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IN-SILICO QSAR ANALYSIS OF SUBSTITUTED DIPIPERIDINES AS CCR2 ANTAGONISTS AND ANTITUMORAL ACRIDONES AS A ANTICANCEROUS AGENT

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ABSTRACT

Abstract- A series of Tricycle quinolones as antitumor acridones and Dipiperidines as CCR2 antagonist were selected, having the cytotoxic activity against both HL-60 and P388 leukemias. A series 1 dataset was selected for Quantitative structural activity relationship (QSAR) analysis using combination of various descriptors such as steric, electronic and topological. Stepwise regression method was used to derive the most significant QSAR equation for predicting the anticancerous activity. Thus 3D QSAR analysis clearly indicated that parameters, MR (Molar Refractivity), Ovality (Steric descriptor), PMI-X (Principle moment –X axis) and Log P (Electronic descriptor) play an important role for biological activity of compounds.

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Introduction

Cancer is a group of diseases in which cells are aggressive (grow and divide without respect to normal limits), invasive (invade and destroy adjacent tissues), and/or metastatic (spread to other location in the body). In recent years great progress has been made in the treatment of cancer, and so the life expectation of patients with cancer has been improved remarkably emerging science within the past decade has created many opportunities for fundamentally new approaches to tackle this disease.[1] Nearly all cancers are caused by abnormalities in the genetic material of the transformed cell [2]. Researchers analyzed more than 23,000 chemical compound through a screening technique to identify those that help fight cancer while leaving healthy cells unharmed. Therefore efforts were directed to develop anti-cancerous agents containing quinolones and dipiperidines rings. Intesive efforts in development of clinically useful drugs for cancer have lead to potent anti –cancerous agents, examination of literature indicated that a number of drugs containing quinolones ring as antibacterial and wide variety of anticancer drugs. For the present QSAR study, two series was selected, Series 1- Tricyclic quinolones as antitumoral acridones which was having the cytotoxic activity against both HL-60 and P388 leukemias and a wide panel of human and rodent solid tumor cells and Series 2- Dipiperidines as CCR2 antagonist.[3-4].

Quantitative structure activity relationship (QSAR) searches information relating chemical structure to biological and other activities by developing a QSAR model. Using such an approach one could predict the activities of newly designed compounds

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before a decision is being made whether these compounds should be really synthesized and tested. Therefore, it was thought worth., to determine the structural features and physiochemical parameters which contribute anticancerous activity[(5-16].

2. Computational methods

A] Chemical Data

A series-1 Tricyclic quinolones as a antitumoral acridones and series 2 Dipiperidines as a CCR2 antagonist taken from the reported study[4]. The 2D QSAR models were prformed using simple regression and multiple regression method. The 3D QSAR was performed by using chem. 3D includes MOPAC computations.

B] Data Set

All the compounds were performed using chem. 3D Ultra 10.0 software from Cambridge Soft.com. Chem 3D provides computational tools based on molecular mechanics for optimizing models, conformational searching , molecular dynamics and calculating single point energies for molecules. Simple energy minimization and computing properties and more advanced energy minimization is done using CS MOPAC. CS MOPAC includes MOPAC 2000, the latest version (10.0) supported by Fujistu Corporation.

C] Biological Activities

The EC_{50} um values wear converted into- $logIC_{50}$ from the reported in vivo data for the Tricyclic quinolones as antitumoral acridones (Series 1) and have been tabulated in Table 1. The IC50 um values were converted into –logIC50 from the reported in vivo new Dipiperidines as CCR2 antagoinst (Series 2) and have been tabulated in table 2.

