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Modeling of IC^{50} (5-LOX And COX) Activity of Phenol Derivatives Against Leukemia Cells

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ABSTRACT

Phenols derivatives show different inhibitory selectivities towards 5-LOX and COX and induce cell death in leukemia cell lines. For modeling of activity against Leukemia cell lines K562, HL-60, Raji, MOLT4, 32D, Leukocytes, NIH3T3 etc. of phenol derivatives we used three descriptors Mor20e, Mor04m and RDF045m. 5-LOX and COX Values of Bobels are used to build model for Predicted Activity for 5-LOX and COX**.**

Key Words: 5-LOX, COX**,** QSAR, QSPR, 3D MoRSE Descriptors, RDF Descriptors, IC_{50}

INTRODUCTION

In the present study we shall use a series of phenol derivatives for QSAR & QSPR studies. Phenol's derivatives like Bobel-24[1] (2,4,6-Triiodophenol or AM-24) induce caspase-independent mitochondrial cell death in leukemia cells inhibited by Mys. 2,4,6-Triiodophenol was originally designed as a potential anti-inflammatory drug with inhibitory activities against COX (cyclooxygenases) and LOX (lipoxygenases). It is found that it exerts a potent cytotoxic activity against several leukemia cell lines. we predicted the antiproliferative activity of the Phenol derivatives on leukemia cell lines. Its found that it exerts a potent cytotoxic activity against several leukemia lines. There phenols derivatives show different inhibitory selectivities towards 5-LOX and COX and induce cell death in leukemia cell lines.

Prostaglandins and leukotrienes are signaling mediators generated from arachidonic acid by the action of cyclo-oxygenases (COX-1 and COX-2) and 5-lipoxygenases (5-LOX), respectively. COX is expressed in most cells, whereas 5-LOX is mainly expressed in inflammatory cells such as polymorphonuclear leukocytes[2]. Leukotrienes modulate the growth of several cell types and it has

also been shown that various 5-LOX metabolites from arachidonic acid regulate murine and human hematopoiesis[3]. COX and 5-LOX inhibitors are used as anti-inflammatory drugs[4]. Cytotoxic mechanisms of phenol's derivatives do not seem to be directly related to the inhibition of these enzymatic activities. However, it is important to note that the IC_{50} of these compounds for all the tested cell lines are within the concentration range clinically attainable[5]. Interestingly, many phenol's derivatives show lower cytotoxic activity on nontransformed cells (32D, NIH3T3, leukocytes) than in leukemia cell lines, either from myeloid origin (K562, HL60) or lymphoid origin (Raji, MOLT).

MATERIAL AND METHODS

To calculate the different Molecular Descriptor like constitutional, topological, geometrical, charge e.g. 3D-MoRSE[6-7] (3D-Molecular Representation of Structure based on Electron diffraction), RDF[8-9] (radial distribution function); DRAGON Software used in the study.

Activities of phenol derivatives are correlated with Topological indices mention above. The correlations are than subjected to regression analysis using the method of least squares. In each case we have multiple linear regression analysis which gives linear regression models shown in equation 1.1 and 1.2.

$$5\text{-LOX}_{predicted} = (-4.72575 \times Mor20e) + (-1.12911 \times Mor04m) + (-0.45334 \times RDF045m) + 7.370393 \quad ...1.1$$

$$COX_{predicted} = (38.00935 \times Mor20e) + (5.192296 \times Mor04m) + (9.387485 \times RDF045m) - 28.3476 \quad ...1.2$$

By regression Statistics we get correlation coefficient is 0.99, r^2 is 0.98, and Standard Error approx zero for model for COX inhibition which described by equation 1.2

RESULT AND DISCUSSIONS

For modeling of activity against Leukemia cell lines K562, HL-60, Raji, MOLT4, 32D, Leukocytes,

