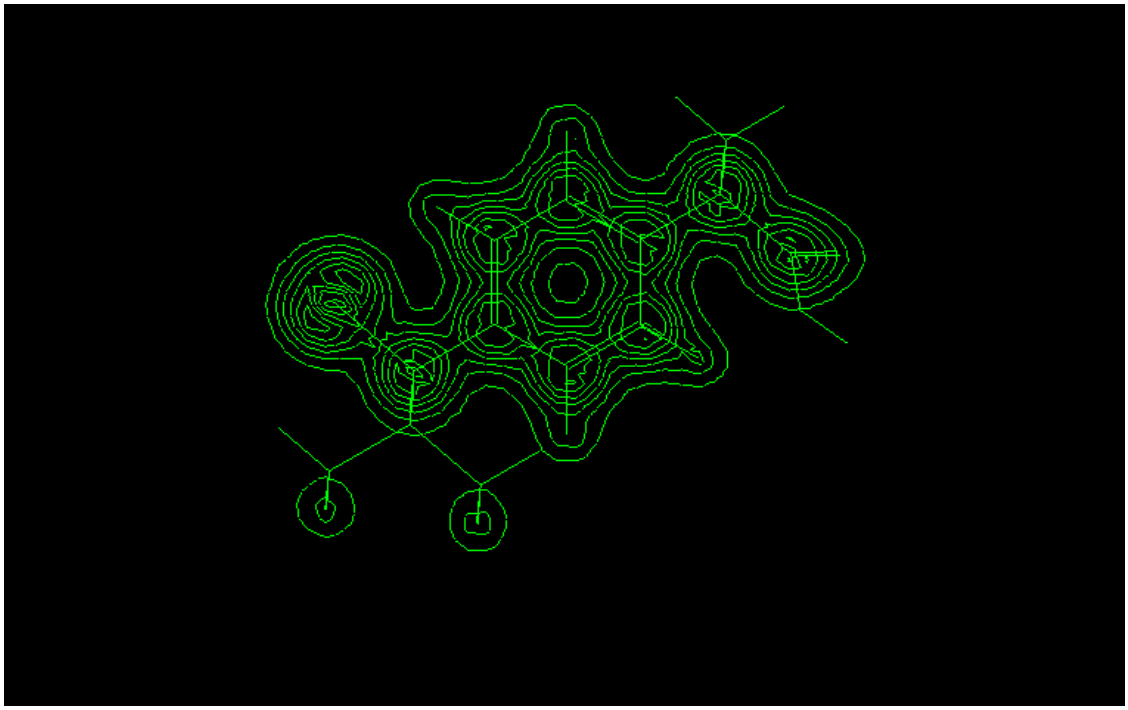


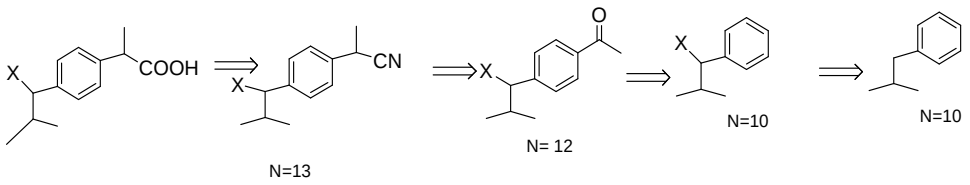
Fig 3: Derivative-I Method: PM3 single point ESP and Log P = 3.78, W = 470

The ESP shows that the negative and positive regions in Ibuprofen and derivative-I are very same hence bromo derivative may be as active as ibuprofen. Log P values further supports this conclusion.

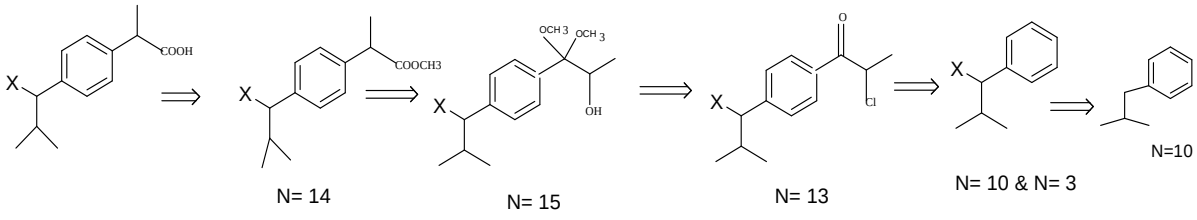
Retrosynthetic Analysis:

Prediction of good synthetic rout is as another task. To select a good synthetic path by retro synthetic approach is not very easy task, because of number of types of reactions and reagents in organic chemistry. To overcome these difficulties and to select a good synthetic route various approaches like SYNGEN, CAOS, CAMEO etc. [5, 6] guide us. All the approaches have their own advantages & limitations. Plausible retro synthetic approaches of target molecules are depicted in scheme 1, 2 and 3.

