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Research Article

Computer Aided Designing of New Non Steroidal Anti Inflammatory Drugs (NSAIDs) considering Ibuprofen as a Lead Compound followed by suggestion of a Good Synthetic Route

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Abstract

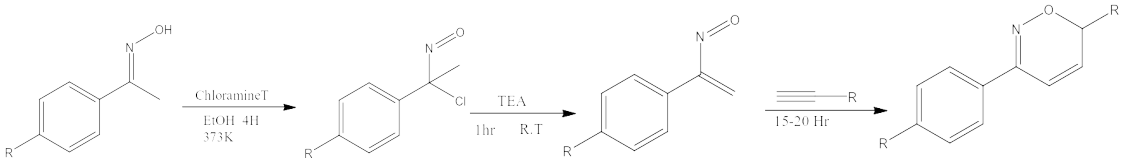
Discovery of a new drug is a very difficult task. Pharmaceutical and biotechnology companies need to make huge investments in the discovery of a single drug. Most pharmaceutical or biotechnology companies claim that it costs anywhere between $800 million to $900 million and a time span of twelve to fifteen years to discover a new drug. In silico-chemico-biological approach computer plays very important role in discovery of new dug, not only it can save money but also time, and are believed to offer means of improved efficiency for the industry. 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, HOMO (Highest occupied molecular orbital) and LUMO (lowest unoccupied molecular orbital) energies and pka by using different software such as VegaZZ, Mopac, ADME and ChemDraw etc. and compared them with the lead compound, Ibuprofen. The newly designed compounds, which are having the comparable properties with the lead compound, are selected and a good synthetic rout is suggested by following rules of green chemistry.

Key words: Designing, 6*H*-1, 2-Oxazine and its derivatives, Physicochemical Properties

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 somewhat 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 substituent's could be easily prepared, being able to predict activity was no longer necessary, simply make 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. Pharmaceutical and biotechnology companies need to make huge investments in the discovery of a single drug. Most pharmaceutical or biotechnology companies claim that it costs anywhere between $800 million to $900 million and a time span of twelve to fifteen years to discover a new drug. In silico-chemico-biological approach[3] computer plays very important role in discovery of new dug, not only it can save money but also time, and are believed to offer means of improved efficiency for the industry. 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. Pharmaceutical and biotechnology companies need to make huge investments in the discovery of a single drug. Most pharmaceutical or biotechnology companies claim that it costs anywhere between $800 million to $900 million and a time span of twelve to fifteen years to discover a new drug. In silico-chemico-biological approach computer plays very important role in discovery of new dug, not only it can save money but also time, and are believed to offer means of improved efficiency for the industry. 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. This is continuation of our earlier work[4] We wish to report here a simple hypothesis, in which certain physical properties such as Heat of formation, Dipole moment , Ionization potential ,HOMO,LUMO energies, should be calculated for newly design 6*H*-1,2-Oxazine by Cyclization of Ketoximes with Derivatives of Terminal Acetylene Compounds and compared with the lead compound Ibuprofen .The derivatives which are having comparable properties are selected and a good synthetic rout is suggested by following rules of green chemistry.



1a, R1=H; R2=CH2OH 2a, R1=H; R2=PH 3a, R1=H; R2=CO2Et 4a, R1=H; R2=C3H7

1b, R1=CH3 2b, R1=CH3 3b, R1=CH3 4b, R=CH3

1c, R1=Cl	2c, R1=Cl	3c, R1=Cl	4c, R1=Cl
1d, R1=OCH3	2d, R1=OCH3	3d, R1= OCH3	4d, R1=OCH3
1e, R1=NO2	2e, R1=NO2	3e, R=NO2	14e, R1=NO2

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 can be designed but also various molecular descriptors[6] can be calculated. Similarly the same calculation can be done for the lead compound Ibuprofen followed by comparison of these values. Various compounds were designed and physical properties were calculated, However for comparison twenty compounds, calculations are depicted in Table-1.

Sr. No.	Mol. ID.	Heat of Formation	Ionization potential	Dipole	MLOGP	ALOGP
1	1a	15.51	9.2	2.44	1.63	1.71
2	1b	6.12	9.04	2.43	1.91	2.20
3	1c	8.88	9.10	2.447	2.18	2.38
4	1d	-22.64	8.86	1.60	1.37	1.70
5	1e	7.08	9.78	6.24	1.63	1.61
6	2a	102	9.15	2.71	3.55	3.84
7	2b	79	9.01	2.72	3.79	4.32
8	2c	82	9.07	2.99	4.06	4.50
9	2d	50.46	8.83	1.69	3.22	3.82
10	2e	80.10	9.76	6.88	3.48	3.73
11	3a	-19.49	9.54	5.29	2.10	2.52
12	3b	-29	9.37	5.62	2.37	3.01
13	3c	-26.00	9.39	4.48	2.63	3.19
14	3d	-57.91	9.15	5.29	1.85	2.51
15	3e	-27	10.15	3.27	2.15	2.42
16	4a	43.06	9.15	2.67	3.02	3.58
17	4b	33.63	9.01	2.71	3.28	4.07
18	4c	36.35	9.07	3.03	3.55	4.25
19	4d	34.76	8.83	1.78	2.71	3.57
20	4e	34.50	9.75	6.83	2.95	3.48
21	Ibuprofen	-	9.398	2.229	3.23	3.582

Results and Conclusion

After comparing the various values of MLOGP, ALOGP, Austin Model 1 IP, Austin Model 1 dipole, the methoxy methyl and chloro derivatives are having quite good comparable properties with Ibuprofen.

Reference

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