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Research Article

PREDICTION OF BIOLOGICAL ACTIVITIES OF NITROIMIDAZOLE BY QSAR

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ABSTRACT

Nitroimidazole class drugs are solely depending upon the reduction of nitro group for its biological activity. The novel electronic parameter; Extended Huckel Partial Atomic Charges [EHPAC] of oxygen for nitro group are significantly correlating with one electron reduction potential (E_7^1). QSAR analysis of twenty two compound using electronic parameter; EHPAC along with other physicochemical parameter were carried out against *Bacteroides fragilis* NCTC 9343. It was found that the pMIC shows good correlation (r = 0.927, r^2= 0.860, r^2 (adj) = 0.822, r^2 (pred) = 0.756 and least-squared error = 0.0040) with electronic descriptor; which governs the electron density around nitro group and various biological activities.

Keywords: Nitroimidazole, partial charges, cytotoxicity, anaerobe.

INTRODUCTION

The biological effects of nitroimidazole are believed to be closely related to the "nitro: nitro radical anion" redox cycle, and the relationship of biological activity with theoretical electron affinity is therefore not surprising.[1] This excellent correlation does suggest, however, that theory might provide useful new information in predicting biological effects to aid in the design of new drugs. The redox potential of bio reducible drugs is therefore crucial beginning in understanding how these compounds may be applied to combat diseases which flourish under redox environment.[2]

Anaerobes have evolved special electron-transfer proteins to deal with low-potential redox reactions, characterized by the possession of iron-sulfur proteins such as ferredoxins and rubredoxins. Since the voltage span for the acceptance of a single electron is 60 mV, one may expect some weak electron transfer reactions down to the potential of -0.4 V in aerobes but below that the domain of anaerobic organism. Even between the values of -0.35 and -0.4 V the aerobic cell would be considerably acidic and hypoxic, so it is not surprising that the 2-nitroimidazoles being selectively reduced under hypoxia but having redox potential too positive to be usefully considered as possible antianerobic drugs.[3] It was well-established that polarogrpahic determined E_7^1 value (one electron reduction potential) correlates significantly with radiosensitization efficiency[4,5] aerobic cytotoxicity, mutagenicity and hypoxic cytotoxicity[6] of various standard nitroimidazole drugs. The more electron-affinic the drug (the more positive the E_7^1 value) the greater the radiosensitization and cytotoxicity, which varies in general by an order of magnitude for each 100 mV change in E_7^1.[7]

In one of our work it was established that computed [EHPAC] of oxygen for nitro group was significantly correlating with one electron reduction potential; r = 0.9768, r^2=0.9542, r^2 (adjusted) = 0.9477, F value = 146.0945, standard error = 0.0112. The experiment also showed that EHPAC is negatively correlating to the DNA damage; r=0.9633, r^2=0.9281, r^2 (adjusted) = 0.9160, F value = 77.41, standard error = 0.08248. There arises considerable interest for this novel electronic parameter for correlating various biological activities of nitroimidazole.[8]

MATERIALS & METHODS

Computational Chemistry

Twenty two compounds from series of differently substituted nitroimidazole derivatives, as antianerobic activity, were obtained from literature and selected for the study. These compounds were randomly divided into training and test sets, the former set consisting of fifteen compounds and the remaining six compounds were taken as test set. The structures of all compounds used in this study were sketched by using Visualizer module of Discovery studio 2.1 software (Accelrys Inc., USA). An energy minimization of all the compounds was done using Smart Minimizer method until the root mean square gradient value becomes smaller than 0.001 kcal/mol followed by geometry optimization by semi empirical MOPAC-AM1 method (Astin Method-1). Further, optimized structures for all compounds were aligned with compound 1 and these structures were used for calculation of various descriptors.

The molecular geometries of each of the twenty two nitroimidazole compounds were built by using standard bond lengths and angles with Chem. Office Ultra 11.0.[9] These structures were initially optimized using MM_2 force field method until the root mean square gradient value becomes smaller than 0.001 Kcal/mol. The resulting optimized structure was processed through the Extended Huckel Partial Atomic Charges on oxygen of nitro group in nitroimidazole.[10] The values of various descriptors were shown in table 3.

Biological Activities

The *in vitro* activity, of all the compounds used for QSAR analysis was tested against *Bacteroides fragilis* NCTC 9343, obtained from literature.[11] The result was obtained in millimolar concentrations, mmolar/L was given in Table 1,1a. For every compound of the series, the experimental values of microbiological activity were used in the negative logarithmic scale (pMIC) to achieve normal distribution.

Molecular Descriptors

In this research work three types of descriptors were generated to provide an as complete description of each molecule. The first class represents the lipophilic properties, the second expresses the electronic property, and third one is steric properties the molecular descriptors were depicted in table 2.

