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First QSAR report on FSH receptor antagonistic activity: Quantitative investigations on physico-chemical and structural features among 6-amino-4-phenyltetrahydroquinoline derivatives

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This paper is dedicated to Prof. S.C. Chaturvedi on the occasion of Guru Poornima.

Abstract—A quantitative attempt has been made to correlate the structure–activity relationship (SAR) among the recently reported 6-amino-4-phenyltetrahydroquinoline derivatives as antagonists for the Gs-protein-coupled human follicle-stimulating hormone (FSH) receptor. The compounds used for the present study have been reported to show high antagonistic efficacy in vitro using a CHO-hFSHR(luc) assay. Our QSAR investigations revealed a hydrophobic type of interactions between these ligands and the FSH receptor, hence confirming the presence of a lipophilic pocket on the active site of the target structure. The positive coefficient of C log *P* variable in our derived QSAR model suggests that more hydrophobic ligands are crucial for their FSH receptor antagonistic efficacy. In exploring the structural requirements among these congeners, we found an amide linkage as conducive to their FSH receptor antagonistic activity. Also, an unsubstituted 4-phenyl ring of the tetrahydroquinoline scaffold is favorable for their FSH receptor antagonistic activity. The results discussed herein could be useful in understanding the nature of interactions of these newly identified ligands as FSH receptor antagonists and in designing more potent ligands based on this novel 6-amino-4-phenyltetrahydroquinoline scaffold.
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Since the seminal work of Hansch almost 40 years ago,[1] QSAR research has been considered a major tool in drug discovery to explore the ligand–receptor/enzyme interactions. QSAR is an effective way of optimizing or correlating the biological activity within congeneric series with certain structural features or with atomic, group or molecular descriptors, such as lipophilicity, polarizability, and electronic and steric properties. Previously, we reported several examples of adopting a QSAR approach to probe the nature of interactions of various classes of ligands towards the cyclooxygenase enzyme.[2–8] Herein, we report our attempt to rationalize the physico-chemical and structural features among novel 6-amino-4-phenyltetrahydroquinoline derivatives in relation to their FSH receptor antagonistic activity using QSAR approach. To our knowledge this is the first QSAR report on this special category of drugs.

FSH plays a crucial role in the control of human fertility. FSH is a member of the family of pituitary glycoproteins and exerts its effect through interacting with G-protein-coupled specific receptors.[9] FSH receptors are found in the gonads and have been localised to the Sertoli cells of the testis and the granulosa cells of the ovary.[10] Hence inhibition of the FSH receptor that is present in the ovaries would be a novel, fruitful approach for contraception. Some of the antagonists for the FSH receptor have been published[11] and most of them exist in patents.[12,13] Recently, Van Straten et al. reported a series of 6-amino-4-phenyltetrahydroquinoline derivatives as potent antagonists for the FSH receptor.[14] Hence we attempted to adopt a QSAR approach for this novel category of drugs with an objective of identifying the necessary physico-chemical and structural features among 6-amino-4-phenyltetrahydroquinoline derivatives for their FSH receptor antagonistic activity.