D] QSAR Studies

2D QSAR analysis were generated with the help of cluster analysis; values of different parameters with various variables were calculated. QSAR were generated with values of different parameters and $-logEC_{50}$ value for series 1 with $–logIC_{50}$ value for series 2. For series 1 For Series 1, values of parameters (dd, HF, HCL, Log p, MR, Ovality, PMI-X, PMI-Y, PMI-Z) given in Table 3 for series 2, values of parameters (dd, , HCL, Log p, MR, PMI-X, PMI-Y, and PMI-Z) given in table 4, Before generating QSAR equation , we specified the dependent and independent variables, $-logEC_{50}$ (for series 1) and $-logIC_{50}$ (for series 2) were specifies as dependent variables and parameters (descriptors) specified as independent variables. Several regression method were available in QSAR including simple linear regression , multiple regression, stepwise regression, correlation matrix. However, in both series multiple and simple regression analysis were performed and the following QSAR equation were obtained.

2D QSAR Equation for series 1

Equation 1

BA = [0.735311(±2.07504)]+MR [0.915798(±1.18534)] + Ovality [0.025352(±0.077593)] + PMI –X[-0.071875 (±0.0297738)]

n=24, r=0.80358, r^2= 0.645741, s=0.406711, F=11.5444

Equation 2

BA =[0.452296(±1.77109)]+MR[0.994072(±1.00661)]+ Ovality[±0.0282486(±0.065234)] +PMI-X [-0.0645181(±0.0257905)]

N=24, r= 0.832181, r^2=0.692526, s=0.289905, F=13.5138

2D QSAR Equation for Series 2

Equation 3

BA = HLC [0.470948(±1.95003)]+MR [0.698657(±1.18444)]+Log P[0.75711(±1.21417)] +[-0.0620102(±0.0324307)]

N=23, r=0.816721, r^2=0.667034,s=0.382266, F=12.6876

Equation 4

BA=HLC [-0.0940374(±1.69381)]+MR [1.49286(±1.05208)] +Log P [0.0362255(±0.0639052)] +[-0.0497168(±0.0288786)]

N=23, r=0.856319, r^2=0.733282, s= 0.270146, F=16.4956

Generation of 3D QSAR equations

We selected -logEC50 (for series 1) and -logEC50 (for series 2) as depended variables. Then, selected parameters (descriptors) as independent variables. Performed stepwise regression multiple regression and correlation matrix in both series (Table 3 and 4) following equation were obtained.

3D QSAR Equation for series 1

Equation 5

BA = [1.70052(± 1.75521)] +MR [1.27303(± 1.0478)] + Ovality [-0.936999(± 1.24819)] +PMI –X [-0.054438(±0.0277297)]

n=24, r=0.847258, r^2=0.717847, s=0.266031, F=11.265

Equation 6

BA = [0.969029(±2.32034)] +MR [1.02359(+1.34752)] +Ovality[0.00930576(± 0.0631949)] + PMI-X [-0.0638021 (± 0.0334746)]

n=24, r= 0.801201, r^2= 0.641922, s= 0.411096, F =11.3537

3D QSAR Equation for series 2

Equation 7

BA = [1.55566(±1.86152)] + HCL [0.877239(±1.16145)] +MR [-0.0249271(±0.0485403)] + Log p[-0.0822551(±0.0361763)]

N=23, r=0.811119, rˆ2= 0.657914, s=0.392736, F=12.1805

Equation 8

BA =[0.8227(±1.92397)] +HLC[0.974222(±1.2097)] +MR [0.0261284(±0.0772489)] + Log p [-0.0642896(±0.0331118)]

N=23, r=0.805876, rˆ2=0.649436, s=0.402469, F=11.7328

Table – 3 Values of calculated physicochemical parameters and biological activity for series 1

