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The study of inhibition of DNA synthesis by hydroxyurea(s)

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Abstract. A novel method for the study of inhibition of DNA synthesis by hydroxyurea(s) using topological indices and frontier molecular orbital energies: E_{homo}, E_{lumo} and E_{total} is described. The data suggest that the inhibitory activities of urea(s) can be successfully modelled by these molecular descriptors. Excellent results are obtained in multivariate systems as well as upon introducing a dummy parameter.

Keywords. QSAR studies, DNA synthesis; hydroxyureas; Wiener index; frontier molecular orbital energy; topological indices.

1. Introduction

Of late it has been known that the anticancer agents like hydroxyguanidine generally have hydroxyurea as a functional group. The antitumour activity of guanidine is well-known [1]. Young [2] has shown that, like hydroxyurea, hydroxyguanidine also inhibits DNA synthesis. The synthesis of a series of new hydroxyguanidine, thiosemicarbazones, designed primarily with the aim of combining the structural features of both hydroxyguanidine and carboxaldehyde, is also reported in the literature [3,4].

Inhibition of ribonucleotide reductase (RR) by hydroxyurea is well-known and it is widely believed that the essential functional group is –CHNHOH– [5,6]. RR catalyses one of the rate-determining steps of the DNA synthesis and its activity has also been found to be highly correlated to the proliferation of cells [7]. The activities of three other major enzymes of DNA synthesis, namely thymidylate synthetase (Tds), thymidine kinase (Tk) and DNA polymerase (DNAT) are not increased to the extent of that of RR [8,9].

The observed decrease in the biosynthesis of DNA is occasioned by the inhibitory effect of the drug upon the enzymatic conversion of ribonucleotides to deoxyribonucleotide [10]. The molecular mechanism by which hydroxyurea inhibits deoxyribonucleotide synthesis is not known.

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It is worthy of mention that the selective inhibition of RR has been used as a part of the overall strategy in the designing of chemotherapeutic agents. Although a large number of RR inhibitors are known, only hydroxyurea is currently available for clinical use. Inhibitors like guanazoles and thiosemicarbazones show significant *in vitro* activity against cell growth but their *in vivo* toxicities have evolved from their chemical use [11,12].

For the purpose of designing new potentially active compounds, the hydrophilic character of the hydroxyurea molecule should be modified in such a manner that the optimum balance of lipophilicity and hydrophilicity is achieved while retaining the important functional group, –CHNHOH–. In view of this, Gale and coworkers [13] synthesised several arylhydroxamic acids and assisted their activities as regards their effects on biosynthesis of DNA. These benzohydroxamic acids and their substituted derivatives exhibit interesting biological and chemical property [14]. Recently, Khadikar and coworkers [15] reported a QSAR (quantitative structure activity relationship) study on the effect of benzohydroxamic acids on DNA synthesis and observed that the functional group CHNHOH, as mentioned above, is responsible for the inhibitory activity of benzohydroxamic acids also.

Chan and others [10,16] have designed and synthesized a series of 2-hydroxy-1H-isoindol-1,3-diones and performed their QSAR analysis. Recently, one of the present authors (VKA) also has reported QSAR studies [6] on some anticancerous, antiviral and cytostatic agents. Both studies confirm that the functional group –CHNHOH– is necessary for the activity.

In an effort to clarify the relation between molecular structure and the inhibitory activity of hydroxyurea and its several derivatives, Khadikar and coworkers [17] have used the Wiener index [18] and its decomposition products [19,20] for investigating the role of the compounds under present study against Tds and DNA inhibition. These are the molecular invariants whereby the structure of the molecule is transformed into a number. The data needed for the study were adopted from the work of Young [2]. In a univariate correlation Khadikar and coworkers [17] found that the inhibitory activity of hydroxyurea and its derivatives are poorly correlated to the Wiener indices. However, these results slightly improve when the correlation is factorised into two groups. This factorised correlation suffers from the drawback that due to factorization poor sampling is achieved. However, they did not investigate these results using more accurate and more efficient multivariate analysis.