Keywords: 6-Amino-4-phenyltetrahydroquinoline derivatives; Human FSH receptor antagonists; QSAR.
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The FSH receptor antagonistic activity of 6-amino-4-phenyltetrahydroquinoline derivatives was reported as IC_{50} in nanomolar units using a CHO-hFSHR(luc) assay. For the present QSAR study, the reported activity is converted to the negative logarithm in terms of molar units ($_pIC_{50}$). All the compounds used for the analysis with their observed, converted activity and QSAR predicted activity are listed in Table 1. The linear regression analysis was performed using systat version 10.2. The physico-chemical properties such as C log *P* and CMR were calculated using ChemDraw ultra 6.0 software, supplied by Cambridge soft corporation, USA. C log *P* is the calculated partition coefficient of compounds in octanol/water and a measure of the hydrophobicity of compounds. CMR is the calculated molar refractivity based on the Lorentz–Lorentz equation, $MR = (n^2 - 1)/(n^2 + 2)\ MW/d$, where n is the index of refraction, MW represents molecular weight of the compound and d is the density. It is a measure of volume and polarizability of whole molecules. Suitable indicator variables were used to account for the structural variation due to the wide range of substituents among the congeners. An indicator variable designated as I with a relevant subscript was assigned 1.0 when a particular substituent or chemical feature is present and 0 if absent. The use of indicator variables allowed us to combine all the aliphatic, aromatic, and 6-biphenyl containing tetrahydroquinolines as a single larger dataset, which would be expected to give more reliable and predictive QSAR models. All the physico-chemical and indicator variables derived for the present study are listed in Table 2. The correlation matrix was used to correlate the biological activity with the various physico-chemical and structural predictor variables (Table 3). The forward stepping regression method was used to build a QSAR model. This method initially generates a QSAR model containing only one variable, which is chosen to be the one with a high t statistic and subsequent variables were added based on their relative importance as determined by t statistics. For the current dataset of 19 compounds the QSAR model development was restricted to a maximum of three variables in accordance to the general accepted rule of thumb (5:1 for compounds:descriptor) during forward stepping regression. Descriptors with intercorrelation above $|r| > 0.5$ were not taken into consideration while accomplishing this task.

The QSAR models were evaluated by using the statistical parameters like correlation coefficient (r) or coefficient of determination (r^2), adjusted r^2 (r^2_{Adj}), standard error of estimate (s), Fischer F value, and Student's t distribution. The latter is used to assess the significance of the individual regression terms. The figures within the parentheses following the coefficient terms are the standard error of the regression terms and the constants. The Durbin–Watson (DW) test was employed to check the serial correlation in residuals. Since the DW values in all the derived models are greater than 1.4, there is probably no serious autocorrelation in the residuals. A data point is considered as an outlier if it has a large magnitude (when the residual value exceeds twice the standard error of estimate of the model). Self-consistency of the derived models is ensured using the leave-one-out (loo) process and the predictability of each model was assessed using cross-validated r^2 or q^2.

The observed FSH receptor antagonistic activity is considered as the dependent variable, and the calculated physico-chemical properties and indicator variables as independent variables while performing the forward stepping regression. Initial regression set to single variable resulted in the following QSAR model

$$_pIC_{50} = 1.300(\pm 0.283) I_{NH\text{–}(CO)[X\text{–}Y]} + 6.267(\pm 0.234),$$
$$n = 19,\ r = 0.744,\ r^2 = 0.554,\ r^2_{Adj} = 0.527,\ s = 0.574,$$
$$F = 21.077,\ p = 0.000,\ q^2 = 0.432,\ S_{press} = 0.647,$$
$$SDEP = 0.612,\ DW = 1.440.$$

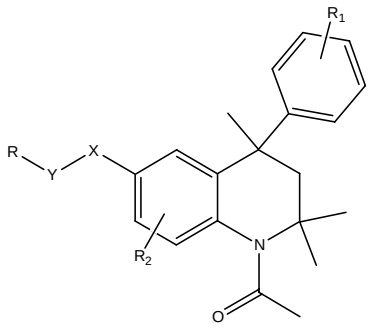
The above QSAR model is a monoparametric regression equation modeled for FSH receptor antagonistic activity for 19 reported tetrahydroquinoline derivatives. The single indicator variable $I_{NH\text{–}(CO)[X\text{–}Y]}$ shows a moderately good correlation with the observed activity. The value of the $I_{NH\text{–}(CO)[X\text{–}Y]}$ descriptor is assigned 1 when an amide linkage, X–Y = NH–(CO) of general structure (Table 1) is present and 0 for others. Other linkages at that position include reversed amides, X–Y = C(O)–NH compound **12**; urea linkage, X–Y = NH–C(O)NH compound **10**; sulfonamide linkage, X–Y = NH–$S(O)_2$, compound **9**; alkylated amino linkage, X–Y = NH bond where Y = bond means that Y is absent and only connects X and R in compound **11** where R is a benzyl, substituted at the para position with a *t*-butyl group; an ester linkage, X–Y = O–C(O), compound **18** and methoxylated linkage X–Y = O–CH_2, compound **19**. The positive contribution of the indicator variable $I_{NH\text{–}(CO)[X\text{–}Y]}$ shows that an amide linkage of type X–Y = NH–(CO) connecting the 6-position of tetrahydroquinolines and other substitutents at R is favorable for FSH receptor antagonistic activity or in other words linkages such as reversed amides, sulfonamide, urea, alkylated amino groups, ester, and methoxyl are detrimental for the activity.