Compound No.	Dipole/ Dipole (dd)	Henry's Law constant (HLC)	Log (Log p)	Mol Refra Ctivity Cm^3/Mol (MR)	Ovality (Ovality)	Pricipal Moment			-log EC 50
						X (PMI-X)	Y (PMI-Y)	Z (PMI-Z)	
A1	4.0805	20.156	4.88	155.12	1.51	3334.118	9456.121	12157.16	-1.15
A2	2.5247	21.58	3.75	175.12	1.73	3915.129	9456.234	13251.23	-1.20
A3	2.4654	21.95	3.49	142.18	1.29	3825.121	9561.345	12541.21	-0.20
A4	2.9937	20.73	3.94	139.12	1.69	4062.181	9712.281	13547.32	-0.63
A5	2.2139	20.45	4.17	149.09	1.87	3642.921	9541.123	12547.36	-0.58
A6	1.9885	19.45	4.12	147.52	1.94	5124.781	9453.621	12354.62	-0.15
A7	2.3576	21.89	3.15	149.16	1.70	3699.129	9542.368	12426.58	-1.76
A8	3.1593	23.21	4.12	143.22	1.78	4424.319	9324.621	12487.35	-0.53
A9	3.5348	21.54	4.12	144.12	1.75	4512.126	9872.314	12451.36	-0.86
A10	3.2133	19.34	3.75	145.31	1.67	4346.636	9542.314	12581.23	-1.20
A11	4.1925	20.15	3.91	145.01	1.92	4826.191	9856.211	13251.62	-0.46
A12	4.0679	20.37	4.12	138.12	1.84	1621.121	9875.621	13254.35	-0.66
A13	2.7563	21.45	3.86	139.15	1.71	4236.162	9852.126	12654.25	-0.53
A14	4.2816	20.12	3.61	135.12	1.84	5123.527	9541.236	13584.26	-0.86
A15	3.1672	21.41	4.51	147.53	1.78	4565.111	9854.321	13842.65	-0.99
A16	2.0392	21.84	4.09	148.12	1.67	4514.321	9872.136	12581.34	-0.94
A17	2.1674	21.54	4.81	149.12	1.28	6547.128	9985.324	13251.23	-0.53
A18	2.1221	21.12	3.42	135.21	1.67	3215.511	9752.316	12581.34	0.21
A19	2.5328	22.42	4.45	144.12	1.63	3649.126	9852.364	13421.59	-0.79
A20	4.3414	21.65	4.68	139.12	1.67	2547.129	9842.315	13254.62	-0.63
A21	3.1972	21.15	3.63	140.12	1.57	5442.321	9873.261	12546.35	-1.38
A22	3.1571	21.13	4.73	140.31	1.72	4236.124	9421.365	12621.34	-0.59
A23	1.9451	19.85	3.75	149.12	1.79	5316.637	9421.321	12431.25	-0.45
A24	2.3749	20.54	4.32	146.21	1.82	5321.261	9852.214	12531.21	-1.41

Table -4 Values of calculated physicochemical parameters and biological activity for series 2