In view of the above and in an attempt to suggest more effective methods of modelling inhibition of DNA synthesis, as well as Tds inhibition by hydroxyurea and its derivatives, we have now calculated frontier molecular energies E_{homo}, E_{lumo} and E_{total} for these compounds and combined them with the Wiener indices used by Khadikar and coworkers [17] for obtaining better modelling methods. In addition, a dummy index (indicator coefficient, IC) is also introduced in the correlation analyses. Excellent results are obtained in multivariate analysis. The results are discussed below.

2. Methodology of modelling activity

A set of hydroxyurea derivatives together with hydroxyurea itself used in the present investigation is given in table 1. Their effects upon the rates of incorporation of thymidylate synthetase (Tds) and biosynthesis of DNA inhibition are also given in table 1. Note that these inhibitory activities are adapted from the work of Young [2].

Table 1. Hydroxyurea and its derivatives, their abbreviated forms and inhibitory effect upon incorporation of labeled precursors into DNA, RNA and protein of HeLa monolayers [2,13].

Compounds	Abbreviation	% Inhibition	
		Tds	DNA
Hydroxyurea	HU	92	100
Methoxyurea	MeOU	0	0
N-methyl-hydroxyurea	NMeHU	92	133
1-methoxy-1-methylurea	1MeO1MeU	0	0
N-ethyl-hydroxyurea	NEtHU	91	91
N-acetyl-hydroxyurea	NAcHU	89	111
3-phenyl-1-hydroxyurea	3PhHU	91	38
Di-hydroxyurea	DHU	94	108
N-hydroxyurethane	NHURT	92	92
N-hydroxyguanidine	NHGU	88	110
Guanidine	GU	0	0
3-phenyl-1-hydroxy-2-thiourea	3PH1H2TU	91	30

The calculation of W and its decomposition products were the calculation procedure as described earlier [18–20]. However, the same is described briefly as below.

2.1 *Wiener index (W)*

If $d(u, v|G)$ is the distance [17] of the vertices u and v of the graph G (i.e. the number of edges in the shortest path that connects u and v), $V(G)$ is the vertex set of G, then,

$$W = W(G) = \frac{1}{2} \sum_{u \in V(G)} \sum_{v \in V(G)} d(u, v|G). \tag{1}$$

For an acyclic molecular graph Wiener [18] discovered a remarkably simple method for the calculation of W. Let e be an edge of an acyclic molecular graph G (= a tree). Let $n_1(e|G)$ and $n_2(e|G)$ be the number of vertices of G lying on two sides of the edge e, then,

$$W = W(G) = \sum_{e \in E(G)} n_1(e|G) n_2(e|G). \tag{2}$$

Here $E(G)$ denotes the edge set of the graph G.

Recently, Luckovits [19,20] proposed decomposition of W into contributions attributable to single bonds (Ws) and double bonds (Wd):

$$W = Ws + Wd, \tag{3}$$

provided the compound does not contain any triple bond and does not have any aromatic nucleus.

In case the compound under study contains single, double and triple bonds, as well as an aromatic nucleus, then the decomposition of W into such contributions is given by the following equation:

$$W = Ws + Wd + Wt + Wa. \quad (4)$$

Note that *Wt* and *Wa* are the decomposition products of *W* attributed to the presence of triple bonds and aromatic nucleus.

2.2 *E_{homo}, E_{lumo} and E_{total} orbital energies*

Along with the Wiener indices mentioned above, the frontier orbital energies – the energy of highest occupied molecular orbital (E_{homo}), the energy of lowest unoccupied molecular orbital (E_{lumo}) and the total π-electron energy (E_{total}) were also used as molecular parameters for modelling the activities of hydroxyurea and its derivatives. These energies were calculated from HMO version 1.1 supplied by Wiesner (Department of Oncology and Immunology, New York). The data so obtained are recorded in table 2. The values of these energies are given in β units.

Table 2. Wiener indices (*W*, *Ws*, *Wd*), indicator coefficient (IC) and frontier molecular orbital energies (E_{homo}, E_{lumo}, E_{total}) for hydroxyurea and its derivatives used in the present investigation.

