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QSAR Studies on 3-Nitro-2,4,6-trihydroxy Benzamide Derivatives as Photosynthetic Electron Transport Inhibitors

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A series of 3-nitro-2,4,6-trihydroxy benzamide and thio-amide derivatives possessing potent herbicidal activity by inhibiting photosynthetic electron transport was subjected for quantitative structure activity relationship analysis. The herbicidal activity was co-related with certain topological, 3-D structure dependent thermodynamic and charge dependent, descriptors for the minimum energy confirmations. Out of various descriptors studied, partition coefficient (log P), Wienier Index (WienI) and specific polarisability (Sp_{pol}) showed appreciable co-relation with activity. This study should enable prediction of activity of unknown compounds belonging to this category.

Key Words: QSAR, Benzamides, Herbicidal activity, Photosynthetic electron transport inhibition.

INTRODUCTION

Photosynthesis has been regarded as an important target for herbicide action and photosynthetic electron transport (PET) is essential for photoresponse. In fact, various compounds inhibiting photosynthesis constitute the largest class of commercial herbicides[1,2]. All of those inhibitors, including ureas, triazines, bis carbamates and phenols, interrupt photosynthetic electron transport (PET) by binding to quinine-binding protein (D1-protein)[3]. Certain commonly used herbicides are simazine, atrazine bromocil, a isocil, bipyridylium, diquat and paraquat[4].

A basic property of plants is ability to carryout photosynthesis and thus they provide organic carbon which forms the basis of food chain on earth.

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The photochemical reactions of photosynthesis proceed in the thylakoid membranes of the chloroplast and are mediated by the photosystems (PS), PSI and PSII catalyzing vectorial electron transport across the thylakoid membrane.

Honda *et al.*[5] reported a series of 3-nitro-2,4,6-trihydroxy benzamide as potent inhibitors of PET which were designed based on the structures of phloroglucinol derivatives like grandinol. The PET inhibitory activity was shown to depend on electronic parameters in the co-relation analysis. Computer aided drug design (CADD) or Computer-assisted molecular design (CAMD) has developed important tools for drug development by application of various molecular modeling softwares. Among the many, quantitative structure activity relationship (QSAR) has been a useful tool for drug design, particularly when the structure of target is unknown[6,7]. The QSAR equations are evaluated on the basis of various statistical terms like correlation coefficient (r), standard error (s) and Fischer test (F-test). The regression models can then be used for prediction of new molecules[8]. In the present work, we performed QSAR analysis for the PET-inhibitory activity of 3-nitro-2,4,6-trihydroxy benzamides using various topological, 3D-structure dependent, thermodynamic and charge dependent descriptors. The general structure of these compounds is as follows:

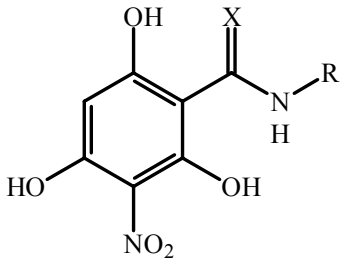

Fig. 1. 3-Nitro-2,4,6-trihydroxy benzamides

EXPERIMENTAL

The PET-inhibitory activity for a series of 3-nitro-2,4,6-trihydroxy benzamide and thioamide derivatives containing 49 compounds was subjected for QSAR analysis by multiple linear regression (MLR) technique. The literature values of the activity and the general structure of the compounds are given in Fig. 1 and Table-1. The PI_{50} data were used for QSAR analysis as a dependent parameter. Structures of compounds were built using 2D sketcher tool provided in the modeling environment of alchemy 2000 (Tripos, USA) software. The geometric optimization were performed using alchemy-2000 version of Sci QSAR 3.0 software (Tripos, USA) at a gradient of 1.0 KCal/Em with delta energy change of 0.001 Kcal/mL under tripos standard force field.

