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QSAR Study On Some Orally Active Uracil Derivatives as Human Gonadotropin–Releasing–Hormone Receptor Antagonists

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Abstract

Motivation. Antagonism of human gonadotropin–hormon–releasing receptor (hGnRH–R) using peptide antagonists is a way to treat a variety of sex–hormone–dependent diseases. However, low bioavailability of these peptide antagonists intensifies the need for some orally active small molecules, which may act as hGnRH–R antagonists. To find more active compounds, QSAR study was performed on some orally active substituted uracil derivatives.

Method. A QSAR study of 32 derivatives of orally active substituted uracils was done using topological and quantum chemical descriptors. Correlation and multiple regression analyses were performed to develop QSAR models.

Results. Results show that the importance of ETSA and RTSA indices of two particular atoms. ETSA index of the atom number 17 and RTSA index of the atom number 19 are important because these atoms may involve in electronic interaction and van der Waals interaction with the receptor respectively. The study also shows the importance of average atomic charges of atom numbers 1, 2, 3, 4, 5, 6 and 9. It suggests the importance of approximate surface area in biological activity. Frontier electron density for electrophilic attack at atom number 24 is also found to be useful for the small molecular antagonism towards the receptor.

Conclusions. The pharmacophoric requirement for the substituted uracil derivatives for their human GnRH–R antagonism is illustrated optimally by two tetravariate QSAR models. These models show that compounds with reduced surface area, higher atomic charge and lower electrophilic attack at the atom number 24 may have an increased binding affinity towards hGnRH receptor.

Keywords. Oral uracil antagonists; human gonadotropin–releasing–hormone receptor; electrotopological state atom index; ETSA; refractotopological state atom index; RTSA; quantitative structure–activity relationship; QSAR.

Abbreviations and notations

hGnRH–R, Human gonadotropin releasing hormone receptor	Avgqc, Average atomic charge of atom
ETSA, Electrotopological state atom index	$f^{(E)}$, Frontier electron density
RTSA, Refractotopological state atom index	QSAR, Quantitative structure–activity relationship

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1 INTRODUCTION

Gonadotropin–releasing hormone (GnRH) plays an important role in the biology of reproduction [1]. It is the central regulator of the reproductive hormonal cascade and was isolated from mammalian hypothalami as a decapeptide (pGlu–His–Trp–Ser–Tyr–Gly–Leu–Arg–Pro–Gly–NH_2) [2]. Secretions of luteinizing hormone (LH) and follicle–stimulating hormone (FSH) are under the positive control of GnRH. In neurons of hypothalamus, it is synthesized from a 92 amino acid precursor molecule and released to the local vasculature in a pulsatile manner and activates the specific receptors in the anterior pituitary gland leading to the release of gonadotropins, LH and FSH. These hormones, in turn, are released into the general circulation and bind to the receptors on cells in the ovaries or testes to stimulate steroidogenesis and gametogenesis. Receiving this stimulation, gonads synthesize and secret the steroid sex hormones (estrogen and progesterone in females and testosterone in males). These steroid sex hormones, in turn, exert their effects on development of secondary sexual characteristic throughout the body [3–4]. Thus, GnRH exerts its actions by binding to and activating the GnRH receptor (GnRH–R) in the pituitary gland. This receptor belongs to the Class A G–protein–coupled receptor (GPCR) family [5]. The notion that antagonism of the GnRH–R in the pituitary gland is an effective way to treat diseases which are exaggerated by the presence of steroidal sex hormones. Thus, endometriosis, uterine fibroids, benign prostate hyperplasia, fertility disorders, precocious puberty as well as prostate, ovarian and breast cancers [6–10] are originated from hypothalamic–pituitary–gonadal axis physiology and may be treated using hGnRH–R antagonists.

GnRH–R agonists are clinically used in the treatment of sex–steroid–dependent diseases. These agonists mimic GnRH to stimulate receptors on the pituitary gland, mediating the release of LH and FSH. After a transient rise in hormone production or the ‘flare effect’, the administration of GnRH–R agonists desensitizes the receptor resulting in a down–regulation of GnRH–Rs. GnRH–R down–regulation leads to a decrease in the circulating levels of LH, testosterone and estrogen with consequent decline in gonadal gametogenesis and steroid biosynthesis. This phenomenon has successfully lead to an extensive application of GnRH peptide agonists for the treatment of a variety of sex–hormone–dependent diseases. Peptide agonists such as leuprolide [11] are commercially available. Treatment with a GnRH agonist initially leads to ‘flare effect’ but GnRH antagonists act immediately at the receptor and quickly suppressing the release of FSH and LH. A number of peptide antagonists such as cetrotide [6] are currently available in the market. Due to the low oral bioavailability, administrations of these peptides are normally routed avoiding gastrointestinal tract and used as injection or depot formulation. Responding to the need for a more convenient route of administration, search for new orally active small molecule GnRH–R antagonists was intensified in the last few years and several distinct classes of such molecules have been reported [12].

As a part of our composite program of rational drug design [13–44], a quantitative structure–

activity relationship (QSAR) study was carried out using electrotopological state atom and refractrotopologicl state atom (ETSA and RTSA respectively) indices, atomic charges as well as quantum chemical descriptors on a series of substituted uracils which are orally active human GnRH–R antagonists. This was done to get an insight into the structural information for more potent inhibitors for the treatment of various sex–steroid–dependent diseases including prostate and breast cancers. The general structure of the substituted uracils is shown in Figure 1. The binding affinity (K_i) values of uracil derivatives were collected from the published work of Tucci *et al.* [45] and were used for the QSAR study.

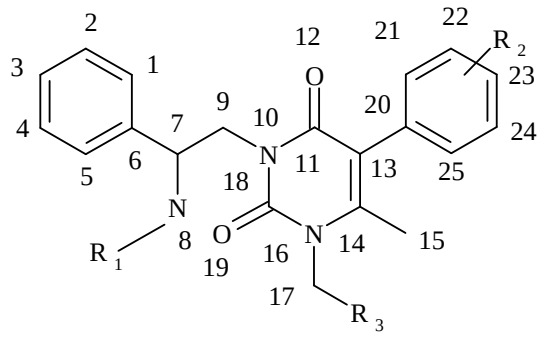

Figure 1. General structure of orally active substituted uracils with arbitrary numbering.