	Wiener indices				MO energies		
Compound	*W*	*Ws*	*Wd*	IC	E_{homo}	E_{lumo}	E_{total}
HU	120	112	8	1	0·8239	–1·1777	13·9554
MeOU	120	112	8	0	–0·2223	–0·1181	14·1837
NMeHU	120	112	8	1	–0·3548	–0·1257	14·4677
1MeO1MeU	120	112	8	0	–0·1694	–0·3858	14·8926
NEtHU	165	156	9	1	0·5148	–0·9701	16·2932
NAcHU	220	210	10	1	–0·1250	–0·5240	18·4406
3Ph1HU	355	342	13	1	0·6902	–0·9868	22·2424
DHU	165	156	9	0	0·7699	–1·1987	18·1773
NHURT	120	112	8	1	0·8200	–0·9823	17·2960
NHU	165	149	16	1	0·6609	–1·2356	13·1499
GU	120	106	14	0	0·8005	–1·2156	8·9319
3Ph1H2TU	560	534	26	1	0·5703	–0·9516	21·0668

Table 3. Correlation matrix for the correlation of Tds and DNA inhibition by hydroxyurea and its derivatives using Wiener indices and frontier MO energies.

	Tds	DNA	*W*	*Ws*	*Wd*	E_{homo}	E_{lumo}	E_{total}
Tds	1·0000							
DNA	–0·0141	1·0000						
W	–0·1355	–0·7910	1·0000					
Ws	–0·1157	–0·7943	0·9999	1·0000				
Wd	–0·5977	–0·3087	0·5152	0·4875	1·0000			
E_{homo}	0·1151	–0·5244	0·0555	0·0497	0·1833	1·0000		
E_{lumo}	0·0646	0·4116	–0·0681	–0·0563	–0·3492	–0·9465	1·0000	
E_{total}	0·3262	–0·7351	0·8173	0·8307	0·0493	0·1064	–0·0084	1·0000

Table 4. Regression parameters and quality of correlations of inhibitory activities against Tds by the compounds used in the present study using Wiener indices (*W*, *Ws*, *Wd*) and frontier MO energies (E_{homo}, E_{lumo}, E_{total}).

Correlation parameter (s)	*Ai* $i = 1, 2, 3, 4$	*B* const.	Standard deviation (*sd*)	Correlation coeff. (*R*)	*F*-ratio
W E_{total}	$A_1 = -0.0289$ $A_2 = 0.8364$	82·0274	1·4227	0·0072	3·645
Ws E_{total}	$A_1 = -0.0303$ $A_2 = -0.8663$	81·4763	1·4303	0·7673	3·580
W, E_{homo} E_{total}	$A_1 = -0.0288$ $A_2 = 0.1771$ $A_3 = 0.8314$	82·0099	1·5871	0·7713	1·958
W, E_{lumo} E_{total}	$A_1 = -0.0289$ $A_2 = -0.0333$ $A_3 = 0.8370$	81·9924	1·5906	0·7702	1·944
Ws, E_{homo} E_{total}	$A_1 = -0.0302$ $A_2 = 0.1345$ $A_3 = 0.8620$	81·4687	1·5971	0·7680	1·918
Wd, E_{homo} E_{total}	$A_1 = -0.4230$ $A_2 = 0.8195$ $A_3 = 0.2143$	91·1781	1·7246	0·7223	1·455
Wd E_{lumo} E_{total}	$A_1 = -0.4381$ $A_2 = -0.8211$ $A_3 = 0.2276$	90·7591	1·7478	0·7133	1·138
W, E_{homo}, E_{total} IC	$A_1 = -0.0180$ $A_2 = 1.2322$ $A_3 = 0.6176$ $A_4 = -2.7572$	85·2284	0·7914	0·9615	9·179
W, E_{lumo}, E_{total} IC	$A_1 = -0.0203$ $A_2 = -1.1144$ $A_3 = 0.6835$ $A_4 = -2.6001$	83·9917	0·9321	0·9462	6·408
Ws E_{homo}, E_{total} IC	$A_1 = -0.0187$ $A_2 = 1.2086$ $A_3 = 0.6332$ $A_4 = -2.7627$	84·9240	0·8158	0·9540	8·593
Ws, E_{lumo}, E_{total} IC	$A_1 = -0.0211$ $A_2 = -1.0699$ $A_3 = 0.7009$ $A_4 = -2.6010$	83·6783	0·9539	0·9435	6·084
Wd E_{homo}, E_{total} IC	$A_1 = -0.2867$ $A_2 = 1.7343$ $A_3 = 0.2342$ $A_4 = -2.9650$	91·2539	0·7129	0·9689	11·487
Wd, E_{lumo}, E_{total} IC	$A_1 = -0.3296$ $A_2 = -1.8418$ $A_3 = 0.2611$ $A_4 = -2.8535$	90·3197	0·9094	0·9488	6·770