RESULTS

Generation of QSAR models along with their statistics

Fifteen compounds from 5-nitroimidazole and 2-nitroimidazole series were randomly selected to generate QSAR model. QSAR model were built using multiple linear regression protocol of the Discovery Studio 2.1. Statistical qualities of the generated models were judged by parameters such as regression coefficient (r^2), adjusted r^2 (r^2 adj), cross-validated r^2 (r^2cv), Four best equation were selected for QSAR analysis, given in table 4.

Validation of QSAR models

Predictive ability of QSAR model is validated by two techniques to determine reliability of generated model, internal and external validation.

Internal Cross-validation

Cross validation (CV) technique is used to determine quality of model internally. Cross-Validation technique uses Leave-one-out, Leave-Some-Out or Leave- Many-Out methods. The quality of the model was analyzed by the value of correlation coefficient of the cross-validation, r^2cv=0.841, as shown in table 5 and figure 1 (It should be greater than 0.5).[12]

External Cross-validation

The actual validation of the model is done by means of external validation. The QSAR model was used to show predictions of compounds not included in the training sets. The actual activity, predicted activity and residuals for test set compounds were shown in table 6 and figure 2.

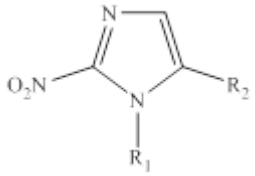
DISCUSSION

In the present study, five preselected descriptors were screened for twenty two nitroimidazole derivatives by multiple linear regression analysis. The inter-correlation of the descriptors used in the selected models was very low. The correlation matrix for the descriptors used was shown in table 7.

The intercorrelation matrix was prepared; LUMO and HOMO was inter- correlating significantly, so HOMO was omitted from the model generation. To further check the inter-correlation of descriptors, variance inflation factor (VIF) analysis was performed. The VIF values of these descriptors were found to be 1.1053 (EHPAC), 4.2880 (HOMO), 3.5842 (LUMO), 1.6652 and 1.3294 (MV). All the VIF values were found to be less than 10. Thus, from the VIF analysis, it is clear that the descriptors used in the final models have low inter-correlation.[13]

The models were also evaluated for their capacity to predict the activity of training set and test set compounds, i.e., internal and external cross-validation, respectively. The results for the equation 1 were summarized in table 5 and 6. Figure 1 and 2 depicts the plots of observed vs. predicted activity for training and test set compounds, respectively. The models displayed satisfactory r^2pred. For all the models, r^2pred was found to be in the acceptable range. As expected, electronic parameter EHPAC, with linear relationship, emerged as an indispensable descriptor for nitroimidazole along with other structural, spatial and lipophilic descriptors.

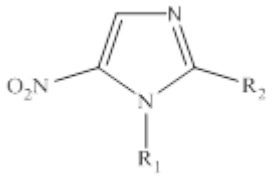
Table 1: 2-Nitroimidazole and their pMIC values



2-Nitroimidazoles

No.	R_1	R_2	MIC mmol/l	pMIC
1	CH_3	CHO	0.0035	2.455932
2	CH_3	$CH=N(O)CH_3$	0.005	2.30103
3	CH_3	$COOCH_3$	0.0035	2.455932
4	$CH_2CH_2SO_2CH_3$	H	0.005	2.30103
5	$CH_2CONHCH_2C_6H_5$	H	0.0035	2.455932
6	$CH_2CH(OH)CH_2F$	H	0.0035	2.455932
7	$CH_2CH(OH)CH_2C1$	H	0.0023	2.638272
8	$CH_2CH(OH)CH_2OCH_3$	H	0.0023	2.638272
9	$CH_2CH(OH)CH_2OCH(CH3)_2$	H	0.0023	2.638272
10	$CH_2CH(OH)CH_2OCH_2CH=CH_2$	H	0.0023	2.638272
11	$CH_2CH(OH)CH_2OC2H_5$	H	0.0023	2.638272
12	CH_3	$CH=CH_2$	0.0000023	5.638272
13	CH_3	CH_2OH	0.0015	2.823909
14	H	H	0.005	2.30103

Table 1a: 5-Nitroimidazole and their pMIC values



5-Nitroimidazole

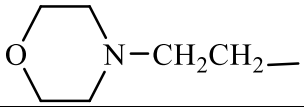
No.	R_1	R_2	MIC mmol/l	pMIC
15		H	0.0023	2.638272
16	$CH_2CH_2SO_2CH_2CH_3$	CH_3	0.00015	3.823909
17	CH_2CH_2OH	4-FC_6H_4	0.00035	3.455932
18	$CH_2CH(OH)CH_2C1$	CH_3	0.0005	3.30103
19	CH_3	CH_2OCONH_2	0.0001	4
20	CH_3	CH_3	0.0015	3.5
21	CH_2CH_2OH	CH_3	0.0001	4
22	H	CH_3	0.230	0.638272