2 MATERIALS AND METHODS

2.1 Biological Activity

For the development of QSAR models with substituted uracils, the binding affinity (K_i in nM) data of those substituted uracils towards human GnRH–R were taken from [45] and the negative logarithm of K_i (pK_i) was utilized as the biological activity parameter. Tucci *et al.* [45] evaluated these synthesized compounds for their ability to inhibit [^{125}I–Tyr^5, DLeu^6, NMeLeu^7, Pro^9–Net] GnRH agonist binding to the cloned human, monkey and rat GnRH–Rs following the method described by Perrin *et al.* [46]. The binding affinity data of substituted uracils are shown in Table 1.

2.2 Parameters and Dataset Used

The negative logarithm of the binding affinity (pK_i) of the substituted uracils towards human GnRH–R was used as the dependent parameter to develop QSAR models. Electrotopological state atom index (ETSA), refractotopological state atom index (RTSA), quantum chemical descriptors like atomic charges, frontier electron density for highest occupied molecular orbital (HOMO) and approximate surface area (SA) were considered for the QSAR study as independent parameters. Arbitrary numbering (shown in Figure 1) was used to calculate ETSA and RTSA indices. The negative logarithms of K_i (pK_i) were used for developing QSAR model to get linear relationship with the independent variables and are shown in Table 1. Semiemperical quantum chemical

descriptor calculations of these substituted uracils were done according to the AM1 method [47] using Hyperchem Release 7.0 Pro Package [48]. Quantum chemical descriptors such as atomic charges (Q), molecular orbital energies (HOMO, LUMO), Frontier electron density, approximate surface area (SA) were considered and calculated by Hyperchem Release 7.0 Pro Package [48].

ETSA and RTSA indices were calculated atom wise using the computer program "Mouse" [49] developed in our laboratory. Before the calculations, atom of these molecules were numbered arbitrarily keeping the serial number of atoms same in all molecules as shown in Figure 1.

Table 1. Binding affinity data of the substitute uracil derivatives

Cpd[a]	R_1	R_2	R_3	K_i (nM)	pK_i
1	H	3MeO	2,5–$F_2C_6H_4$	2.3 ± 0.1	8.638
2	H	3,4–OCH_2O	2,5–$F_2C_6H_4$	3.4 ± 0.3	8.468
3	H	3,4–OCH_2CH_2O	2,5–$F_2C_6H_4$	5.1 ± 0.4	8.292
4	H	4–MeS	2,5–$F_2C_6H_4$	13.0 ± 2.3	7.886
5	H	4–PhO	2,5–$F_2C_6H_4$	8.5 ± 0.9	8.070
6	H	2–Cl	2,5–$F_2C_6H_4$	2.8 ± 0.9	8.553
7	H	2–F	2,5–$F_2C_6H_4$	5.6 ± 0.7	8.252
8	H	2–F,3–Me	2,5–$F_2C_6H_4$	3.1 ± 0.2	8.509
9	Me	3MeO	2,5–$F_2C_6H_4$	6.4 ± 0.5	8.194
10	Me	3,4–OCH_2O	2,5–$F_2C_6H_4$	5.6 ± 0.7	8.252
11	Me	3,4–OCH_2CH_2O	2,5–$F_2C_6H_4$	13.0 ± 2.5	7.886
12	H	2–F	$MeOCH_2$	1200.0 ± 210.0	5.921
13	H	2–F	c–Pr	880.0 ± 83.0	6.055
14	H	2–F	i–Pr	570.0 ± 69.0	6.244
15	H	2–F	c–Hx	140.0 ± 24.0	6.854
16	H	2–F	$PhCH_2$	880.0 ± 100.0	6.055
17	H	2–F	2–Py	64.0 ± 9.0	7.194
18	H	2–F	3–Py	980.0 ± 120.0	6.009
19	H	2–F	Ph	53.0 ± 4.0	7.276
20	H	2–F	4–FC_6H_4	63.0 ± 5.0	7.201
21	H	2–F	3– FC_6H_4	61.0 ± 4.0	7.217
22	H	2–F	2– FC_6H_4	20.0 ± 2.0	7.699
23	H	2–F	2–ClC_6H_4	14.0 ± 4.0	7.854
24	H	2–F	2–BrC_6H_4	4.6 ± 0.9	8.337
25	H	2–F	2–MeC_6H_4	20.0 ± 5.0	7.699
26	H	2–F	2–MeOPh	100.0 ± 37.0	7.000
27	H	2–F	2–$CF_3SC_6H_4$	180.0 ± 19.0	6.745
28	H	2–F	2–$CF_3C_6H_4$	3.1 ± 0.3	8.509
29	H	2–F	2–CF_3–5–FC_6H_4	3.9 ± 0.3	8.409
30	H	2–F	2,6–$F_2C_6H_4$	5.6 ± 0.7	8.252
31	H	2–F	2–Cl–6–FC_6H_4	0.61 ± 0.1	9.215
32	H	2–F	2–Cl–4–F C_6H_4	21.0 ± 6.0	7.678

[a] Compound number

2.2.1 Electrotopological state atom index

Electrotopological state atom (ETSA) index, developed by Kier and Hall [50–52], is an atom/ sub–molecular descriptor encoding both electronic character and topological environment of each skeletal atom in a molecule. It is derived from the chemical graph theoretic approach and has two basic components: (1) the intrinsic topological and electronic state (I_i) of an atom; (2) the effect of

the environment (perturbation factor, ΔI_j) influencing the atom considering differences in the intrinsic topological states of different atoms and topological distance among these which determine the magnitude of interactions.