TABLE-1
ACTIVITY DATA OF 3-NITRO-2,4,6-TRIHYDROXY BENZAMIDE DERIVATIVES IN PHOTOSYNTHETIC ELECTRON TRANSPORT INHIBITION

Compd. no.	X	R	I_{50}	log I_{50}	PI_{50}
1	O	Ethyl	1.458	0.163	6.1
2	O	Propyl	1.467	0.166	6.0
3	O	Butyl	1.458	0.163	6.1
4	O	Pentyl	1.389	0.142	7.0
5	O	Hexyl	1.376	0.138	7.2
6	O	Heptyl	1.343	0.128	7.8
7	O	Octyl	1.328	0.123	8.1
8	O	Nonyl	1.319	0.120	8.3
9	O	Decyl	1.315	0.119	8.4
10	O	Undecyl	1.315	0.119	8.4
11	O	Tridecyl	1.328	0.123	8.1
12	O	Benzyl	1.519	0.181	5.5
13	O	(R)-1-Phenethyl	1.467	0.166	6.0
14	O	3-Phenylpropyl	1.403	0.147	6.8
15	O	4-Phenylbutyl	1.365	0.135	7.4
16	O	2-Phenoxyethyl	1.458	0.163	6.1
17	O	2-(4-Cl phenoxy)ethyl	1.383	0.140	7.1
18	O	Phenyl	1.441	0.158	6.3
19	O	2-Cl-phenyl	1.477	0.169	5.9
20	O	3-Cl-phenyl	1.410	0.149	6.7
21	O	4-Cl-phenyl	1.383	0.140	7.1
22	O	4-Br-phenyl	1.376	0.138	7.2
23	O	2F-phenyl	1.467	0.166	6.0
24	O	3F-phenyl	1.417	0.151	6.6
25	O	4F-phenyl	1.433	0.156	6.4
26	O	3,5-Cl_2-phenyl	1.410	0.149	6.7
27	O	3,4-Cl_2-phenyl	1.376	0.138	7.2
28	O	2,4-Cl_2-phenyl	1.389	0.142	7.0
29	O	2,3-Cl_2-phenyl	1.477	0.169	5.9
30	O	3-CF_3-phenyl	1.396	0.144	6.9
31	O	4-CF_3-phenyl	1.353	0.131	7.6
32	O	2-Me-phenyl	1.487	0.172	5.8
33	O	3-Me--phenyl	1.417	0.151	6.6
34	O	4-Me-phenyl	1.458	0.163	6.1
35	O	4-Et-phenyl	1.425	0.153	6.5

Compd. no.	X	R	I_{50}	log I_{50}	PI_{50}
36	O	4-iPr-phenyl	1.410	0.149	6.7
37	O	4-Pr-phenyl	1.389	0.142	7.0
38	O	2-MeO-phenyl	1.449	0.161	6.2
39	O	3-MeO-phenyl	1.433	0.156	6.4
40	O	4-MeO-phenyl	1.477	0.169	5.9
41	O	4-NO_2-phenyl	1.410	0.149	6.7
42	S	Ethyl	1.417	0.151	6.6
43	S	Butyl	1.389	0.142	7.0
44	S	Hexyl	1.338	0.126	7.9
45	S	Heptyl	1.315	0.119	8.4
46	S	Octyl	1.302	0.114	8.7
47	S	Nonyl	1.311	0.117	8.5
48.	S	Decyl	1.319	0.120	8.3
49	S	Phenyl	1.389	0.142	7.0

Various topological descriptors, 3D structure dependent, thermodynamic and charge dependent parameters were calculated by using molecular mechanical methods of SYBYL force field under alchemy. Various topological parameters[9-11] were molecular connectivity index ($^{o}X^{v}$), first order valance molecular connectivity index ($^{1}X^{v}$). Third order molecular connectivity index (^{3}X) obtained from hydrogen suppressed graph of the molecules and calculated according to the methods of Kier and Hall[10]. A third order molecular shape index ($^{3}K_{\alpha}{}^{0}$), which encodes an atom identity, involves in assessing the shape of a molecule. Thermodynamic parameter considered was logarithm of partition co-efficient (log P), which plays an important role in transport of drugs across biological membrane to receptor site[12]. Molecular polarizability was calculated based on additive approach given by Miller[13]. Charge dependent parameter, dipole moment (m) was computed based on the 3-D structure and charges calculated by the Gasteriger-Marsili method implemented in Sci QSAR software and are expressed in debye[13].

