CHAPTER 4

LITERATURE SURVEY: CANCER AND QSAR

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INTRODUCTION

During the last fifteen years many attempts have been made for studying quantitative correlations of different types of anticancer compounds of diverse molecular types like nitrosoureas dialkanol amine, diaminitriazines, aniline esters, quinozolines analogues, substituted triazines, aromatic nitrogen mustards, triazinoimidazoles, thiosemicarbazone, bisquaternary ammonium heterocycles etc. It is very difficult to get meaningful generalization about the particular physicochemical parameter responsible for anticancer activity because of the use of different types of biological models. Few examples of anticancer agents on which QSAR has been applied are gives as follows:

1. QSAR Studies of PC-3 cell line inhibition activity of TSA and SAHA-like hydroxamic acids

Quantitative structure–activity relationships (QSAR)has been performed by Di-Fei Wang Olaf Wiest, Paul Helquist, Hsuan-Yin Lan-Hargest and Norbert L. Wiech on the series of new trichostatin A (TSA)-like hydroxamic acids for the inhibition of cell proliferation of the PC-3 cell line ,with a hope to find important physico chemical parameter that effects its activity.[129] The best regression model shows that the PM3 atomic charge on the carbonyl carbon in the CONHOH moiety(Qco), globularity (Glob), and the hydrophilic component of the solvent-accessible surface area (FISA) describe the IC_{50} of 19 inhibitors of the PC-3 cell line with activities ranging over five

orders of magnitude with an R^2=0.92 and F=59.2. This information will be helpful in the further design of novel anticancer drugs for treatment of prostate cancer and other diseases affected by HDAC inhibition.

2. Quantitative Structure-Activity Relationship Study of Histone Deacetylase Inhibitors

Histone deacetylases (HDACs) have become a novel target for the discovery of drugs against cancer and other diseases. as it play a critical role in gene transcription The authors have performed QSAr studies on histone deacetylase inhibitors (HDACIs) as novel anticancer drugs[130] . They have reported a comprehensive quantitative structure-activity relationship (QSAR) study of HDACIs in the hope of identifying the structural determinants for anticancer activity. They have identified, collected, and verified the structural and biological activity data for 124 compounds from various literature sources and performed an extensive QSAR study on this comprehensive data set by using various QSAR and classification methods. A highly predictive QSAR model with R^2 of 0.76 and leave-one-out cross-validated R^2 of 0.73 was obtained. The overall rate of cross-validated correct prediction of the classification model is around 92%. The QSAR and classification models provided direct guidance to their internal programs of identifying and optimizing HDAC inhibitors

3. QSAR Study on Some Substituted Glutamine Analogs as Anticancer Agents

Glutamine is a major substrate for the cancer cell after glucose. It supplies major portions of nitrogen atoms in DNA and RNA synthesis Structural variations of glutamine may antagonize enzymes involved in DNA and RNA synthesis. A QSAR

(quantitative structure-activity relationship) study was performed by authors on some of its analogs in order to get insight about important physico chemical parameters influencing its anticancer acivity as well as to overcome the symmetry restriction of *De Novo* model and time consuming determination of partition coefficients of Hansch analysis. The QSAR study was performed using the Fujita Ban model. A good QSAR model was obtained considering anticancer activity, *i.e.*, log % of tumor weight inhibition which expresses the biological activity, of thirty 5-N-substituted-2-(substituted benzenesulphonyl)-L-glutamines as dependent variable and substitutional contribution at specific position as independent variable as evidenced by the statistical data (r = 0.8122, s = 0.1196, F = 1.3755). Substituent at the 3' and 5'-positions of the phenyl ring lead to a general decrease in anticancer activity, but a Br at the 4'-position and a Cl at the 2'-position were positively correlated to the total activity[131]

