5-benzyl-3-(9H-yl) IMIDAZOLIDINE-2, 4-dione: A SMART BIOMOLECULAR SENSITIVE MATERIAL

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Abstract

Cancer is considered to be one of the most dangerous diseases in the world. Hydantoin based chemo compounds are well known as anticancer agents. The present article reports biological activities of 5-benzyl-3-(9H-yl) imidazolidine-2, 4-dione. Quantitative structure activity relationship (QSAR) and computer simulation methodology have been employed for the systematic study of this chemo molecule to understand its sensitivity. The chemo compound under present investigation is found to be a good anticancer agent. There is further scope for laboratory synthesis and testing to prove practical applicability of this biomaterial.

Keywords: Biological Activity, Computer Simulation, QSAR, Descriptors, Anticancer Agent.

Introduction

Apart from advanced researches the human society even in the 21st century, is facing to the curses of numerous diseases like Cancer, Acquired Immune Deficiency Syndrome (AIDS), Tuberculosis, Diabetes, Cardio-vascular diseases etc. Research of millions of dollars has not yet found the right cure for these diseases. The danger of spreading of diseases is more in underprivileged and developing countries. World Health Organization (WHO) has prepared Global burden diseases report under the instruction of World Bank in the year 1990 to understand the issue of danger level of diseases in developing and under developed countries. According to this report (1), there would be the likelihood of health crisis in the

year 2020. Hence it is the urgent need to concentrate research on the most attributable diseases such as Cardio-vascular diseases, unipolar depression, cerebrovascular disease, Chronic Lung disease, and Lower respiratory track diseases, HIV, Tuberculosis and Cancer(2). This report insists on need to have advanced tools to fight against the challenges due to the above mentioned diseases. Failing may result in pandemonium in the civilized world and uncontrolled spread of these threats. Hence the civilized world has to reinvent the wheel of progress. The essence of the QSAR methodology is to develop a relationship between an observed property and structural features of a molecule. By considering a set of molecules, a predictive model is developed that can then be used to predict the activity of other molecules. In this research work the QSAR and computer simulation methodology has been used to find the sensitivity of 5-Benzyl-3-(9H-yl) Imidazolidine-2, 4-Dione, the biomolecular material, in light of anticancer agent for chemotherapy.

Experimental

Present study deals with the QSAR study of 5-Benzyl-3-(9H-yl) Imidazolidine-2, 4-Dione, which is a Hydantoin based series compound. The main aim of the experiment is to evaluate Multiple Regression Analysis for the series of newly designed Hydantoin based compounds for understanding the properties of molecules participates in anti-cancer activities.

Stepwise Experimental Procedure

Known Compound Set Preferred

In QSAR methodology the first step is search of the Hydantoin based molecule series with known anti-cancer activities from literatures survey. This set of compounds with known activity is treated as Training Set

(Table 1) for the design of QSAR model. The known set of Hydantoin

based molecule is procured from the work of Zuping Xia et.al.(3) and this set of molecules is treated as Training Set. The results showing physic-chemical propertieshave been incorporated in Table 2.

Table 1: Physio-Chemical properties of HYDANTOIN based compounds (Training set)

Mol. No.	IUPAC Name	Molecular Formula	Mol. WT. (amu)	Biological Activity
1	5,5-diphenyl imidazolidine-2,4-dione	$C_{15}H_{12}N_2O_2$	252.274	1.92
2	3-ethyl-5,5-diphenyl Imidazolidine-2,4-dione	$C_{19}H_{16}N_2O_2$	280.328	3.76
3	3-butyl-5,5-diphenyl Imidazolidine-2,4-dione	$C_{19}H_{20}N_2O_2$	308.382	4.29
4	3-butyl-5,5-bis (4-chlorophenyl) imidazolidine-2,4-dione	$C_{19}H_{18}Cl_2N_2O_2$	377.272	4.99
5	5,5-bis(4-bromophenyl -3-butylimidazolidine-2,4-dione	$C_{19}H_{18}Br_2N_2O_2$	466.174	4.71
6	3-pentyl-5,5-diphenyl imidazolidine-2,4-dione	$C_{20}H_{22}N_2O_2$	322.409	4.53
7	3-hexyl-5,5-diphenyl imidazolidine-2,4-dione	$C_{21}H_{24}N_2O_2$	336.436	5.02