MLR analysis was carried out to find out the factors responsible for the biological activity. It is an attempt to maximize the fitting of data to the regression equation by minimizing the squared deviation (standard deviation) from the regression equation for the biological activity and maximizing the variance (r^2) by adjusting each of the available parameter up or down. MLR and other statistical analysis were performed by adopting standard protocol[8,14,15]. Acceptability of the regression equation was examined by the correlation coefficient (r), square correlation coefficient (r^2), Fischer's

statistical value (F) and root mean square deviation (RMSD). Regression constants were considered at 95 % confidence interval. A compound was considered an outlier for a particular equation (eqn.) when the residual values (difference between calculated and experimental values) exceeded twice the value of RMSD of the equation. Correlation matrix of various parameters used in regression equations is shown in Table-2.

RESULTS AND DISCUSSION

Total 16 different parameters were calculated and used in QSAR analysis. Several equations containing maximum up to 6 parameters were generated by MLR method. Most of the equations, thus obtained, were statistically not acceptable. An equation (eqn. 1) containing 4 parameters showed satisfactory values of co-relation coefficient.

$$PI_{50} = 27.91 + 0.0101 \times m.w.-0.37 \times Max_{Qp} + 32.81 \times Max_{Neg}-91.78 \times Sp_{pol}$$
$$R = 0.79, R^2 = 0.63, F = 20.56, RMSD = 0.53 \quad (1)$$

This equation consisted two very closely related terms (Max_{Qp} and Max_{Neg}), which represented the electronic environment on a molecule. Hence, it was thought worthwhile to replace one of these parameters by another parameter (dipole moment). The resulting equation did not offer any improvement in co-relation values. While deletion of dipole moment from the regression gave an equation with improved F-values (eqn. 2).

$$PI_{50} = 27.97 + 0.0101 \times m.w. + 33.23 \times Max_{Neg} - 91.42 \times Sp_{pol}$$
$$R = 0.79, R^2 = 0.63, F = 27.95, RMSD = 0.53 \quad (2)$$

Even this equation was considered insignificant due to fact that two parameters representing electronic properties were present. Therefore, analysis was repeated to get a new equation (eqn. 3), with better distribution of independent parameters.

$$PI_{50} = 19.50 + 1.45 \times \log P - 7.09 \times WienI - 1.23 \times Sp_{pol}$$
$$R = 0.85, R^2 = 0.73, F = 41.76, RMSD = 0.43 \quad (3)$$

This equation was considered as model equation and removal of an outlier compound (compd. no. 15) gave the best equation (eqn. 4) as follows:

$$PI_{50} = 17.64 + 1.35 \times \log P - 1.89 \times WienI - 1.11 \times Sp_{pol}$$
$$R = 0.89, R^2 = 0.80, F = 59.57, RMSD = 0.38 \quad (4)$$

This equation was satisfactorily cross-validated by leave one out method. It was then used for calculating the activities, which gave satisfactory results with minimum residual values. The experimental and calculated activities are shown in Table-3.

From this equation it was observed that partition coefficient (log P), Wienier index (WienI) and specific polarizability (Sp_{pol}) are the determinant of activity. Increase in log P, with a decrease in $Wien_I$, Sp_{pol} shall favour the activity. In general, presence of a fatty alkyl substitution on the