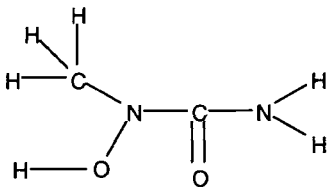

Figure 1. Molecular structure of NMeHU.

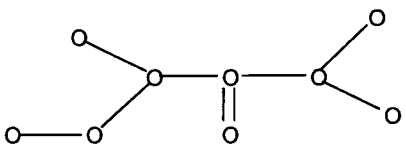

Figure 2. Molecular graph of NMeHU.

2.3 *Regression analysis*

The regression analysis for modelling the activities of hydroxyurea and its derivatives were calculated using MSTAT software. The correlation matrix derived from this program is given in table 3. The regression parameters as well as quality of different monovariate and multivariate correlations are recorded in tables 4 and 5. The extent of modelling is summarized in tables 6 and 7.

As usual, the molecular graph G for the compounds under the present study were obtained by suppressing all the C–H bonds in the compounds listed in table 1. Thus, for example, if N-methylhydroxyurea (NMeHU) is represented by its molecular structure as shown in figure 1 then, suppressing all the three C–H bonds in the Me group and representing all the atoms by a dot "." or by a small circle "O", produces the molecular graph of NMeHU as shown in figure 2. All the three Wiener indices (*W*, *Ws* and *Wd*) were calculated from such graphs of the respective hydroxyurea derivatives and are presented in table 2. The frontier molecular orbital energies, E_{homo}, E_{lumo} and E_{total}, are also given in table 2.

3. Results and discussion

A perusal of table 1 shows that MeOU, 1MeO1MeU and Gu are inactive towards both Tds and DNA inhibition. Therefore, these compounds are deleted in the univariate as well as multivariate regression analyses. From the data presented in table1 the following conclusions are drawn with regard to the influence of Wiener indices (*W*, *Ws*, *Wd*) on the activities.

(i) The inhibition of hydroxyurea and its derivatives used in the present investigation increases with a decrease in Wiener indices (*W*, *Ws*, *Wd*).
(ii) The inhibition follows a linear relationship with these Wiener indices.

Table 5. Regression parameters and quality of correlations of inhibitory activities against DNA by the compounds used in the present study using Wiener indices (*W*, *Ws*, *Wd*) and frontier MO energies (E_{homo}, E_{lumo}, E_{total}).