Electronic factors include the concept of polarity, charge and energy levels. Topological factors attribute the arrangement of atoms across the skeleton, concepts of steric relations and bulk as well as the relationships between various non–bonded parts of a molecule. The intrinsic value includes both electronic and topological information. The count of pi and lone pair of electrons give important electronic information. The important topological attribute is the relative location of the atoms within the molecule or the relative degree of mantle–atom or buried–atom nature.

The intrinsic state value of an atom is expressed as:

$$I_i = [(2/N)^2\delta^v + 1]/\delta \quad (1)$$

Where N stands for the principle quantum number of the valence electrons, δ^v and δ indicate the count of valence electrons and sigma electrons associated with the atom i in the hydrogen–suppressed graph.

The perturbation effect (ΔI_j) stands for the influence of information field on the intrinsic atom value (I_i). It is the function of the difference in intrinsic values I_i (of an atom i) and I_j (of atom j) and expressed as:

$$\Delta I_j = f(I_i - I_j) \quad (2)$$

The influence of the atom j on the atom i decrease with the increase in the topological distance in the shortest path (graph separation) between atom i and j. To account for this Eq. (2) is modified with a function r_{ij}^2, which is the square of graph separation, i.e., the count of skeletal atoms in the shortest path connecting the atoms i and j including both atoms. The general expression for the perturbation effect is as follows:

$$\Delta I_j = \sum (I_i - I_j)/ r_{ij}^2 \quad (3)$$

Summation of the intrinsic state of an atom and the field is called electrotopological state (E–state) of the atom and expressed as:

$$S_i = I_i + \Delta I_j \quad (4)$$

Both the bonded and non–bonded interactions are considered in the E–state. The bonded interactions depend on difference in electronegativity among the adjacent atoms and the non–bonded component may act through the inductive effect across the skeleton. The non–bonded interaction is a function of the graph separation factor and the difference of electronegativity. Thus, E–state represents electronic distribution information modified by both local and global topology. The information encoded in the E–state value for an atom is the electronic accessibility at that atom. This index has been used to determine the pharmacophore moieties of biologically active

congeneric compounds.

2.2.2 Refractotopological state atom index

Refractotopological state atom (RTSA) index is a descriptor of atoms for QSAR study defined by Carrasco *et al.* [53]. RTSA index is based on the influence of the dispersive forces of each atom on the other atoms in a molecule modified by the molecular topology. It depends on the atomic refractivities and the topological environment of the atom. The sum of the atomic refractivities, *i.e.*, molar refractivity is directly proportional to the polarizability of a substance that determines London force/dispersive force [54] between nonpolar molecules. The RTSA index (R_i) of an atom *i* in a molecule is composed of an intrinsic refractivity (AR_i) and the perturbation effect (ΔAR_i) in the non–hydrogen depleted graph and is shown in equation (5).

$$R_i = AR_i + \Delta AR_i \quad (5)$$

As RTSA index expresses the atomic contribution of the molar refractivity related to dispersive forces in biologically active sites and also contains topological information about the chemical structure of the atomic environment. It is useful in modeling the dispersive / van der Waals interactions with receptors.

2.2.3 Atomic charge

Atomic charge is the difference between the charge on the core and the electron density on the atom.

2.2.4 Frontier electron density

Frontier electron theory [55] assumes that the least tightly bound electron would be the most reactive with an electrophilic reagent. The π–electrons in HOMO, thus, would be important in a reaction. The electrophilic reactivity is predicted to occur at a position in the molecule that has the highest electron density in HOMO.

2.3 Statistical Analysis

Multiple regression analysis was performed using the binding affinity (K_i in nM) data of the substituted uracils towards human GnRH–R as the dependent variable and topological indices as well as quantum chemical descriptors as the independent variables. The statistical analysis was done using the software “Multi Regress” [56] developed in our laboratory. The correlation analysis [57] of the independent parameters and the biological activity was carried out. Intercorrelated parameters were eliminated in a stepwise fashion. The statistical quality of the regression equations were judged by the parameters like correlation coefficient (*R*), adjusted R^2 (R^2_A), variance ratio (F) at specified degrees of freedom (df), probability factor related to F–ratio (p), standard error of the

estimate (SEE). Significant level of the regression coefficient and intercept of all equations were determined by *t*–statistics and *p*–values of the corresponding parameters. All possible combinations of parameters were considered to build QSAR model. The descriptors used to develop QSAR equations are recorded in Table 2.

Table 2. ETSA indices, RTSA indices and semi–empirical quantum chemical descriptors