4. Anti-Cancer Activities of 1,4-Naphthoquinones: A QSAR Study

Certain drugs used in therapy of solid tumor contain Quinone moiety viz. anthracyclines, daunorubicin, doxorubicin, mitomycin, mitoxantrones and saintopinThe cytotoxic effect of Quinone is due to **(1)** formation of semiquinone radical which transfer an electron to oxygen to form superoxide ,which is catalysed by flavoenzymes as NADPH-cytochrome-P-450 reductase.The hydroxyl ion generated by super oxide of quinone and semiquinone,cause DNA stand breaks.**(2)** inhibition of DNA topoisomerase-II.the author performed QSAR studies on different series of 1,4-Naphthoquinones against four different cancer cell lines that are L1210, A549, SNU-1, and K562, to understand the chemical-biological interactions. The

results showed that the activities of 1,4- naphthoquinones depend largely on hydrophobic parameter.[132]

5. Quantitative Structure-Antitumor Activity Relationships of Camptothecin Analogues

The authors carried out QSAR studies of 167 tested camptothecins analogs using the mean 50% growth inhibitory concentrations (GI50) for 60 cell lines as the dependent variables[133]. Different statistical methods, including stepwise linear regression, principal component regression (PCR), partial least-squares regression (PLS), and fully cross-validated genetic function approximation (GFA) were applied to construct quantitative structure-antitumor relationship models. For our data set, the GFA method performed better in terms of correlation coefficients and cross-validation analysis. A number of molecular descriptors were identified as being correlated with antitumor activity. Included were partial atomic charges and three interatomic distances that define the relative spatial dispositions of three significant atoms (the hydroxyl hydrogen of the E-ring, the lactone carbonyl oxygen of the E-ring, and the carbonyl oxygen of the D-ring). The cross-validated r^2 for the final model was 0.783, indicates a predictive QSAR model

6. Cyclohexyl-octahydro-pyrrolo[1,2-a]pyrazine-based inhibitors of human N-myristoyltransferase-1

N-myristoyltransferase (NMT), catalyzes the attachment of myristate to the N-terminus of an acceptor protein., is an emerging therapeutic target. The authors carried outQSAR studied on 32 cyclohexyl-octahydro-pyrrolo[1,2-*a*]pyrazine (COPP)

derivatives with IC_{50} values ranging from 6 micromolar to millimolar concentrations. A QSAR equation ($r^2 = 0.72$) was derived for the series.[134] The most potent inhibitor (**24**, containing 9-ethyl-9H-carbazole) demonstrated competitive inhibition for the peptide-binding site of NMT-1, and noncompetitive inhibition for the myristoyl-CoA site. , these studies establish an efficient assay for screening for inhibitors of human NMT, and identify a novel family of inhibitors that compete at the peptide-binding site and have activity in intact cells.

7. QSAR modeling of thalidomide analogues as antiangiogenic and prostate cancer inhibitor

QSAR studies have been carried out by authors on thalidomide analogues acting as dual inhibitors of angiogenesis and prostrate cancer[135] The studies showed that the presence of fluorine atom is essential for both activities. Studies highlighted that LUMO and partition coefficient play a significant role in antiangiogenic activity while repulsive energy and molar refractivity contribute to anticancer activity.

8. QSAR Study on 5-N-Substituted-2-(Substituted Benzenesulphonyl) Glutamines as Antitumor Agents

Glutamines,a non essential amino acid supplies its amide nitrogen in the bio synthesis of other amino acids,purine and pyrimodine bases and helps in tumor growth .Hence the efforts were made to synthesise series of Glutamine analogs and QSAr studies were performed to identify important physico chemical parameters which influence their activity.[136]The studies revealed that aliphatic substitution of glutamines analogsmight have played an important role in hydrophobic interaction with possible glutamine receptor.The studies highlighted that field effect parameter at R_1 position

and resonance at R_2 position are important for activity At least one free hydrogenatom in amide moiety is essential for activity