Correlation parameter (s)	*Ai* $i = 1, 2, 3$	*B* const.	Standard deviation (*sd*)	Correlation coeff. (*R*)	*F*-ratio
W	$A = -0.2762$	147.2448	18.2311	−0.7910	10.027
Ws	$A = -0.2825$	145.5190	18.1037	−0.7943	10.253
W	$A_1 = -0.2669$	159.4107	12.3325	0.9259	15.011
E_{homo}	$A_2 = -29.1269$				
W	$A_1 = -0.2677$	168.8943	16.1813	0.8685	7.672
E_{lumo}	$A_2 = 25.7477$				
W,	$A_1 = -0.1985$	175.8638	19.2999	0.8065	4.650
E_{total}	$A_2 = -2.5393$				
Ws,	$A_1 = -0.2740$	158.0247	11.9215	0.9309	16.240
E_{homo}	$A_2 = -29.3777$				
Ws,	$A_1 = -0.2752$	168.0098	15.7926	0.8752	8.179
E_{lumo}	$A_2 = 26.3664$				
Ws,	$A_1 = -0.2089$	171.9511	19.3074	0.8063	4.645
E_{total}	$A_2 = 2.3194$				
Wd,	$A_1 = -2.5973$	236.9518	20.1827	0.7859	4.039
E_{total}	$A_2 = -6.7320$				
E_{homo},	$A_1 = -27.2580$	218.2171	16.5005	0.8628	7.282
E_{total}	$A_2 = -6.4106$				
E_{lumo},	$A_1 = 29.0430$	238.3624	17.6481	0.8412	6.052
E_{total}	$A_2 = -6.8251$				
W,	$A_1 = -0.2719$	125.6088	8.3983	0.9732	23.842
E_{homo}	$A_2 = -82.2473$				
E_{lumo}	$A_3 = -66.5881$				
W,	$A_1 = -0.2139$	178.6686	13.2259	0.9320	8.818
E_{homo},	$A_2 = -28.4368$				
E_{total}	$A_3 = -1.7344$				
W,	$A_1 = -0.1742$	204.0349	16.7490	0.8885	4.996
E_{lumo}	$A_2 = 26.8565$				
E_{total}	$A_3 = -3.0354$				
Ws,	$A_1 = -0.2769$	125.5750	8.3450	0.9735	24.146
E_{homo}	$A_2 = -79.8334$				
E_{lumo}	$A_3 = -63.2209$				
Ws,	$A_1 = -0.2301$	173.5867	12.9846	0.9346	9.198
E_{homo}	$A_2 = -28.7890$				
E_{total}	$A_3 = -1.3875$				
Ws,	$A_1 = -0.1874$	200.1174	16.6044	0.8905	5.107
E_{lumo}	$A_2 = 27.1828$				
E_{total}	$A_3 = -2.7563$				
Wd,	$A_1 = -5.0502$	97.4895	24.9465	0.7299	1.520
E_{homo}	$A_2 = -123.5796$				
E_{lumo}	$A_3 = -122.4452$				
Wd,	$A_1 = -1.8925$	235.4172	17.0128	0.8847	4.801
E_{homo}	$A_2 = -25.0935$				
E_{total}	$A_3 = -6.3548$				
Wd,	$A_1 = -1.4222$	248.3199	19.0589	0.8528	3.555
E_{lumo}	$A_2 = 25.3069$				
E_{total}	$A_3 = -6.7610$				

Table 6. Estimated values for Tds inhibition using (5)–(7).

Compound	Obs.* Tds inhib.	Estimated Tds inhibition					
		I (5)		II (6)		III (7)	
		Est.	Res.	Est.	Res.	Est.	Res.
HU	90	90·69	−0·69	89·9	0·10	89·95	0·05
NMeHU	92	91·73	0·27	91·56	0·44	91·57	0·43
NEtHU	91	90·42	0·58	90·18	0·82	90·20	0·80
NAcHU	89	89·52	−0·52	89·75	−0·75	89·75	−0·75
3Ph1HU	91	90·97	0·03	90·67	0·33	90·67	0·33
DHU	94	94·27	−0·27	94·44	−0·44	94·43	−0·43
NHURT	92	91·47	0·53	92·01	−0·01	92·00	0·00
NHGU	88	87·99	0·01	88·50	−0·50	88·44	−0·44
3Ph1H2TU	91	90·08	0·98	89·98	0·92	90·09	0·91

*Abbreviations: Obs. – observed; inhib. – inhibition; est – estimated; res – residue

Table 7. Estimated values for DNA inhibition using (8), (9), (10) (11).

Compound	Obs.* DNA inhib.	Estimated DNA inhibition							
		I (8)		II (9)		III (10)		IV (11)	
		Est.	Res.	Est.	Res.	Est.	Res.	Est.	Res.
HU	100	103·39	−3·39	103·14	−3·14	103·64	−3·64	105·37	−5·37
NmeHU	133	137·72	−4·72	137·77	−4·77	130·52	2·48	138·00	−5·00
NetHU	91	100·39	−9·39	100·64	−9·39	93·98	−2·98	100·48	−9·48
NacHU	111	104·35	6·65	104·17	6·65	111·02	−0·02	103·19	7·81
3Ph1HU	38	44·57	−6·57	44·06	−6·06	38·02	−0·02	44·45	−6·54
DHU	108	103·50	4·44	103·25	4·75	103·24	4·76	99·69	8·31
NHURT	92	92·95	−0·95	92·25	−0·25	90·95	1·05	89·56	2·44
NHGU	110	96·13	13·87	97·79	12·21	108·62	1·35	101·78	8·22
3Ph1H2TU	30	31·36	−1·36	31·00	1·00	30·08	−0·08	31·05	−1.05