Cpd[a]	S_{17}	R_{19}	qC_1	qC_2	qC_3	qC_4	qC_5	qC_6	qC_9	Avgqc[b]	SA	logP	$f^{(E)}{}_{24}$[c]
1	–0.388	–0.598	–0.124	–0.130	–0.128	–0.130	–0.111	–0.069	–0.067	–0.108	3.570	597.710	0.013
2	–0.401	–0.576	–0.124	–0.130	–0.128	–0.130	–0.111	–0.069	–0.067	–0.108	3.510	562.000	0.040
3	–0.401	–0.600	–0.122	–0.130	–0.128	–0.130	–0.113	–0.068	–0.067	–0.108	3.140	577.950	0.041
4	–0.361	–0.652	–0.124	–0.130	–0.128	–0.130	–0.110	–0.069	–0.067	–0.108	3.910	614.650	0.145
5	–0.397	–0.659	–0.125	–0.130	–0.127	–0.130	–0.109	–0.070	–0.067	–0.108	5.250	643.950	0.117
6	–0.402	–0.618	–0.125	–0.130	–0.128	–0.130	–0.110	–0.068	–0.067	–0.108	4.340	560.850	0.000
7	–0.481	–0.547	–0.125	–0.130	–0.128	–0.130	–0.109	–0.068	–0.067	–0.108	3.960	544.770	0.001
8	–0.482	–0.579	–0.125	–0.130	–0.128	–0.130	–0.110	–0.068	–0.067	–0.108	4.430	580.410	0.001
9	–0.365	–0.650	0.115	0.132	0.129	0.132	0.117	0.065	0.057	0.106	3.980	625.330	0.000
10	–0.379	–0.628	–0.113	–0.132	–0.129	–0.132	–0.118	–0.067	–0.057	–0.107	3.910	594.490	0.040
11	–0.379	–0.651	–0.112	–0.133	–0.130	–0.132	–0.118	–0.067	–0.057	–0.107	3.550	612.810	0.041
12	0.239	–0.451	–0.124	–0.131	–0.128	–0.130	–0.111	–0.068	–0.068	–0.108	1.740	562.020	0.001
13	0.535	–0.500	–0.124	–0.131	–0.128	–0.130	–0.111	–0.068	–0.067	–0.108	2.620	505.130	0.000
14	0.424	–0.551	–0.125	–0.130	–0.128	–0.130	–0.109	–0.069	–0.067	–0.108	3.120	555.160	0.001
15	0.535	–0.661	0.125	0.131	0.128	0.130	0.110	0.068	0.067	0.108	3.800	550.950	0.000
16	0.358	–0.648	0.124	0.031	0.128	0.130	0.111	0.068	0.067	0.108	3.930	585.370	0.000
17	0.146	–0.574	–0.124	–0.131	–0.128	–0.130	–0.110	–0.069	–0.068	–0.108	1.540	533.710	0.000
18	0.195	–0.603	0.124	0.130	0.128	0.130	0.111	0.069	0.068	0.108	1.570	531.620	0.000
19	0.258	–0.628	–0.124	–0.130	–0.128	–0.130	–0.111	–0.069	–0.068	–0.108	3.680	543.600	0.000
20	0.090	–0.604	–0.125	–0.130	–0.127	–0.130	–0.109	–0.070	–0.068	–0.108	3.820	556.240	0.001
21	0.018	–0.597	–0.124	–0.130	–0.128	–0.130	–0.110	–0.069	–0.068	–0.108	3.820	555.720	0.000
22	–0.112	–0.587	–0.125	–0.130	–0.128	–0.130	–0.109	–0.069	–0.068	–0.108	3.820	548.030	0.001
23	0.131	–0.680	–0.124	–0.131	–0.128	–0.130	–0.111	–0.069	–0.068	–0.108	4.200	569.580	0.001
24	0.216	–0.743	–0.125	–0.130	–0.128	–0.130	–0.109	–0.069	–0.068	–0.108	4.470	579.070	0.001
25	0.263	–0.679	–0.125	–0.130	–0.128	–0.130	–0.110	–0.069	–0.068	–0.108	4.150	570.690	0.000
26	0.150	–0.658	–0.125	–0.130	–0.128	–0.130	–0.110	–0.068	–0.068	–0.108	3.430	587.850	0.002
27	–0.258	–0.704	0.125	0.130	0.127	0.130	0.110	0.070	0.069	0.109	5.710	622.880	0.000
28	–0.470	–0.589	–0.123	–0.131	–0.128	–0.130	–0.112	–0.069	–0.069	–0.109	4.570	579.620	0.000
29	–0.709	–0.559	–0.124	–0.130	–0.127	–0.130	–0.110	–0.070	–0.069	–0.109	4.700	596.300	0.000
30	–0.481	–0.547	–0.125	–0.130	–0.128	–0.130	–0.110	–0.068	–0.067	–0.108	3.960	545.090	0.000
31	–0.238	–0.640	–0.125	–0.130	–0.128	–0.130	–0.109	–0.068	–0.067	–0.108	4.340	565.100	0.000
32	–0.036	–0.657	–0.124	–0.130	–0.127	–0.130	–0.110	–0.070	–0.068	–0.109	4.340	583.730	0.000

[a] Cpd is compound number
[b] Avgqc is the average of atomic charges of atom number 1, 2, 3, 4, 5, 6 and 9
[c] $f^{(E)}{}_{24}$ is the frontier electron density at atom number 24

2.4 Validation of the QSAR Model

For the internal validation, Leave–One–Out (LOO–) cross validation method [58] was used. By using this, the predictive powers of these equations were validated. Predicted residual sum of square (PRESS), total sum of squares (SSY), cross–validated R^2 (R^2_{cv}), the standard deviation based on PRESS (S_{PRESS}) and the standard deviation error of prediction (SDEP) were considered for the validation of these models.

3 RESULTS AND DISCUSSION

Various combination were tried to get the regression equations after correlation analysis. QSAR equations were developed in a stepwise fashion and important models are reported here. The best univariate equation was obtained using the electrotopological state atom index of atom number 17 (S_{17}) of the general structure (Figure 1) as shown in Eq. 6.

$$pK_i = 7.442\ (\pm 0.107) - 1.974\ (\pm 0.297)\ S_{17}$$
$$n = 32 \quad R = 0.772 \quad \%EV = 59.553 \quad R^2_A = 0.582 \quad F(1,30) = 44.171 \quad p<0.00001 \qquad (6)$$
$$SEE = 0.580 \quad PRESS = 11.346 \quad SSY = 24.920 \quad R^2_{cv} = 0.545 \quad S_{PRESS} = 0.615 \quad SDEP = 0.595$$

Eq.(6) explains 58.20% and predicts 54.50% of variances in the biological activity data.

Definitions of statistical parameters used in the analysis of QSAR models are shown in Table 3.