Compound no	Dipole/ Dipole (dd)	Finish @ Heat of Formation Kcal/Mol (HF)	Henry's Law constant (HLC)	Log P (Log p)	Mol Refractivity Cm^3/Mol (MR)	Ovality (Ovality)	Principal Moment			-log EC50
							X (PMI-X)	Y (PMI-Y)	Z (PMI-Z)	
B1	-3.0965	-168.0364	21.156	3.288	145.14	1.663704	4471.969	11196.49	14797.96	-2.82
B2	-2.9247	-37.6236	23.38	2.612	143.377	1.637319	3895.339	10238.15	13317.32	-2.32
B3	-3.0764	-43.8287	19.885	3.901	143.718	1.644239	3925.051	10318.01	13411.38	-2.06
B4	-2.8937	-35.6549	19.928	3.414	138.676	1.617409	3331.148	9768.181	12338.1	-1.90
B5	-2.0329	-124.873	19.794	3.731	139.109	1.648721	4071.931	11213.98	14471.69	-1.30
B6	-2.885	-191.3265	18.989	4.335	144.65	1.669704	5438.581	12429.6	16892.47	-1.18
B7	-2.1386	-49.2864	20.189	4.531	148.286	1.673409	4669.999	12628.32	16432.04	-0.60
B8	4.0423	-209.6588	23.71	3.499	141.02	1.672811	4509.169	13117.81	16767.78	-1.18
B9	4.2348	-211.2574	19.66	4.047	139.542	1.669431	4600.586	13514.74	17279.27	-1.30
B10	4.2443	-172.7857	19.875	4.447	144.13	1.681717	4616.936	15226.34	18999.57	-0.89
B11	4.0805	-202.8794	20.955	3.762	145.789	1.689192	4526.188	13779.25	17391.56	--1.22
B12	4.1999	-210.7483	19.66	4.047	139.542	1.668483	4550.051	13070.13	16725.66	-1.70
B13.	4.023	-166.5691	23.179	3.086	144.026	1.6771	4553.63	13236.	16883.46	-0.60
B14	3.9296	-199.9902	20.955	3.762	145.789	1.684775.2140 114789.72	5075.617	13888.54	18068.49	-0.40
B15	4.5222	-121.5213	19.684	4.225	144.443	1.672357.7388 566	4775.21	12156.56	16036.7	-0.60
B16	-2.0392	-161.5463	22.534	3.099	149.358	2125.4811.681 72859.82663	4789.72	11617.7	15379.46	-3.53
B17	-2.4521	-49.5744	22.465	3.863	141.171	1.622747.8468 04	2357.738	17136.86	18569.69	-3.83
B18	-6.4521	-42.2358	22.204	2.747	131.561	2479.6261.604 7276	2125.481	12420.22	13950.9	-3.04
B19	-3.6292	-54.7682	22.465	3.863	141.171	1.662233	2859.826	17439.61	19510.33	-2.86
B20	-6.4054	-199.1301	21.265	3.668	137.535	1.660547	2747.846	19049.5	21057.99	-2.08
B21	-3.6292	-54.1419	22.465	3.863	141.171	1.651827	2479.626	18721.28	20542.73	-1.40
B22	2.4111	-243.4993	22.536	4.273	138.103	1.670922	2786.768	20780.5	22509.71	-1.00
B23	-0.4001	-77.6614	19.53	4.551	147.193	1.679562	4436.737	15544.75	19162.13	-2.51

Table -5 Observed predicted and calculated activity of (Series 1)

Comp	Observed activity	Predicted activity	Calculated activity	O-P Residue	O-P residue
B1	-2.82	-1.9069	-2.03903	-0.9131	-0.78097
B2	-2.32	-2.68907	-2.58299	0.36907	0.26299
B3	-2.06	-1.56048	-1.60421	-0.49952	-0.45579
B4	-1.90	-1.99913	-1.97897	0.09913	0.07897
B5	-1.30	-1.83734	-1.76087	0.53734	0.46087
B6	-1.18	-1.29304	-1.2763	0.11304	0.0963
B7	-0.60	-1.28764	-1.15278	0.68764	0.55278
B8	-1.18	-2.26496	-2.03539	1.08496	0.85539
B9	-1.30	-1.57808	-1.54342	0.27808	0.24342
B10	-0.89	-1.28649	-1.24002	0.39649	0.35002
B11	-1.22	-1.75583	-1.71287	0.53583	0.49287
B12	-1.70	-1.52113	-1.54342	-0.17887	-0.15658
B13	-0.60	-2.59289	-2.25683	1.99289	1.65683
B14	-0.40	-1.82731	-1.71287	1.42731	1.31287
B15	-0.60	-1.45946	-1.37603	0.85946	0.77603
B16	-3.53	-1.52479	-2.1694	-2.00521	-1.3606
B17	-3.83	-1.44403	-1.74909	-2.38597	-2.08091
B18	-3.04	-1.1946	-2.57462	-0.8454	-0.46538
B19	-2.86	-1.58623	-1.74909	-1.27377	-1.11091
B20	-2.08	-1.84647	-1.87195	-0.23353	-0.20805
B21	-1.40	-1.80026	-1.74909	0.40026	0.34909
B22	-1.00	-1.78763	-1.51362	0.78763	0.51362
B23	-2.51	-0.834383	-1.12715	-1.67562	-1.38285