Table 2 : Calculated parameters of Training Set I molecules (Hydantoin based molecules)

Mol. No.	HF (Kj/ mol)	BP	MP	Tc	Pc	Vc	GE (Kj/ mol)	Log P	Clog P	Henry Law	CMR	MR (cm3\ mol)	B.A. (p*I* 50)	ΔG (Kcal/ mol.)
1	133 .92	855 .5	666 .7	1036	38. 8	741 .5	376. 25	2.1 4	2.0 85	14. 8	7.2 226	69. 61	1.9 2	- 9.34 694
2	114 .01	861 .5	694 .7	1015 .6	30. 1	796 .5	476. 71	2.7 2	2.7 8	14. 33	8.1 502	79. 41	3.7 6	- 8.88 176
3	72.	907	717	1024	24.	908	493.	3.6	3.8	14.	9.0	88.	4.2	-

	73	.3	.3	.5	6	.5	55	2	38	09	778	61	9	9.79961
4	18.31	992.1	802.2	1056.5	22.3	1006.5	450.43	4.74	5.264	14.35	10.060	97.82	4.99	-10.4487
5	102.45	1049.5	861.97	1084.52	27.56	1032.5	502.93	5.28	5.564	14.89	10.631	103.99	4.71	-12.0574
6	52.09	930.18	728.6	1030.23	22.48	964.5	501.97	4.04	4.367	13.96	9.5416	93.21	4.53	-9.96578
7	31.45	953.06	739.87	1039.76	20.57	1020.5	510.39	4.46	4.896	13.84	10.005	97.81	5.02	-10.3555

Designing of Known Molecular Structure

The known molecular series of molecules is designed virtually (in-silico) using computer based molecule design software CHEMDRAW (4,5). Both 2D and 3D structures are designed. While designing molecules virtually, precautions are being taken for 3D as it tends to lock in "Local Minima". Full care is being taken to see that all molecules are reaching to their "Global Minima" and hence the designed molecules are verified for their 3D structures. Total seven molecules are designed and verified. Semi-empirical QM/MM2 method is used to design 3D molecules with ready-made computer based tools. The final structure of the molecule is having very less total energy and having minimum strain. In table 2 and 3 for Hydantoin (Training Set) and Hydantoin (Test Set) based molecules respectively, the various physio-chemical properties are derived using the advanced computer model for each known molecules and these properties are listed(table 2).

Table 3 : Structure, IUPAC name and molecular formula of Hydantoin based compounds of Test Set I.

Mol. No.	IUPAC Name	Molecular Formula	Mol. Wt. (amu)
1a	3-(9*H*-fluoren-9yl) -5-benzyl imidazolidine-2,4-dione	$C_{23}H_{15}N_5O_3$	409.406

2a	3-(9*H*-fluoren-9yl)-5-isopropyl imidazolidine-2,4-dione	$C_{19}H_{18}N_2O_2$	306.366
3a	3-(9*H*-fluoren-9yl) -5-isobutyl imidazolidine-2,4-dione	$C_{20}H_{20}N_2O_2$	320.399
4a	5-benzyl-3- cyclopentyl imidazolidine- 2,4-dione	$C_{15}H_{18}N_2O_2$	258.322
5a	5-benzyl-3- cyclohexyl imidazolidine- 2,4-dione	$C_{16}H_{20}N_2O_2$	272.349
6a	5-benzyl-3-(cyclohexylmethyl) imidazolidine-2,4-dione	$C_{17}H_{22}N_2O_2$	286.376
7a	5-benzyl-3- (9*H*-fluoren-9-yl)imidazolidine-2,4-dione	$C_{23}H_{18}N_2O_2$	354.411
8a	3-benzhydryl-5-phenylimidazolidine- 2,4-dione	$C_{12}H_{18}N_2O_2$	342.399

Table 4 : Calculated parameters of Test Set I molecules (Hydantoin based molecules)