Table 3. Important statistical parameters used

Statistical parameters	Explanation
n	Number of data points
R	Correlation coefficient
% EV	Percentage of explained variances
R^2_A	Adjusted R^2
F	Ratio between the variances of observed and calculated activities
P	Probability factor related to F–ratio
SEE	Standard error of estimate
PRESS	Predicted residual sum of squares
SSY	Total sum of squares
R^2_{cv}	Squared cross–validated correlation coefficient
S_{PRESS}	Standard error of PRESS
SDEP	Standard deviation of error of prediction

Different combinations were tried to build bivariate equations also and details of non–important models are avoided. Eq. (7) was obtained when refractotopological state atom index of atom 19 (R_{19}) as shown in general structure (Figure 1) was combined with S_{17}.

$$pK_i = 5.020\ (\pm 1.000) - 2.003\ (\pm 0.275)\ S_{17} - 3.945(\pm 1.623)\ R_{19}$$
$$n = 32 \quad R = 0.815 \quad \%EV = 65.277 \quad R^2_A = 0.641 \quad F(2,29) = 28.652 \quad p<0.00001 \qquad (7)$$
$$SEE = 0.537 \quad PRESS = 10.395 \quad SSY = 24.919 \quad R^2_{cv} = 0.545 \quad S_{PRESS} = 0.599 \quad SDEP = 0.570$$

Eq.(7) explains 64.10% and predicts 54.50% of variances in the biological activity data.

Another bivariate equation (Eq. 8) was obtained when qC_9 (atomic charge of atom number 9) was combined with S_{17}.

$$pK_i = 7.238\ (\pm 0.133) - 1.816\ (\pm 0.285)\ S_{17} - 4.748(\pm 2.041)\ qC_9$$
$$n = 32 \quad R = 0.812 \quad \%EV = 64.777 \quad R^2_A = 0.636 \quad F(2,29) = 28.039 \quad p<0.00001 \qquad (8)$$
$$SEE = 0.541 \quad PRESS = 10.980 \quad SSY = 24.919 \quad R^2_{cv} = 0.559 \quad S_{PRESS} = 0.615 \quad SDEP = 0.586$$

Eq.(8) explains 63.60% and predicts 55.90% of variances in the biological activity data.

The best trivariate and tetravariate equations were obtained in stepwise fashion also. The trivariate model (Eq. 9) was obtained when partition coefficient (logP) was combined with S_{17} and qC_9.

$$pK_i = 6.296\ (\pm0.437) - 1.503\ (\pm0.301)\ S_{17} - 5.309(\pm1.298)\ qC_9 + 0.251\ (\pm0.112)\ \log P$$
$$n = 32 \quad R = 0.843 \quad \%EV = 69.121 \quad R^2_A = 0.680 \quad F(3,28) = 22.977 \quad p<0.00001 \qquad (9)$$
$$SEE = 0.507 \quad PRESS = 10.847 \quad SSY = 24.919 \quad R^2_{cv} = 0.564 \quad S_{PRESS} = 0.623 \quad SDEP = 0.583$$

In Eq. (9) the positive coefficient of the partition coefficient indicates that compounds with low polarity may have high binding affinities.

Another trivariate model was developed using Avgqc (average of atomic charges of atom number 1, 2, 3, 4, 5, 6 and 9) with S_{17} and R_{19}.

$$pK_i = 3.378\ (\pm0.891) - 1.791\ (\pm0.235)\ S_{17} - 5.510(\pm1.406)\ R_{19} - 4.080\ (\pm1.078)\ \text{Avgqc}$$
$$n = 32 \quad R = 0.882 \quad \%EV = 76.240 \quad R^2_A = 0.754 \quad F(3,28) = 32.658 \quad p<0.00001 \qquad (10)$$
$$SEE = 0.445 \quad PRESS = 7.985 \quad SSY = 24.919 \quad R^2_{cv} = 0.679 \quad S_{PRESS} = 0.534 \quad SDEP = 0.449$$

Eqs. (9) and (10) explain 68.00% and 75.40% of variances respectively and predict 56.40% and 67.90% of variances in the biological activity data respectively.

In our efforts to further explore the relationship, the tetravariate Eq. 11 was developed using S_{17}, R_{19}, approximate surface area (SA) and Avgqc.

$$pK_i = 7.802\ (\pm1.688) - 2.260\ (\pm0.273)S_{17} - 8.002(\pm1.566)R_{19} - 0.010\ (\pm0.003)\text{SA} - 3.601(\pm0.990)\text{Avgqc}$$
$$n = 32 \quad R = 0.908 \quad \%EV = 80.663 \quad R^2_A = 0.799 \quad F(4,27) = 31.897 \quad p<0.00001 \qquad (11)$$
$$SEE = 0.401 \quad PRESS = 7.029 \quad SSY = 24.919 \quad R^2_{cv} = 0.718 \quad S_{PRESS} = 0.510 \quad SDEP = 0.46$$

Eq. 11 shows an improvement of the correlation coefficient with respect to the previous models and explains up to 79.90% of variance in the biological activity data. The significant value of R^2_{cv} confirms the validity of the model and appreciable predictivity. The negative coefficient of R_{19} indicates that the higher value of this index may be detrimental to the biological activity. Oxygen atom of the carbonyl group (atom number 19) may be responsible for the dispersive / van der Waals interaction with the receptor.

The importance of the approximate surface area of the whole molecule in binding affinity is also demonstrated. The negative coefficient of the approximate surface area may imply that the higher value of the whole molecular surface area corresponds to the lower binding affinity towards the receptor. The lower value of S_{17} indicates the higher binding affinity. With the decrease in the average atomic charge (of atom number 1, 2, 3, 4, 5, 6 and 9), the binding affinity may also decrease as evidenced from Eq. 11.

Deletion of outliers (compound number 31 and 27), which might act through different mechanism(s) of action, improved the statistical qualities of Eq. 11 as shown in Eq. 12.

$$pK_i = 6.786\ (\pm1.388) - 2.231\ (\pm0.225)S_{17} - 7.651(\pm1.297)R_{19} - 0.007\ (\pm0.003)\text{SA} - 2.481(\pm0.868)\text{Avgqc}$$
$$n = 30, \mathbf{DC = 31, 27} \quad R = 0.937 \quad \%EV = 85.464 \quad R^2_A = 0.859 \quad F(4,25) = 45.017 \quad p<0.00001 \qquad (12)$$
$$SEE = 0.325 \quad PRESS = 4.683 \quad SSY = 21.620 \quad R^2_{cv} = 0.783 \quad S_{PRESS} = 0.433 \quad SDEP = 0.395$$

Here **DC** is the deleted compound. This equation explains 85.90% of variance in the biological activity data.