Forward stepping regression set to two variables resulted in the following statistically sound biparametric regression equation

$$_pIC_{50} = 1.501(\pm 0.253) I_{NH\text{–}(CO)[X\text{–}Y]} - 0.871(\pm 0.323)$$
$$I_{sub[R_1]} + 6.267(\pm 0.200),\ \ n = 19,\ r = 0.833,\ r^2 = 0.693,$$
$$r^2_{Adj} = 0.655,\ s = 0.490,\ F = 18.08,\ p = 0.000,$$
$$q^2 = 0.567,\ S_{press} = 0.583,\ SDEP = 0.535,\ DW = 1.795.$$

The above QSAR model is fairly good in terms of all its statistical parameters. The second indicator variable, $I_{sub[R_1]}$ is added to the previous QSAR model. A t value of −2.7, greater than the tabulated value shows that its inclusion is statistically significant above 95% confidence interval. This second indicator variable $I_{sub[R_1]}$ is assigned a value of 1 for compounds bearing substituents at the R_1 position, example 4-Me in compound **13**; 2-MeO in compound **14**, and 4-OH in compound **15**, and 0 for others with H at that position. The negative coefficient of $I_{sub[R_1]}$ indicates an unsubstituted 4-phenyl

Table 1. 6-Amino-4-phenyltetrahydroquinoline derivatives, observed and predicted activities



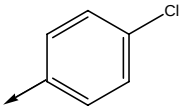
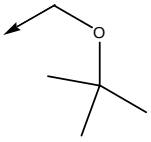
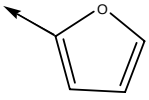
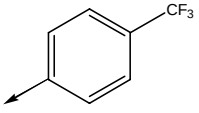
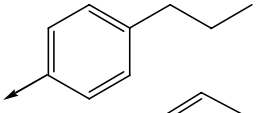
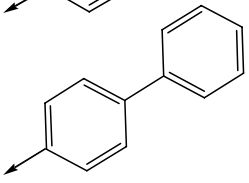
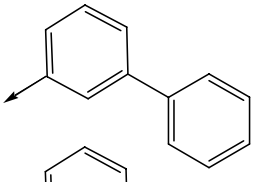
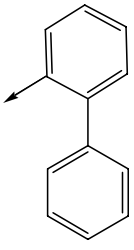
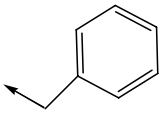
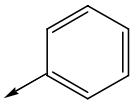
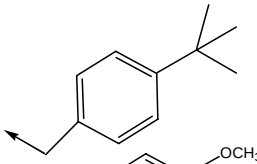
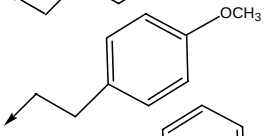
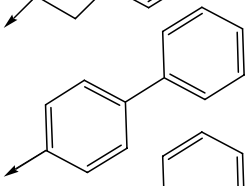
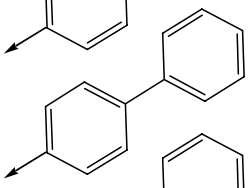
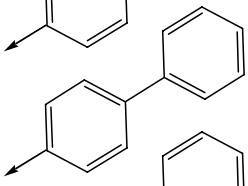
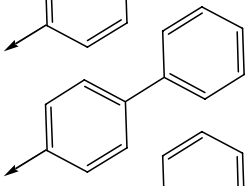
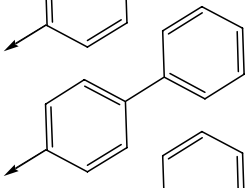
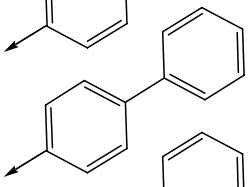
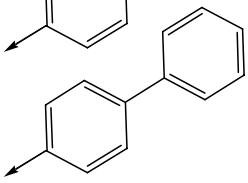
Compound No.	Substitution					Obs.[a] activity (IC_{50} nM)	Obs.[a] activity ($_pIC_{50}$)	QSAR pred.[b] activity	|Res.|[c]
	X	Y	R	R_1	R_2				
1	NH	C(O)		H	H	31	7.51	7.73	0.22
2	NH	C(O)		H	H	76	7.12	7.29	0.17
3	NH	C(O)		H	H	27	7.57	7.02	0.55
4	NH	C(O)		H	H	7	8.16	7.77	0.40
5	NH	C(O)		H	H	5	8.30	7.85	0.45
6	NH	C(O)		H	H	28	7.55	8.07	0.52
7	NH	C(O)		H	H	9	8.05	7.99	0.06
8	NH	C(O)		H	H	25	7.60	7.89	0.29
9	NH	$S(O)_2$		H	H	2800	5.55	5.90	0.35