Table 2: Descriptor used in QSAR models

No.	Descriptors	Definition
1	CLogP	Log of the octanol-water partition coefficient
2	Molar volume	Steric parameter
3	HOMO	Energy of highest occupied molecular orbital (HOMO)
4	LUMO	Energy of lowest unoccupied molecular orbital (LUMO)
5	EHPAC	Electronic parameter, Extended Huckel partial atomic charge on oxygen of nitro group

Table 3: Physicochemical descriptors used in training (1-10, 15-19) and test (11-14 , 20-22) compounds

No.	EHPAC	HOMO	LUMO	CLogP	MV
1	-0.742	-5.504	0.69	-0.733	91.92
2	-0.737	-4.932	1.945	-0.809	145.77
3	-0.762	-4.747	1.827	-1.077	139.6
4	-0.746	-4.727	1.245	0.059	98.78
5	-0.768	-4.751	4.52	-1.47	99.46
6	-0.758	-4.654	0.508	-0.99	67.91
7	-0.759	-4.951	4.535	-1.232	145.08
8	-0.776	-6.366	0.821	-0.255	156.4
9	-0.747	-5.248	1.237	0.39	150.23
10	-0.767	-4.642	1.808	-0.786	137.54
11	-0.777	-5.045	1.317	-1.443	114.56
12	-0.737	-5.161	0.801	0.412	112.84
13	-0.78	-4.276	2.656	-0.941	93.63
14	-0.773	-4.759	1.594	-1.48	110.44
15	-0.836	-4.304	2.93	-1.146	79.57
16	-0.852	-4.477	2.284	-0.328	97.41
17	-0.84	4.475	9.027	-2.679	69.62
18	-0.823	-4.71	2.146	-1.428	125.19
19	-0.84	-4.663	0.41	-0.92	107.01
20	-0.835	-4.846	0.17	-1.805	136.85
21	-0.844	-5.929	0.643	0.321	103.92
22	-0.848	-5.704	0.951	0.575	150.57

Table 4: Generation of QSAR models along with their statistics

Eq. No.	Description	r	r^2	r^2 (adjd)	r^2 (pred)	LSE
1	pMIC = -7.747 + 0.0082*(CLogP) + 0.000175 * (M V) -13.34 *(EHPAC)	0.927	0.860	0.822	0.756	0.0040
2	pMIC = -7.248+ 0.00788*(CLogP) + 0.001106*(LUMO) -12.98 *(EHPAC)	0.924	0.854	0.814	0.692	0.0042
3	pMIC = -7.238+ 0.104*(CLogP) - 12.96 * (EHPAC)	0.924	0.853	0.828	0.768	0.0042
4	pMIC = -6.743 - 12.21* (EHPAC)	0.915	0.837	0.825	0.762	0.046

Table 5: Internal validation of training compound as per equation 1

Comp No.	pMIC (observed)	pMIC (predicted)	Residual
1	2.4	2.168355	0.231645
2	2.3	2.110456	0.189544
3	2.4	2.440679	-0.04068
4	2.3	2.22941	0.07059
5	2.46	2.510472	-0.05047
6	2.46	2.375486	0.084514
7	2.64	2.400347	0.239653
8	2.64	2.637119	0.002881
9	2.64	2.254468	0.385532
10	2.64	2.509404	0.130596
15	2.94	3.416768	-0.47677
16	3.82	3.640037	0.179963
17	3.46	3.455816	0.004184
18	3.3	3.249019	0.050981
19	4.0	3.476783	0.523217

Table 6: External cross-validation of test compounds as per equation 1

Comp No.	pMIC (observed)	pMIC (predicted)	Residual
11	2.64	2.672823	-0.03282
13	2.82	2.713401	0.106599
14	2.3	2.618459	-0.31846
20	3.5	3.447364	0.052637
21	4	3.579259	0.420741
22	4	3.642632	0.357368

Table 7: Inter correlation matrix of descriptors used in QSAR models

	EHAPAC	HOMO	LUMO	Clogp	MV	pMIC
EHAPC	1					
HOMO	0.021	1				
LUMO	-0.022	0.832742	1			
Clogp	-0.188	-0.58237	-0.54162	1		
MV	-0.002	-0.43778	-0.30464	0.247901	1	
pMIC	-0.308	0.239394	0.207906	0.007626	-0.2698	1