Combination of the parameter, the frontier electron density for the electrophilic attack at the atom number 24 ($f^{(E)}_{24}$) with S_{17}, R_{19} and Avgqc gives rise to Eq. 13.

$$pK_i = 3.381\ (\pm 0.866) - 1.939\ (\pm 0.234) S_{17} - 6.205 (\pm 1.373) R_{19} - 5.078\ (\pm 2.467)\ f^{(E)}_{24} - 4.457 (\pm 1.037) \text{Avgqc}$$
$$n = 32 \quad R = 0.899 \quad \%EV = 78.729 \quad R^2_A = 0.779 \quad F(4,27) = 28.384 \quad p<0.00001$$
$$\text{SEE} = 0.421 \quad \text{PRESS} = 7.301 \quad \text{SSY} = 24.919 \quad R^2_{cv} = 0.707 \quad S_{PRESS} = 0.520 \quad \text{SDEP} = 0.478 \qquad (13)$$

Eq. (13) explains up to 77.90% of variance in the biological activity data. It shows that $f^{(E)}_{24}$ contributes to pK_i. The negative coefficient of $f^{(E)}_{24}$ suggests that the higher probability of electrophilic attack at the atom number 24 may be detrimental to the biological activity. Stepwise deletion of compounds 31, 27 and 15 for the reason stated above, improved the statistical qualities of the equation obtained as shown in Eq. 14:

$$pK_i = 3.260\ (\pm 0.595) - 2.148\ (\pm 0.167) S_{17} - 6.398 (\pm 0.956) R_{19} - 5.376\ (\pm 1.695)\ f^{(E)}_{24} - 3.961 (\pm 0.830) \text{Avgqc}$$
$$n = 29, \text{DC} = \mathbf{31}, \mathbf{27}, \mathbf{15} \quad R = 0.953 \quad \%EV = 88.607 \quad R^2_A = 0.893 \quad F(4,24) = 59.304 \quad p<0.00001$$
$$\text{SEE} = 0.284 \quad \text{PRESS} = 2.971 \quad \text{SSY} = 21.020 \quad R^2_{cv} = 0.859 \quad S_{PRESS} = 0.352 \quad \text{SDEP} = 0.320 \qquad (14)$$

Eq. (14) explains 89.30% variances and predicts 85.90% of the binding affinity data. The correlation matrix is shown in Table 4.

Table 4. Correlation matrix for the relationship among variables used to develop QSAR equations and biological activity

	S_{17}	R_{19}	qC1	qC2	qC3	qC4	qC5	qC6	qC9	Avgqc	SA	logP	$f^{(E)}_{24}$	*pKi*
S_{17}	1.00	–0.04	0.24	0.24	0.24	0.24	0.24	0.24	0.24	0.24	–0.50	–0.45	–0.33	–0.77
R_{19}		1.00	–0.30	–0.29	–0.29	–0.29	–0.29	–0.29	–0.30	–0.30	–0.52	–0.55	–0.18	–0.23
qC1			1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	0.15	0.01	–0.17	–0.42
qC2				1.00	1.00	1.00	1.00	1.00	1.00	1.00	0.14	0.01	–0.18	–0.42
qC3					1.00	1.00	1.00	1.00	1.00	1.00	0.14	0.01	–0.18	–0.42
qC4						1.00	1.00	1.00	1.00	1.00	0.14	0.01	–0.18	–0.42
qC5							1.00	1.00	1.00	1.00	0.14	0.01	–0.18	–0.42
qC6								1.00	1.00	1.00	0.14	0.01	–0.18	–0.43
qC9									1.00	1.00	0.15	0.01	–0.16	–0.43
Avgqc										1.00	0.14	0.01	–0.18	–0.42
SA											1.00	0.59	0.53	0.35
logP												1.00	0.15	0.52
$f^{(E)}_{24}$													1.00	0.20
pKi														1.00

In all these equations, probability values are less than 0.05 and, therefore, F is statistically significant. The student *t*–values and the associated probability values (*p*) of the tetravariate equations are given in Table 5.

Table 5. *t*–values and *p*–values of all tetravatiate QSAR model

Eq. No.	Intercept/Parameter	t–value	p–value	Eq. No.	Intercept/Parameter	t–value	p–value
11	Intercept	4.623	0.000	12	Intercept	4.889	0.000
	S_{17}	–8.262	0.000		S_{17}	–9.911	0.000
	R_{19}	–5.108	0.000		R_{19}	–5.889	0.000
	SA	–2.713	0.011		SA	–2.501	0.019
	Avgqc	–3.641	0.001		Avgqc	–2.858	0.008
13	Intercept	3.905	0.000	14	Intercept	5.481	0.000
	S_{17}	–8.297	0.000		S_{17}	–12.865	0.000
	R_{19}	–4.519	0.000		R_{19}	–6.691	0.000
	$f^{(E)}_{24}$	–2.058	0.049		$f^{(E)}_{24}$	–3.172	0.004
	Avgqc	–4.299	0.000		Avgqc	–4.773	0.000

Confidence interval is less than 95%

Table 6. Observed (Obs.), calculated (Calc.), residual (Res.), LOO–predicted (LOO–pred) and predicted residual (Pres.) activities of Eqs. (11) and (12)