Table 1 (*continued*)

Compound No.	Substitution					Obs.[a] activity (IC_{50} nM)	Obs.[a] activity ($_pIC_{50}$)	QSAR pred.[b] activity	|Res.|[c]
	X	Y	R	R_1	R_2				
10	NH	C(O)NH		H	H	580	6.24	5.82	0.43
11	NH	Bond		H	H	930	6.03	6.61	0.58
12	C(O)	NH		H	H	1880	5.73	5.98	0.25
13	NH	C(O)		4-Me	H	50	7.30	6.95	0.35
14	NH	C(O)		2-OMe	H	170	6.77	6.96	0.19
15	NH	C(O)		4-OH	H	240	6.62	6.78	0.16
16	NH	C(O)		H	7-Me	5	8.30	7.91	0.39
17	NH	C(O)		H	8-OMe	30	7.52	8.11	0.59
18	O	C(O)		H	H	54	7.27	6.49	0.78
19	O	CH_2		H	H	166	6.78	6.76	0.02

[a] Observed activity.
[b] Predicted activity using loo cross-validation of QSAR model.
[c] Difference between observed and loo predicted activity.

ring of tetrahydroquinolines is conducive to FSH receptor antagonistic activity among these congeners. The two indicator variables used in the above QSAR model are orthogonal (intercorrelation $|r| = 0.294$):

Further addition of the statistically significant descriptor to this model resulted in the following triparametric regression equation providing some physico-chemical meaning to the above two models:

$$_pIC_{50} = 0.304(\pm 0.081)C\log P + 1.621(\pm 0.190)$$
$$I_{NH-(CO)[X-Y]} - 1.079(\pm 0.245)I_{sub[R_1]} + 4.168(\pm 0.576),$$
$$n = 19,\ r = 0.918,\ r^2 = 0.843,\ r^2_{Adj} = 0.811,$$
$$s = 0.363,\ F = 26.76,\ p = 0.000,\ q^2 = 0.754,$$
$$S_{press} = 0.453,\ SDEP = 0.403,\ DW = 2.576.$$

Table 2. Calculated physico-chemical and structural variables

Compound No.	Clog *P*	CMR	$I_{NH–(CO)[X–Y]}$	$I_{sub[R_1]}$	$I_{sub[R_2]}$	$I_{Bp[X–Y]}$
1	6.31	13.01	1	0	0	0
2	4.80	12.48	1	0	0	0
3	4.57	11.73	1	0	0	0
4	6.63	13.03	1	0	0	0
5	6.95	13.91	1	0	0	0
6	7.28	15.03	1	0	0	1
7	7.28	15.03	1	0	0	1
8	6.82	15.03	1	0	0	1
9	5.38	13.35	0	0	0	0
10	5.75	12.89	0	0	0	0
11	7.66	14.34	0	0	0	0
12	5.78	14.06	0	0	0	0
13	7.78	15.49	1	1	0	1
14	7.20	15.65	1	1	0	1
15	6.62	15.18	1	1	0	1
16	7.13	15.49	1	0	1	1
17	7.38	15.65	1	0	1	1
18	8.34	14.81	0	0	0	1
19	8.55	14.78	0	0	0	1