*Abbreviations: as in table 6

(iii) Degeneracy is observed both in the activities as well as in Wiener indices.
(iv) Both the inhibition and Wiener indices are influenced by substituents in hydroxyurea.
(v) In case of MeOU, IMeO–1MeU and GU the Tds and DNA inhibitions are zero and are thus not governed by their Wiener indices (*W*, *Ws* and *Wd*).
(vi) In spite of the observed degeneracy, the correlation between the activities (Tds and DNA inhibition) and the Wiener indices are very good.

A close look at table 4 indicates that Tds inhibition is not governed by any of the single correlation parameters (*W*, *Ws*, *Wd*, E_{homo}, E_{lumo} and E_{total}), therefore, no univariate correlation is possible for modelling Tds inhibition. In case of bi- and tervariate correlations the inhibition of Tds is poorly monitored. All such correlations have the correlation coefficient of the order of 0·7. In order to improve the correlation potential,

we have introduced an indicator coefficient (IC). By introducing IC excellent multivariate correlations with correlation coefficients of the order of 0·96 are obtained. The most prominent correlations are W–E_{homo}–Et–IC, Ws–E_{homo}–E_{total}–IC and Wd–E_{homo}–E_{total}–IC. This indicates that the correlation potential of Wiener indices W, Ws and Wd is similar for modelling Tds inhibition by hydroxyurea and its derivatives. The following regression equations are proposed respectively for these multivariate correlations.

(i) W–E_{homo}–E_{total}–IC

$$\%\text{Tds (inhibition)} = -(0{\cdot}0180)W + (1{\cdot}2322)E_{homo} + (0{\cdot}617688)E_{total} - (2{\cdot}7572)\text{IC} + 85{\cdot}2284. \quad (5)$$

(ii) Ws–E_{homo}–E_{total}–IC

$$\%\text{Tds (inhibition)} = -(0{\cdot}0187)Ws + (1{\cdot}2086)E_{homo} + (0{\cdot}6332)E_{total} - (2{\cdot}7627)\text{IC} + 84{\cdot}9240. \quad (6)$$

(iii) Wd–E_{homo}–E_{total}–IC

$$\%\text{Tds (inhibition)} = -(0{\cdot}2867)Wd + (1{\cdot}7343)E_{homo} + (0{\cdot}2342)E_{total} - (2{\cdot}7650)\text{IC} + 91{\cdot}2539. \quad (7)$$

The observed coefficients as well as the constants involved in the above equations confirm the similar potential of W, Ws and Wd in modelling Tds inhibition. In case of Wd–E_{homo}–E_{total}–IC correlation the coefficient and the constants are slightly higher which may be attributed to the double bond character of the compounds under the present study. The indicator coefficient IC = 0 accounts for specific effect of bulky group like $-OCH_3$ and also accounts for the zero activity exhibited by the compounds containing such groups. If the indicator coefficient IC = 1, it takes into account the contribution of the functional group, –CHNOH–, present in the compounds towards inhibitory activity against both Tds and DNA inhibition.

Equations (5)–(7) given above represent very significant correlations and suggest that Tds inhibition is dependent on substitution in hydroxyurea, and their single as well as double bond character, and thus is conductive to the activity and attends an optimum value when correlation becomes multivariate. These equations also indicate that if the substituent is, $-OCH_3-$, its IC will be zero and consequently the activity exhibited will be nil.

We now discuss the DNA inhibition by hydroxyurea and its derivatives using Wiener indices as well as the frontier orbital energies and their combinations. The data presented in table 5 were used for this purpose.

Examination of table 5 indicates that unlike Tds inhibition, the inhibition of biosynthesis of DNA can be modelled by single parameter W as well as Ws. In both the cases "good" correlations resulted. The magnitude of the correlation coefficient indicates that W and Ws have similar correlation potential.