Table – 6 Observed predicted and calculated activity of (Series 2)

Comp	Observed activity	Predicted activity	Calculated activity	O-P Residue	O-P residue
B1	-2.82	-1.9069	-2.03903	-0.9131	-0.78097
B2	-2.32	-2.68907	-2.58299	0.36907	0.26299
B3	-2.06	-1.56048	-1.60421	-0.49952	-0.45579
B4	-1.90	-1.99913	-1.97897	0.09913	0.07897
B5	-1.30	-1.83734	-1.76087	0.53734	0.46087
B6	-1.18	-1.29304	-1.2763	0.11304	0.0963
B7	-0.60	-1.28764	-1.15278	0.68764	0.55278
B8	-1.18	-2.26496	-2.03539	1.08496	0.85539
B9	-1.30	-1.57808	-1.54342	0.27808	0.24342
B10	-0.89	-1.28649	-1.24002	0.39649	0.35002
B11	-1.22	-1.75583	-1.71287	0.53583	0.49287
B12	-1.70	-1.52113	-1.54342	-0.17887	-0.15658
B13	-0.60	-2.59289	-2.25683	1.99289	1.65683
B14	-0.40	-1.82731	-1.71287	1.42731	1.31287
B15	-0.60	-1.45946	-1.37603	0.85946	0.77603
B16	-3.53	-1.52479	-2.1694	-2.00521	-1.3606
B17	-3.83	-1.44403	-1.74909	-2.38597	-2.08091
B18	-3.04	-1.1946	-2.57462	-0.8454	-0.46538
B19	-2.86	-1.58623	-1.74909	-1.27377	-1.11091
B20	-2.08	-1.84647	-1.87195	-0.23353	-0.20805
B21	-1.40	-1.80026	-1.74909	0.40026	0.34909
B22	-1.00	-1.78763	-1.51362	0.78763	0.51362
B23	-2.51	-0.834383	-1.12715	-1.67562	-1.38285

Table -7 Correlation matrix of parameters with biological activity (Series)

	-log EC50	HCL	MR	Log p
-log EC50	1.000			
MR	0.542	1.000		

Ovality	0.654	0.375	1.000	
PMI-X	0.645	0.721	0.528	1.000

Table -8 Correlation matrix of parameters with biological activity (Series 2)

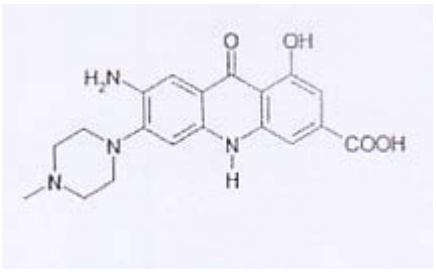
	-log EC50	HCL	MR	Log p
-log EC50	1.000			
HLC	0.125	1.000		
MR	0.142	0.523	1.000	
LOG P	0.255	0.601	0.258	1.000

Observation of the two equation (for Series 1) clearly revealed that parameter MR (Molar refractivity descriptor) is very important for biological activity.

Also comparison of the magnitudes of the regression coefficients indicated that the substitution at position R_3 in the nucleus is more vulnerable. However , the negative sign of the coefficients implies that the hydrophilic substitution will enhance the biological activity. Similarly the field effect of substitution at R_3 position contributes positively to the biological activity, although to lesser extent.

The selected Dipiperidines as CCR2 antagonist series (Series 2) after subjected to QSAR analysis the following structures were proposed having significant activity.