Table (1.2): Predicted IC50 (µmol/L) for COX and 5-LOX

S.No	Phenol Derivative	IC_{50} (µmol/L) COX	5-LOX
1	4-OCH_3	26.2817	1.01481
2	4-OC_2H_5	38.044	Inactive
3	4-OC_3H_7	16.6926	2.73391
4	4-OC_4H_9	51.4389	0.58662
5	4-OC_6H_{13}	38.2196	Inactive
6	H	Inactive	4.69023
7	4-NO_2	Inactive	4.65095
8	4-Cl	23.8554	3.42172
9	4-I	22.8598	1.53725
10	4-CHO	3.81314	4.34386
11	4-F	Inactive	5.06063
12	4-NH_2	7.1542	3.64964
13	4-OH	1.61331	4.38208
14	4-CH_3	6.70446	3.6286
15	4-C_2H_5	7.29642	3.54116
16	4-$NHCOCH_3$	20.5741	2.96949
17	4-CN	Inactive	4.68031
18	4-OC_6H_5	35.8702	0.70736
19	Bisphenol-A	69.266	Inactive
20	4-Br	3.87646	3.96552
21	4-C $(CH_3)_3$	32.9638	1.7658
22	3-NO_2	Inactive	4.41005
23	3-$NHCOCH_3$	22.351	2.51856
24	3-Cl	25.7883	2.976
25	3-$C(CH_3)_3$	16.9575	3.19239
26	3-CH_3	3.92158	3.83743
27	3-OCH_3	6.77432	3.57635
28	3-N $(CH_3)_2$	15.2932	2.61761
29	3-C_2H_5	2.28685	4.03734
30	3-Br	3.31985	3.82402
31	3-CN	Inactive	4.81261
32	3-F	Inactive	4.88429
33	3-OH	1.15232	4.22199
34	3-NH_2	7.37565	3.44287
35	2-CH_3	3.95216	3.88376
36	2-Cl	25.0388	3.07856
37	2-F	Inactive	4.60425
38	2-OCH_3	25.8719	2.77006
39	2-C_2H_5	25.5492	2.69282
40	2-OH	4.39628	3.913
41	2-OH, 4CH_3	12.4433	2.99931
42	2-NH_2	8.63339	3.35983
43	2-CN	Inactive	4.82947
44	2-NO_2	Inactive	4.36136
45	2-Br	7.62182	3.2431
46	2-C $(CH_3)_3$	10.9452	4.02913
47	4-C_3H_7	11.4972	3.10147
48	4-C_4H_9	12.346	3.06799
49	4-C_5H_{11}	19.9172	2.10369

NIH3T3 etc. of phenol derivatives we used three descriptors Mor20e, Mor04m and FDI. Values of Bobels are used to build model for Predicted Activity for 5-LOX and COX**.** By regression Statistics we get correlation coefficient is 0.99, r^2 is 0.98 and Standard Error is very low for Model for 5-LOX inhibition which described by equation 1.1. And correlation coefficient is 0.99, r^2 is 0.98, and Standard Error approx zero for model for COX inhibition which described by equation 1.2.

CONCLUSION

By the study of effect of phenol derivatives on 5-LOX and COX we found that IC_{50} (µmol/L) of 4-OC4H9 shows high potential for 5-LOX and 3-OH for COX. The IC_{50} value of phenol derivatives for 5-LOX and COX is depend on the substitute and its the position.

As size of Leophobic groups is increased than value of IC_{50} is decreased for 5-LOX e.g. 2.103< 3.067< 3.1014 for respectively 4-C_5H_{11}, 4-C_4H_9, 4-C_3H_7. In case of Leophobic groups, para derivatives have low value, meta has high and ortho has higher value of IC_{50} for 5-LOX inhibition e.g. 3.62, 3.83, 3.88 for methyl. However for ethyl ortho derivatives have min and meta has higher value. As electro negativity is increased value of IC_{50} is also increased.(4-I < 4-Br < 4- Cl <4-F). Electron withdrawing group like -NO_2 has higher value at para and min value at ortho. However in case of –CN has higher value at para- and min value at ortho-. But in case of –Cl has higher value at para- and min value at meta-. This is due to hydrogen bond n inductive n mesomeric effect. While electron releasing group like -OH has higher value at ortho- and min value at para-.

Effect of phenol derivatives on COX activity is depend on size of Leophobic groups also, as size of Leophobic groups is increased than value of IC_{50} is increased for COX e. g. 7.29, 11.4, 12.3, 19.9 for respectively 4- C_2H_5, 4-C_3H_7, 4-C_4H_9, 4-C_5H_{11}. In case of Leophobic groups, meta- derivatives have low value, ortho- has high and para- has higher value of IC_{50} for COX inhibition e.g. 3.92, 3.95, 6.70 for methyl. However for ethyl ortho derivatives have higher value. As electro negativity is increased value of IC_{50} is also increased. (4-I < 4- Cl). Electron withdrawing group like -NO_2 has higher value at ortho and min value at para-. However in case of –CN has higher value at para- and min value at meta-. But in case of –Cl has higher value at meta- and min value at para-. This is due to hydrogen bond n inductive n mesomeric effect. While electron releasing group like -OH has higher value at ortho- and min value at meta-.

In conclusion, this work describes the cytotoxic effect of a new series of molecules on leukemia cells by inducing a caspase-independent cell death.

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