	Obs[b]	Eq 11				Eq 12			
Cpd[a]		Calc[c]	Res[d]	LOO–pred[e]	Pres[f]	Calc[c]	Res[d]	LOO–pred[e]	Pres[f]
1	8.638	8.053	0.585	8.005	0.633	8.076	0.562	8.029	0.069
2	8.468	8.254	0.215	8.234	0.234	8.201	0.267	8.176	0.293
3	8.292	8.291	0.001	8.291	0.001	8.267	0.025	8.265	0.027
4	7.886	8.260	–0.374	8.304	–0.418	8.304	–0.418	8.356	–0.470
5	8.070	8.223	–0.043	8.128	–0.057	8.221	–0.15	8.275	–0.204
6	8.553	8.603	–0.050	8.610	–0.057	8.533	0.02	8.530	0.022
7	8.252	8.369	–0.118	8.394	–0.142	8.285	–0.033	8.292	–0.040
8	8.509	8.282	0.226	8.263	0.246	8.269	0.24	8.247	0.261
9	8.194	7.376	0.818	7.042	1.152	7.685	0.508	7.373	0.820
10	8.252	8.299	–0.047	8.302	–0.051	8.306	–0.054	8.310	–0.058
11	7.886	8.306	–0.420	8.352	–0.466	8.347	–0.461	8.400	–0.514
12	5.921	5.807	0.113	5.696	0.225	5.817	0.104	5.706	0.214
13	6.055	6.082	–0.027	6.092	–0.037	5.952	0.104	5.909	0.146
14	6.244	6.256	–0.012	6.259	–0.014	6.219	0.024	6.213	0.031
15	6.854	6.145	0.709	5.884	0.970	6.307	0.547	6.071	0.783
16	6.055	6.106	–0.051	6.123	–0.067	6.347	–0.292	6.466	–0.411
17	7.194	7.276	–0.082	7.284	–0.090	7.174	0.019	7.172	0.021
18	6.009	6.636	–0.628	6.931	–0.922	6.764	–0.755	7.167	–1.158
19	7.276	7.359	–0.084	7.369	–0.093	7.265	0.011	7.263	0.012
20	7.201	7.424	–0.224	7.437	–0.236	7.362	–0.162	7.372	–0.171
21	7.217	7.536	–0.322	7.552	–0.337	7.473	–0.259	7.487	–0.272
22	7.699	7.824	–0.125	7.883	–0.134	7.744	–0.045	7.747	–0.048
23	7.854	7.811	0.043	7.805	0.049	7.754	0.100	7.740	0.114
24	8.337	8.030	0.307	7.915	0.422	7.976	0.361	7.833	0.504
25	7.699	7.493	0.205	7.460	0.238	7.443	0.255	7.402	0.297
26	7.000	7.414	–0.414	7.466	–0.466	7.408	–0.408	7.459	–0.459
27	6.745	7.582	–0.838	7.887	–1.142	—	—	—	—
28	8.509	8.343	0.165	8.331	0.178	8.325	0.184	8.310	0.199
29	8.409	8.481	–0.073	8.495	–0.086	8.505	–0.096	8.524	–0.115
30	8.252	8.366	–0.115	8.390	–0.138	8.238	–0.031	8.289	–0.037
31	9.215	8.367	0.847	8.290	0.924	—	—	—	—
32	7.678	7.867	–0.189	7.881	–0.203	7.846	–0.168	7.859	–0.181

[a]Cpd is compound number, [b]Observed, [c]Calculated, [d]Residual, [e]LOO–predicted, [f]Predicted residual

Table 7. Observed (Obs.), calculated (Calc.), residual (Res.), LOO–predicted (LOO–pred) and predicted residual (Pres.) activities of Eqs. (13) and (14)

	Obs[b]	Eq 13				Eq 14			
Cpd[a]		Calc[c]	Res[d]	LOO–pred[e]	Pres[f]	Calc[c]	Res[d]	LOO–pred[e]	Pres[f]
1	8.638	8.260	0.379	8.236	0.042	8.278	0.360	8.253	0.385
2	8.468	8.010	0.458	7.970	0.498	8.019	0.449	7.979	0.489
3	8.292	8.154	0.138	8.144	0.148	8.167	0.125	8.158	0.134
4	7.886	7.872	0.014	7.856	0.030	7.856	0.030	7.821	0.065
5	8.070	8.126	–0.055	8.154	–0.083	8.127	–0.056	8.156	–0.085
6	8.553	8.477	0.075	8.471	0.082	8.507	0.046	8.502	0.051
7	8.252	8.188	0.064	8.179	0.072	8.220	0.032	8.215	0.036
8	8.509	8.387	0.122	8.374	0.134	8.425	0.084	8.415	0.093
9	8.194	7.645	0.549	7.451	0.743	7.779	0.414	7.505	0.689
10	8.252	8.285	–0.034	8.288	–0.036	8.300	–0.049	8.304	–0.052
11	7.886	8.425	–0.539	8.470	–0.584	8.444	–0.558	8.494	–0.608
12	5.921	6.197	–0.276	6.325	–0.405	6.059	–0.138	6.131	–0.210
13	6.055	5.927	0.128	5.878	0.177	5.737	0.318	5.598	0.458
14	6.244	6.457	–0.213	6.496	–0.252	6.300	–0.056	6.311	–0.067
15	6.854	5.960	0.894	5.645	1.209	—	—	—	—
16	6.055	6.222	–0.166	6.269	–0.214	6.205	–0.149	6.291	–0.235
17	7.194	7.140	0.053	7.136	0.057	7.046	0.148	7.034	0.159
18	6.009	6.258	–0.249	6.334	–0.325	6.267	–0.258	6.408	–0.399
19	7.276	7.259	0.017	7.257	0.018	7.151	0.124	7.138	0.137
20	7.201	7.434	–0.234	7.448	–0.247	7.357	–0.157	7.367	–0.166
21	7.217	7.532	–0.317	7.548	–0.333	7.469	–0.254	7.482	–0.267
22	7.699	7.720	–0.021	7.721	–0.022	7.682	0.016	7.682	0.017
23	7.854	7.828	0.026	7.824	0.030	7.757	0.097	7.742	0.112
24	8.337	8.053	0.284	7.939	0.398	7.976	0.361	7.819	0.518
25	7.699	7.566	0.133	7.543	0.156	7.467	0.232	7.425	0.274
26	7.000	7.645	–0.645	7.712	–0.712	7.565	–0.565	7.628	–0.628
27	6.745	7.763	–1.018	8.138	–1.394	—	—	—	—
28	8.509	8.429	0.080	8.421	0.088	8.466	0.042	8.461	0.047
29	8.409	8.706	–0.297	8.770	–0.362	8.788	–0.379	8.879	–0.470
30	8.252	8.189	0.063	8.180	0.072	8.220	0.031	8.216	0.036
31	9.215	8.294	0.920	8.224	0.991	—	—	—	—
32	7.678	8.009	–0.331	8.038	–0.361	7.969	–0.291	7.997	–0.319

[a]Cpd is compound number, [b]Observed, [c]Calculated, [d]Residual, [e]LOO–predicted, [f]Predicted residual

Eq. (14) is considered to be the best model where the regression coefficient is 0.953 and this explains 89.30% of the variation of the biological activity data. It has the highest F value (F = 59.304) and the lowest SEE value (SEE=0.284). The scatter plot of observed versus calculated values for the tetravariate Equations 12 and 14 are presented in Figure 2.