Structure 1



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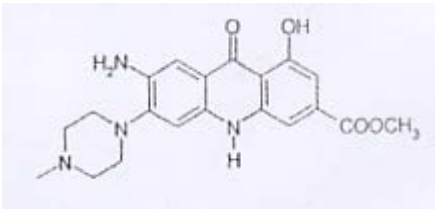

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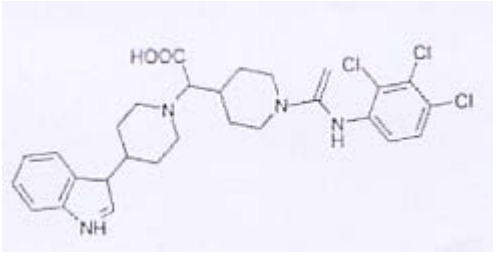

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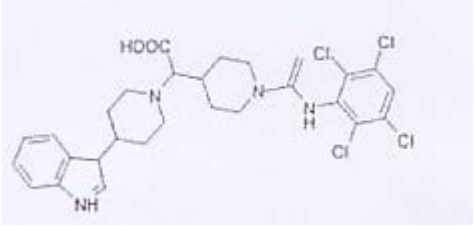

Observation of the two equation (for Series 2) clearly revealed that parameter HCL (Henry law constant). MR (Molar refractivity descriptor) and Log P (lipophilic) is very important for biological activity

Also comparison of the magnitudes of the regression coefficients indicated that the substitution at position R_2 in the nucleus is more vulnerable. However , the negative sign of the coefficients implies that the hydrophilic substitution will enhance the biological activity. Similarly the field effect of substitution at R_2 position contributes positively to the biological activity, although to lesser extent.

Observation of four equation (5, 6, 7 and 8) clearly indicated that parameters, MR (Molar Refractivity), Ovality (Steric descriptor), PMI-X (Principle moment –X axis) and Log P (Electronic descriptor) play an important role for biological activity of compounds

Calculated Activity of Proposed Compounds(Series 1)

Structure of proposed compounds (Structure 1 and 2) were drawn by Chem draw Ultra 10.0. Then copied and pasted in Chem 3D ultra 10.0 windows . Energy minimization for two compounds was performed using MM2 and MOPAC . Compound values for three parameters (HLC, MR and log P) were found using the computed values for was found using the menu. Substituting these values in eq. 1, biological activity of each compound was calculated . The compound values of parameters and calculated activity in terms of - log EC50 of two compound have been tabulated in Table -7

Table -9 Calculated values of Physico-Chemical parameter and Series 1

Compound No.	HCL	MR	Log P	Calculated activity (-logEC$_{50}$)
1	23.28	139.94	3.31	-0.8473
2	21.86	148.71	3.89	-0.9815

In series 2, we have seen that MR (Molar refractivity descriptor) is steric descriptor, it is main parameter contributing to the biological activity.

Critical observation of all the compound in Series 2 we find that increase in electronegative group at R_2 position enhances the biological activity of compounds. Hence , we proposed to incorporate rational changes at R_2

Calculated Activity of Proposed Compounds (Series 2)

Drawn the structure of two compounds (3 and 4), done the minimization by MM2 and MOPAC by Chem 3D ultra 10.0. Found the values of three parameters HCL (Henry law constant, MR (Molar refractivity descriptor) and Log P (lipophilic) by compute properties menu.

Substituting these values in Eq.7, biological activity of each compound was calculated. The computed values of parameters and calculated activity in terms of -logIC_{50} of two compound has been tabulated in Table -8.

Table -10 Calculated Values of Physico-Chemical parameters and Calculated Biological Activity of Proposed Compound (Series 2)

Compound No.	HCL	MR	Log P	Calculated Activity (-logEC_{50})
3	19.47	141.45	4.84	-1.254
4	18.56	154.84	5.75	-0.9924

Discussion regarding the expected enhancement of the biological activity of the proposed structures. If there is an enhancement , our QSAR analysis has predictive power and hence it is successful analysis.

References

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