The data presented in the table 5 also indicate that the DNA inhibition can be more efficiently and successfully modelled by bi- and tervariate-correlations. "Excellent" correlations were obtained with bivariate correlations: W–E_{homo} and Ws–E_{homo}. The latter

correlation was found to be slightly better than the former. Table 5 indicates that the regression expressions for these bivariate correlations are as below.

(i) W–E_{homo}

$$\%\text{DNA (inhibition)} = -(0{\cdot}2669)W-(29{\cdot}1269)E_{homo} + 159{\cdot}4107. \quad (8)$$

(ii) Ws–E_{homo}

$$\%\text{DNA (inhibition)} = -(0{\cdot}2740)Ws-(29{\cdot}3777)E_{homo} + 158{\cdot}0247. \quad (9)$$

Once again, the magnitude of the correlation coefficients as well as the value of the constants confirms that W and Ws have similar potential in modelling DNA inhibition.

The correlation of DNA inhibition still becomes interesting on considering tervariate regressions to the extent that now the correlation coefficients are raised to values of the order of 0·973. Correlations with such a high potential are W–E_{homo}–E_{lumo} and Ws–E_{homo}–E_{lumo}. The regression expressions for such correlations, based on the data given in table 5 are as below.

(i) W–E_{homo}–E_{lumo}

$$\%\text{DNA (inhibition)} = -(0{\cdot}2719)W-(22{\cdot}2430)E_{homo} -(66{\cdot}5881)E_{lumo} + 125{\cdot}6088. \quad (10)$$

(ii) Ws–E_{homo}–E_{lumo}

$$\%\text{DNA (inhibition)} = -(0{\cdot}2769)Ws-(79{\cdot}8334)E_{homo} -(63{\cdot}2209)E_{lumo} + 125{\cdot}5750. \quad (11)$$

The magnitudes of the coefficients and the constants involved in the above equations reveal that the role of W and Ws in exhibiting DNA inhibition is similar.

It is interesting to note that the corresponding correlation involving Wd viz.: Wd–E_{homo}–E_{lumo} has comparatively poor correlation potential as represented by its correlation coefficient of 0·7299. This means that the double bond character of compounds under the present study has no significant role in modelling the inhibition of biosynthesis of DNA. It is also noteworthy that the introduction of indicator coefficients is not needed for modelling DNA inhibition.

4. Conclusion

From the above discussion and results the following conclusions could be drawn.

(i) For inhibitory activity the functional group, –CHNOH–, must be present in all the compounds analogous to hydroxyurea.
(ii) Substituents like $-OCH_3-$ exhibit 0% activity towards DNA as well as towards Tds inhibition.
(iii) Presence of alkyl groups is found to be detrimental for the inhibition of DNA and Tds.

(iv) The presence of a phenyl group at 3-position decreases the inhibition of DNA synthesis roughly in the order of 1/3 activity of hydroxyurea.
(v) Addition of $-CH_3-$ group to nitrogen of the hydroxyurea increases DNA inhibition but it does not have any effect on Tds inhibition.
(vi) Replacement of oxygen by sulphur does not result in any significant advantage.
(vii) Identical di-substitution (di-hydroxyurea) increases the inhibitory potency of hydroxyurea towards both Tds and DNA inhibition.
(viii) Inhibition potential of all the correlation parameters used against Tds in all the bi- and tervariate regressions is similar and thus, all are equally good for modelling Tds inhibition.
(ix) To increase the correlation potential of Tds inhibition, the introduction of a dummy parameter, namely indicator coefficient (IC), was necessary for taking into account the zero activity of compounds containing bulky groups.
(x) On introducing IC, the tervariate correlation gave "excellent" results for modelling Tds inhibition.
(xi) No IC is needed for modelling DNA inhibition.
(xii) Univariate correlations used by Khadikar and coworkers [17] using Wiener indices alone was of poor quality. These have now been improved, using molecular orbital energies together with Wiener indices.

In order to confirm the above findings, we have estimated Tds and DNA inhibition by using (5) to (11). We see that these estimated inhibitions are very close to the observed ones. The data needed for this conclusion are presented in table 6 and 7 respectively for Tds and DNA inhibition.

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