Mol. No.	HF (KJ/mol)	BP	MP	Tc	Pc	Vc	GE (KJ/mol)	Log P	Clog P	Henry's Law	CMR	MR (cm3\mol)	Cal B.A.	ΔG kcal/mol
1	369.54	965.7	966.9	1193.97	26.379	1077.	804.0	0	2.124	17.777	11.288	0	-328.869	-10.7184
2	44.15	787.6	615.9	1003.16	22.504	881.5	418.6	3.1711	3.394	14.543	8.9734	87.355	2.8684	-11.337
3	23.51	799.	92.0	1009.7	20.58	937.	9.437	3.519	3.92	14.420	3.923	427.1	14653.74	-11.752

		2	3	5	6	5		6	3				5	8
4	-106.24	737.9	520.3	966.663	26.763	739.5	245.8	2.004	2.254	13.102	7.3168	71.417	-25.0531	-9.56609
5	-133.04	750.6	528.1	977.467	24.900	787.5	242.2	2.4213	2.813	12.979	7.7806	76.018	-5.3187	-9.44683
6	-153.68	762.2	539.3	982.344	22.675	843.5	250.6	2.8502	3.522	12.856	8.2444	80.750	26.29432	-10.5515
7	203.4	855.5	702.4	1076.45	21.256	10003.	567.2	3.9604	3.884	15.882	10.557	102.97	-5.1799	-11.8205
8	226.82	847.0	738.6	10825.0	24.825	964.5	634.2	4.0395	3.709	15.547	10.197	99.146	275.5739	-11.9076
9	0	0	0	0	0	0	0	1.4416	2.956	30.723	15.094	148.53	129.3045	-9.24438

QSAR using stepwise multiple regression analysis

Stepwise multiple regression analysis performed for both i.e. for Hydantoin based training set and test set molecule series. Hydantoin based molecule series is named as "Training Set I" In the present study, the multiple regression analysis (stepwise) was performed for both the series by treating biological activity as dependent variable and physio-chemical properties as independent variables. The detailed methodology

and results obtained are described in following section. In this methodology, initially 15 variables (properties) of each molecule are supplied to the system. The properties whose co-efficient has negligible values are removed and again the regression is performed. This method is repeated until all the co-efficient are within the acceptable limits. The detail parameters passed to the model system along with the setting for running the multiple regression analysis. The multiple regression equation is listed in Table 5. The report is generated by computer based statistical analysis software by name NCSS (6).

Validation of Model

It is necessary to test the resulted regression equations. In the present study the regression equations were tested with the known molecules, which were not included in training set. It is reported that the experimental biological activity and calculated biological activities of these molecules are nearly matching gives us confidence of our approach. Table 6 depicts the comparison of experimental biological activities with calculated biological activities of known molecules for Hydantoin based molecules respectively.

Table 5: Estimated Model for calculation of biological activity on the basis of regression analysis for Hydantoin based molecule series. (Training Set I).
Y = 2.5051x10-02xC10+ 8.9208 x10-02xC11-8.8081 x 10-02 x C12 + 3.5428x10-02xC13-.3960xC14-.1025xC15-5.9379x10-02xC16-18.1883xC17+ 14.6693 x C18 -1.8915 x C19-14.2594xC20 + 3.0753xC21
Where, C10 -HF (kj/mol), C11 - Boiling Point (BP), C12 - Melting Point (MP), C13 - critical temperature, C14 - critical pressure (Pc), C15 - critical volume (Vc), C16-Gibb's free energy (kj/mol), C17 - Log P, C18 – Clog P, C19- Henry's law constant, C20 – CMR, C21 - molar refractivity (cm3\mol),

Table 6: Comparison of biological activities of Hydantoin based known molecules: Experimental and Calculated.

Molecular Formula	IUPAC Name	Experimental Biological Activity (Known B. A...)	Calculated B. A.
C20H22N2O2	3-pentyl-5,5-diphenyl imidazolidine-2,4-dione	4.53	5
C21H24N2O2	3-hexyl-5,5-diphenyl imidazolidine-2,4-dione	5.02	4.3

Design of Hydantoin based "Unknown" molecules

Just the once equation for calculating biological activity(B.A) is known, knowing the needed contributions by any typical properties of molecules, new set of molecules are designed in-silico for both the types. While preparing these molecules, care is being taken to see that those properties, which enhance the BA, are keenly selected in new molecules while those properties, which reduce BA, are rejected from series. Those molecules which show the positive change in their properties are selected. Positive changes means, by changing the functional group the anti-cancer properties of the molecule should enhance and that can be judged by knowing the values of parameters (properties).