The tetravariate equations provide useful information at the molecular level for the structural requirement of the substituted uracil derivatives as the potential small molecular human GnRH–R antagonists. Leave–One–Out (LOO–) cross validation method confirmed the predictive power of those equations where one compound was deleted once and prediction of the activity of the deleted compound was made based on the QSAR model.

The process was repeated after elimination of another compound until all of these compounds

have been deleted once. The observed, calculated, residual, LOO–predicted and predicted residual values of these equations are shown in Table 6 and 7 respectively.

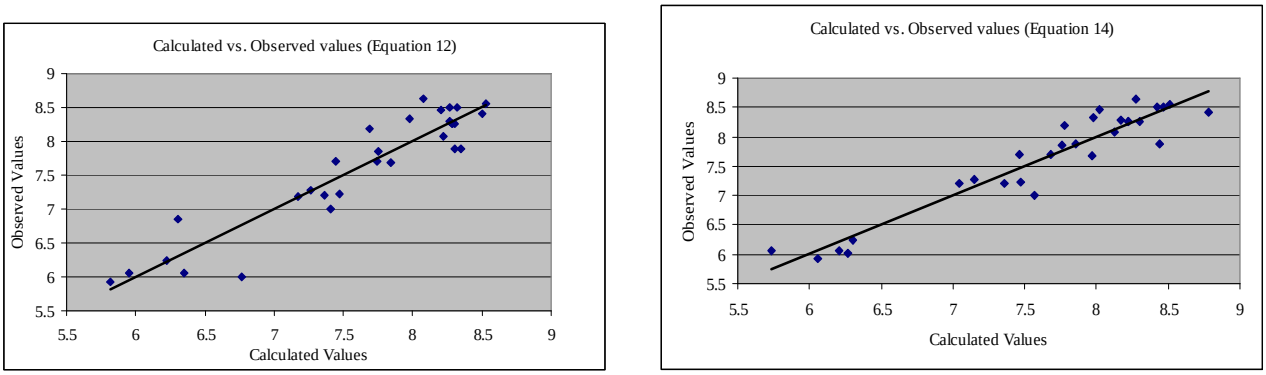

Figure 2. Calculated vs. Observed values for Equations 12 and 14.

4 CONCLUSIONS

Drugs exhibit structural specificity towards their receptors at the fragmental or at the atomic level instead of the whole molecule. In the drug–receptor interaction phenomenon, a portion of the molecule (pharmacophore) play more important role than the other segments. Though basic information for the constitution of the topological indices are derived from the atom level (count of atoms, bonds, paths of bonds etc.), most of these indices are applied to the whole molecule after summing up all components over the whole molecule. The pharmacophoric requirement for the substituted uracils for their human GnRH–R antagonism is illustrated maximally by the two tetravariate QSAR models (equations 12 and 14). These models show the importance of S_{17} for the receptor antagonism. The negative coefficient of this index implies that the lower value may be conducive to the higher activity.

Thus, the atom number 17 may have a role in the electronic interaction of these compounds with the receptor. The antagonistic activity of these compounds increases with the decreasing value of R_{19} where the oxygen atom of the carbonyl group of the molecule may be involved through dispersive / van der Waals interaction. The frontier electron density for the electrophilic attack at the atom number 24 is also important for the binding affinity of these compounds. Its increasing value may decrease the binding affinity. These models also demonstrate that the whole molecule having the increased surface area may not help to increase the antagonistic activity. It also explains that with the increase of the average atomic charge the binding affinity of these compounds may increase. Structural requirements of uracil derivatives are shown in Figure 3.

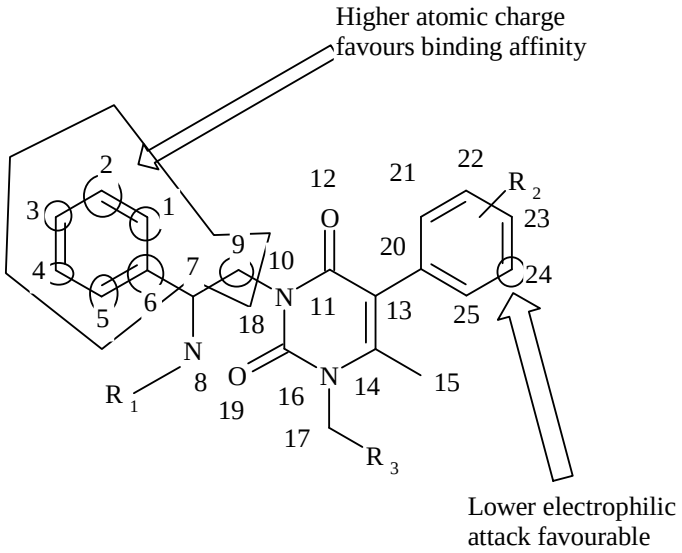

Figure 3. Structural requirements of uracil derivatives.

Thus, designing compounds having the reduced surface area, the higher average atomic charge (of atom number 1, 2, 3, 4, 5, 6 and 9 of the general structure of Figure 1) and the lower electrophilic attack at the atom number 24 may increase the binding affinity of the compounds towards the human GnRH receptor.

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