TABLE-2
CORRELATION MATRIX OF VARIOUS PARAMETERS USED IN REGRESSION EQUATIONS

	Eqn. coff.	PIC_{50}	X 1	XV 0	XVI	log P	Winels	X3	Dipole	Polar	Volume	m.w.	ABSQ	ABSQ ON	Max Q+	KA_3	MaxQ-	Sp_{Pol}
X1	1.92	0.39	1	0.93	0.90	0.66	0.94	0.84	0.10	0.93	0.92	0.94	0.83	0.19	0.16	0.83	-0.17	-0.23
XV0	1.22	0.58		1	0.99	0.83	0.94	0.63	-0.12	0.99	0.99	0.92	0.65	-0.05	-0.07	0.94	0.07	-0.27
XVI	-0.6559	0.60			1	0.82	0.94	0.55	-0.17	0.98	1.00	0.87	0.63	-0.08	-0.11	0.97	0.08	-0.36
log P	0.3209	0.67				1	0.71	0.37	-0.33	0.84	0.79	0.76	0.24	-0.48	-0.23	0.79	0.50	0.01
Winel	2.34e-003	0.38					1	0.66	0.03	0.92	0.95	0.87	0.76	0.11	0.07	0.93	-0.11	0.37
X3	-1.34	0.04						1	0.40	0.63	0.58	0.81	0.78	0.38	0.37	0.41	-0.37	0.11
Dipole	-0.0577	-0.46							1	-0.16	-0.16	0.13	0.42	0.58	0.49	-0.20	-0.70	0.06
Polar	-0.2895	0.56								1	0.98	0.90	0.61	-0.08	-0.14	0.92	0.12	-0.19
Volume	-7.76e-003	0.58									1	0.87	0.67	-0.03	-0.08	0.97	0.05	-0.38
m.w.	2.31e-003	0.47										1	0.71	0.07	0.16	0.78	-0.07	-0.09
ABSQ	-0.4037	0.10											1	0.61	0.48	0.59	-0.56	-0.44
ABSQ ON	-0.6844	-0.44												1	0.36	-0.09	-0.85	-0.27
Max Q+	2.11	-0.12													1	-0.11	-0.47	-0.25
KA_3	0.2651	0.61														1	0.10	0.49
MarQ	-1.34	0.45															1	0.32
Sp_{Pol}	-9.58	-0.28																1

TABLE-3
CALCULATED VALUES OF ACTIVITY USING EQUATION

Compd. no.	PIC_{50} exp	PIC_{50} calc.	Residual
1	6.1	6.189707	-0.089707
2	6.0	6.214054	-0.214054
3	6.1	6.415829	-0.315829
4	7.0	6.721173	0.278827
5	7.2	7.031583	0.168417
6	7.8	7.643631	0.156369
7	8.1	7.751385	0.348615
8	8.3	7.869844	0.430156
9	8.4	8.036813	0.363187
10	8.4	8.422152	-0.022152
11	8.1	8.961240	-0.861240
12	5.5	6.023561	-0.523561
13	6.0	6.353261	-0.353261
14	6.8	6.712660	0.087340
15	6.8	6.909322	-0.109322
16	6.1	6.563749	-0.463749
17	7.1	6.826706	0.273294
18	6.3	5.704703	0.595297
19	5.9	6.206210	-0.306210
20	6.7	6.489616	0.210384
21	7.1	6.236825	0.863175
22	7.2	6.986227	0.213773
23	6.0	6.627134	-0.627134
24	6.6	6.647070	-0.047070
25	6.4	6.318550	0.081450
26	6.7	6.702953	-0.002953
27	7.2	6.784350	0.415650
28	7.0	6.782331	0.217669
29	5.9	6.735189	-0.835189
30	6.9	7.465951	-0.565951
31	7.6	7.223386	0.376614
32	5.8	6.017560	-0.217560
33	6.6	6.059449	0.540551
34	6.1	6.062659	0.037341
35	6.5	6.404120	0.095880
36	6.7	6.890306	-0.190306
37	7.0	6.893252	0.106748
38	6.2	6.160772	0.039228
39	6.4	6.519388	-0.119388
40	5.9	6.008037	-0.108037

Compd. no.	PIC_{50} exp	PIC_{50} calc.	Residual
41	6.7	6.888615	-0.188615
42	6.6	6.841041	-0.241041
43	7	7.867512	-0.867512
44	7.9	7.965857	-0.065857
45	8.4	8.051451	0.348549
46	8.7	8.162088	0.537912
47	8.5	8.174478	0.325522
48	8.3	8.119512	0.180488
49	7.0	6.956740	0.043260

amide nitrogen improves the activity than that of aromatic substitution. Higher activity were observed for compounds having 8 to 11 atoms in the alkyl chain, while aromatic substitution resulted in inferior activity. It may be inferred that the fatty alkyl group increase the lipophilicity, Wiener index, thus favour the activity. Probably, the lipophilicity plays a determining role in transport through biological memberanes, while steric factors are important in interaction with receptor site.

Conclusion

As the objective of this study was to derive an optimally predictive model equation, eqn. 4 was found suitable and it can be used for prediction of PET-inhibitory activity of structurally related compounds.

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