9. QSAR studies on pyrrolo(2,1-d)(1,2,3,4) tetrazinones,a new classof azolotertazines

Authors have performed QSAR studies on some pyrrolo(2,1-d)(1,2,3,4) tetrazinone series of antitumor drugs,usingphysico chemical parameterssuchas equalized electronegativity(X_{eq})Molecular connectivity,($^1X^b$) and hydrophobicity,log P.Anticancer activity of these comounds in COLO-205 cancer cell has been found to correlate well with X_{eq}. The presence of $–CONH_2$ group was found to be important for activity[137]

10. QSA R Analysis of the Anticancer Activity of 2, 5-Disubstituted 9-Aza-Anthrapyrazoles

The authors analyzed anticancer activity of 35 2,5-disubstituted 9-Aza-Anthrapyrazoles (9-aza-APs) employing the Best Multiple Linear Regression (BMLR) for selection of the best descriptors The steric and electrostatic interactions between a probe atom (H^+) and a set of aligned molecules were assessed using the comparative molecular field analysis method. The results from 2D- and 3D-QSAR analyses show that the anticancer activity of the studied series of 9-aza-APs is strongly dependent on electrostatic interactions. A binding of these derivatives to DNA has been discussed as a key factor determining the cytotoxic activity against tumor cell. The hydrogen-bond donor properties of the NH and OH groups in the studied series of compounds also play a key role in the binding process. The stable

ring structure of the 9-aza-APs also appears to be an important factor for the antitumor activity of the compounds.[138]

11. QSAR analysis of 1, 4 dihydro-4-oxo-1-(2-thiazolyl)-1, 8-naphthyridines with anticancer activity

In the present study the authors applied QSAR studies to a series of hundredcompounds belonging to 7-and 3- substituted 1,4 dihydro -4-oxo-1-(2-thiazolyl)-1,8-naphthyridines derivatives The chem-X(version2000)software was used to develop 3D QSAR models. The steric and electrostatic interactions between a probe atom (H^+) and a set of aligned molecules were assessed using comparative molecular field analysis method. Statistically relevant models were derived for both electrostatic and steric fields. A 2D model over a restricted series of close structural analogs were derived as well.A.number of conclusions on the relationship between the type and size of different substuituents and the antitumor activity of compounds were derived[139]

12. Quantitative structure-activity relationship studies of cyclooxygenase inhibitors: a comprehensive analysis

The authors performed quantitative structure-activity relationship (QSAR) analysis of 10 structurally diverse set of compounds recently reported as cyclo oxygenase (COX) inhibitors using C logP, aromatic substituent constants, and suitable indicator variables. These revealed several important physicochemical and structural requirements for COX-1, COX-2 inhibitory activity, and selective inhibition of COX-2 versus COX-1 among these novel ligands. Seventeen QSAR models reported herein provide interesting insights in understanding the hydrophobic, steric, electronic, and

structural requirements of COX inhibition amongst these individual set of compounds. These results may be used further to the design and development of selective COX-2 inhibitors among these newly reported COX inhibitors.[140]

13. Evaluation of electronic, lipophilic and membrane affinity effects on antiproliferative activity of 5-substituted-2-(2, 4-dihydroxyphenyl)-1, 3, 4-thiadiazoles against various human cancer cells

The QSAR studies of 5-substituted-2-(2,4-dihydroxyphenyl)-1,3,4-thiadiazoles set of antiproliferative activity against human cancer cell lines have been performed.[141]The principle factor for determination of activity of compounds is partial charge of nitrogen (q_{N3}, q_{N4}) and carbon (q_{C5}) atoms of the 1,3,4-thiadiazole ring. Biological effect is also connected with molar refractivity (CMR) and lipophilicity of derivatives The analysis of the QSAR equations for individual cell lines indicates both similarities and differences of electron, steric factors and hydrophobic–hydrophilic character of the analogues of the tested set affecting the antiproliferative activity. The partial charge of nitrogen (q_{N3}, q_{N4}) and carbon (q_{C5}) atoms of 1, 3, 4-thiadiazole ring, molecular refractivity and lipophilicity provide valuable information and have a significant role in the assessment of the antiproliferative activity of compounds.