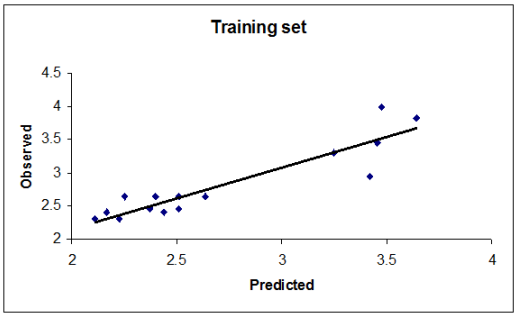


Figure 1: Plot of observed Vs predicted pMIC values for training set compounds (as per equation 1)

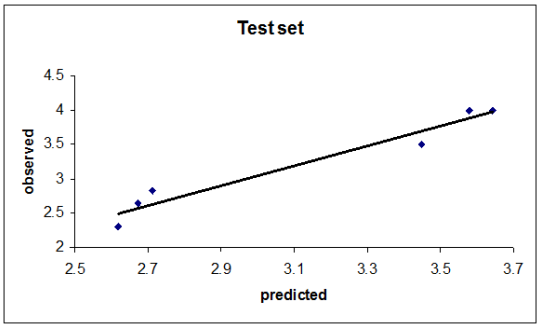


Figure 2: Plot of observed Vs predicted pMIC values for test set compounds (as per equation 1)

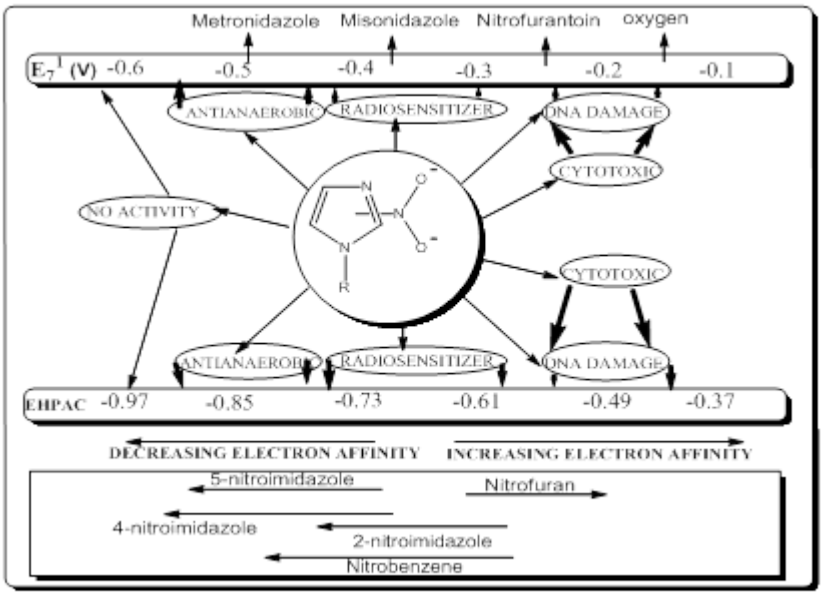


Figure 3: Extended Huckle partial atomic charges and redox Spectrum of various nitroimidazole

CONCLUSION

QSAR study of literature nitroimidazole drug, establish significant correlation between antibacterial activity and EHPAC for oxygen of nitro group against *Bacteroides fragilis*. The correlation is reverse to those obtained for cytotoxicity, mutagenicity and DNA damage activity due to the more electron affinity of the drugs. It was found that; EHPAC values in between (-0.85 to -0.73) have greatest potency against the test organism and also it is the range of reduction for nitroimidazole under anaerobic condition. It indicates that most electron affinic drug are reduced in the aerobic condition while compounds having less electron affinity and having low reduction potential were showing activity against anaerobes. The addition of partition coefficient that was lipophilic parameter values produced positive correlation, imparting better regressed line and increasing the correlation. However, the molar volume as a steric factor was not influencing the activity of nitroimidazole. The other electronic parameters such as LUMO, HOMO was found to be producing no significant change in the R value.

It was concluded that nitroimidazole falling under EHPAC value between (-0.85 to -0.73) for oxygen of nitro group are considered to be safest drug for anaerobic infections. If EHPAC for oxygen is less than -0.85, it is not reduced under anaerobic condition while greater than-0.73 probably shows radio sensitizer activity. The nitroimidazole drugs with EHPAC greater than, -0.61 may be cytotoxicity and produce DNA damage. Some of the 2-nitroimidazole taken in study showing value greater than; -0.61 imparting cytotoxicity indicated in figure 3.

One electron reduction potential governs the DNA damage capacity, toxicity, radio sensitizer, anaerobic activity and aerobic toxicity. Henceforth, EHPAC for oxygen of nitro group can be used to correlates all above biological activity significantly, for nitroimidazole class drugs before synthesizing the compounds and without taking any polarographic half wave reduction potential or one electron reduction potential practically.

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