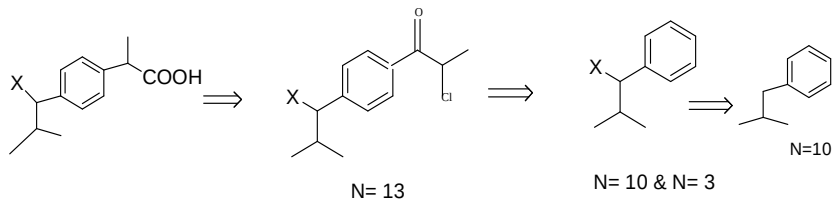
Scheme: 1, 2, 3 [7, 8, 9, 10]



W = 16.25 + 19.5 + 24 + 25 + 30 = 114.75



W = 17.5 + 22.5+ 26+ 25+ 7.5 + 30 = 128.5



W = 16.25 + 15 + 4.5 + 20 = 55.75

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:

$$W=\Sigma\eta iX^{l}$$

Where W = Sum of Weight, ηi- is number of skeletal carbons in each piece, and X is reciprocal of the average yield for each step. The whole quantity X^{li} is related to number of steps l, for each step yield is presumed to be 80 %.

To illustrate the equation let us take scheme 1

ηi- is number of skeletal carbons in first step is 13.Reciprocal of the yield in the first step will be 100/80 i.e. 1.25. Therefore, w =13x1.25 =16.25

Similarly, in the second step no. of skeletal carbons is 13 and reciprocal of yield will be 100/64 i.e. 1.5.So, w = 13x1.5 =19.5 and so on.

RESULTS AND DISCUSSION

Two target molecules I & II were selected by comparing the physical properties such as Heat of formation, Dipole moment & ionization potential. Followed by three Retro synthetic approaches were selected to calculate W using Hendrickson's equation. It is found that scheme number 3,

the W value is the lowest. Therefore this may be selected as a synthetic strategy for compounds I & II.

CONCLUSION

This is very Simple hypothesis based on molecular descriptor and physico-chemical parameters and Hendrickson equation not only to predict an active derivative of α–aryl propanoic acid but also to select a good synthetic route.

Acknowledgement
Authors are thankful to Anjuman Khairul Islam Trust, Mumbai for financial assistance

REFERENCES

[1] C. Hansch, R.M.Muir, T. Fujita, , et.al., *J. Am Chem. Soc*. 85(**1963**) 2817-2824.
[2] R.D.Cramer, D.E. Patterson and J.D.Bunce, *J. Am. Chem. Soc*. 110 (**1988**) 5959–5967.
[3] J.R. Hendrickson, *Acc. Chem. Res.* 19 (**1986**), 274 -281.
[4] R.Todeschini and V.Consonni; "Handbook of Molecular Descriptor" Wily-vch, (**2000**) 303-307
[5] J.R Hendrickson, *Acc. Chem. Res.*, 19 (**1986**), 274 -281.
[6] J.R. Hendrickson., *J. Am. Chem. Soc*., 99 (**1977**) 5439-50.
[7] J.R. *J. Chem. Inf. Compt. Sci*., 19 (**1979**), 129-146;
[8] T.Sakai, Kazuyoshi, M. S. Tsuboi, A.Takida,. M Utaka & S Torii et.al, A, *Bull.Chem.Soc.Jpn*., 62 (**1989**)3537-3541.
[9] Sonawane H. R., Nanjundiah B. S. & Nazeruddin G. M., *Indian Journal of Chemistry*, 33 (**1994**) 705-706.
[10] Sonawane H. R, Kulkarni D.G and. Ayyangar N. R, *Tett. Lett.*,31 (**1990**) 7495 -7496