14. Quantitative Structure-Activity Relationship Analysis of Inhibitors of the Nicotine Metabolizing CYP2A6 Enzyme

The purpose of this study was to develop screening and in silico modeling methods to obtain accurate information on the active center of CYP2A6, a nicotine oxidizing

enzyme. The inhibitory potencies of 26 naphthalene and 16 non-naphthalene derivatives were determined for human CYP2A6 and mouse CYP2A5 enzymes. Several comparative molecular field analysis (CoMFA) models were developed to find out what types of steric and electrostatic properties are required for potent inhibitors.[142] The IC_{50} values of the tested compounds varied from 0.55 to 35 400 μM for CYP2A6 and from 1 to 1500 μM for CYP2A5. The generated CoMFA models were able to accurately predict the inhibition potencies of an external test set of chemicals. Potent and specific inhibitors of the CYP2A6 enzyme can be used in the future to increase nicotine bioavailability and thus make oral nicotine administration feasible in smoking cessation therapy.

15. QSAR analysis of meclofenamic acid analogues as selective COX-2 inhibitors

The use of quantitative structure–activity relationships, since its advent, has become increasingly helpful in understanding many aspects of biochemical interactions in drug research. This approach was utilized to explain the relationship of structure with biological activity of selective COX-2 inhibitors. Presented herein is a series of 21 derivatives of meclofenamic acid with selective COX-2 inhibitory activity. Several statistically significant regression expressions were obtained for both COX-1 and COX-2 inhibition using sequential multiple linear regression analysis method. Two of these models were selected and validated further, which revealed the importance of Kier molecular flexibility index for COX-2 inhibitory activity and the number of hydrogen bond donor atoms for COX-1 inhibitory activity. Additionally, linear correlation of molecular flexibility with COX-1 and COX-2 inhibitory activities

revealed that flexibility of molecules at COX-2 active site can improve the selectivity of COX-2 inhibitors.[143]

16. QSAR Studies on a Series of 7, 8-Dialkyl-1, 3-diaminopyrrolo-[3, 2-*f*] quinazolines with Anticancer Activity

The quantitative structure-activity relationship (QSAR) studies on a series of 7, 8-dialkyl-1,3-diaminopyrrolo-[3,2-f]quinazolines, dihydrofolate reductase (DHFR) inhibitors as potential anticancer agents, have been carried out.[144] Some QSAR models based on their lipophilic and steric parameters were built up *via* a stepwise regression analysis. It is very interesting to find that the established optimal QSAR equation involves only two descriptors: lipophilicity indexes Clog *P* and Clog P^2. The results show that the lipophilicity is a main factor affecting the anticancer activity of this series of antimetastatic agents, and the obtained equation describes a parabolic correlation between pIC_{50} and Clog *P*, and indicates a suitable range of Clog *P* (around 4.43) being very important for optimal pIC_{50} values. These QSAR studies can offer some useful references for understanding the action mechanism and performing the molecular design or modification of this series of antimetastatic agents.

17. Quantitative Structure-Activity Relationship Analysis of New Schiff Bases of Hydroxysemicarbazide as Potential Antitumor Agents

Thirty Schiff bases of hydroxysemicarbazide (Ar-CH=NNHCONHOH) have been synthesized and tested against L1210 murine leukemia cells. The IC_{50} values were found to be in a range from 2.7×10^{-6} to 9.4×10^{-4} M. A total of 17 out of the 30

compounds had higher inhibitory activities than hydroxyurea against L1210 cells Quantitative structure-activity relationship (QSAR) analysis showed that, besides the essential pharmacophore (-NHCONHOH), hydrophobicity, molecular size/polarizability (calculated molar refractivity), and the presence of an oxygen-containing group at the ortho position (I) were important determinants for the antitumor activities. In conclusion, the results obtained in this study show that several Schiff bases of hydroxysemicarbazide are potent inhibitors of tumor cells and warrant further investigation as cancer chemotherapeutic agents.[145]