Confirmation of QSAR model and derived equations.

The properties of designed molecules (Test Set I) are utilized to find out the "Calculated Biological Activities" using the equation, which is already acquired.

Results

Multiple Regression Analysis

Present study envisages the task to find out best regression analysis for two types of molecular series. They are Hydantoin based molecules. The known series of molecules are already tested for their Biological Activities. No model is

valid until it is checked for the accuracy and reproducibility. In this section the observed values i.e. the equations for test series I is used to predict the biological activities of known and unknown set of molecules. The derived equation for test series I and II is depicted in Table 7.

Table 7: Derived equation for Test Series I
Equation 1
$Y = -44.7520 - 1.4321x10^{-02}xC1 + 2.5051x10^{-02}xC10 + 8.9208\ x10^{-02}xC11 - 8.8081\ x\ 10^{-02}\ x\ C12 + 3.5428x10^{-02}xC13 - .3960xC14 - .1025xC15 - 5.9379x10^{-02}xC16 - 18.1883xC17 + 14.6693\ x\ C18 - 1.8915\ x\ C19 - .4577xC2 - 14.2594xC20 + 3.0753xC21 - 3.7251\ x10^{-06}xC3 - 5.4073xC4 + 5.3735\ x\ C5 - 1.3837\ x10^{-03}xC6 - 1.5409\ x10^{-05}xC7 + 4.7809\ x10^{-04}*C8 - 4.6827\ x10^{-07}xC9$

Using this equation the biological activities for the test series I and II are calculated and it is reported that the values are within 98% confidence level which is the great achievement of present work. Table 8 depicts the comparison between the experimental BA with calculated BA. The calculated BA is in excellent agreement with the desired one and hence the work envisaged in the present study is successfully accomplished.

Table 8: Comparison between the experimental BA with calculated BA for training set I

Molecule	B.A. (p*I*50)	Calculated B.A. (p*I*50)
1	1.92	1.9212
2	3.76	3.7622
3	4.29	4.2932
4	4.99	4.9923
5	4.71	4.7123

6	4.53	4.535
7	5.02	5.012
8	**5.12**	**5.1356**
9	4.31	4.367
10	4.56	4.534

Figure 9: Final regression equation for Hydantoin based molecules to predict BA.

Equation 2

$$Y = -44.7520 - 1.4321x10^{-02}xC1 + 2.5051x10^{-02}xC10 + 8.9208\ x10^{-02}xC11 - 8.8081\ x\ 10^{-02}\ x\ C12 + 3.5428x10^{-02}xC13 - .3960xC14 - .1025xC15 - 5.9379x10^{-02}xC16 - 18.1883xC17 + 14.6693\ x\ C18 - 1.8915\ x\ C19 - .4577xC2 - 14.2594xC20 + 3.0753xC21 - 5.4073xC4 + 5.3735\ x\ C5$$

Conclusions

- QSAR and computer simulation methodology have been successfully applied to investigate anticancer properties of 5-Benzyl-3-(9H-yl) Imidazolidine-2, 4-Dione.
- The multiple regression analysis reports the various coefficient values for various physico-chemical properties of molecule. These coefficients help us in rejecting or accepting a particular property for designing a molecule as an anti-cancer agent
- Hydrophobic nature of molecule enhances the anti–cancer activities of Hydantoin based molecules.
- This chemo compound have been predicted to be a very good anticancer agent.

- The QSAR analysis shown enhanced biological activity for this chemo molecule as compared to well established anticancer drugs.
- There is a scope to extend the studies for laboratory synthesis of this chemo compound and to tests its practical applicability.
- QSAR is also a supportive method for Green Chemistry.
- Overall 5-benzyl-3-(9H-yl) imidazolidine-2, 4-dione is a smart biomolecular sensitive material.

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