Table 3. Correlation between observed activity and various calculated physico-chemical and structural variables

	$_pIC_{50}$	Clog *P*	CMR	$I_{NH–(CO)[X–Y]}$	$I_{sub[R_1]}$	$I_{sub[R_2]}$	$I_{Bp[X–Y]}$
$_pIC_{50}$	1.000						
Clog *P*	0.214	1.000					
CMR	0.118	0.778	1.000				
$I_{NH–(CO)[X–Y]}$	0.744	−0.103	0.130	1.000			
$I_{sub[R_1]}$	−0.138	0.184	0.440	0.294	1.000		
$I_{sub[R_2]}$	0.318	0.163	0.387	0.233	−0.149	1.000	
$I_{Bp[X–Y]}$	0.285	0.682	0.866	0.263	0.411	0.325	1.000

The inclusion of the third descriptor, Clog *P*, is statistically significant as reflected from its *t* value of 3.77 greater than the tabulated value above 95% confidence interval. The positive coefficient of Clog *P* indicates that more hydrophobic compounds are favorable for FSH receptor antagonistic activity among these congeners. It also corroborates the presence of a large lipophilic pocket in the FSH receptor active site. The correlation between Clog *P* and the observed FSH receptor antagonistic activity is shown in Figure 1. It shows that this descriptor has good spread in terms of its data. The above triparametric model is excellent in terms of its statistical parameters. It explains 81.1% variance in FSH receptor antagonistic activity among the 19 compounds studied. All three descriptors are free from intercorrelation among one another (see Table 3). The predictive ability of this QSAR model is also good as exemplified by the cross-validated r^2 or q^2 value. The correlation between observed and predicted FSH receptor antagonistic activity is illustrated in Figure 2. Hence, this triparametric model owing to its excellent correlation

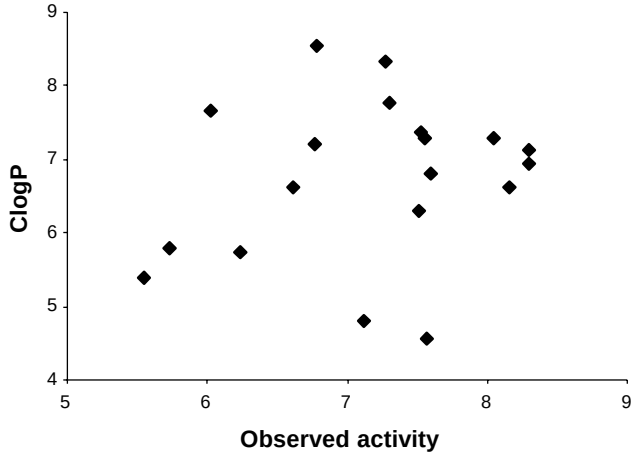


Figure 1. Correlation between Clog *P* and observed activity.

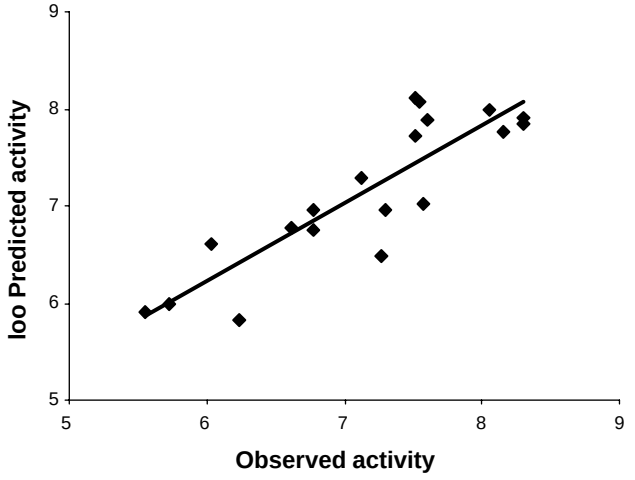


Figure 2. Correlation between observed activity and loo predicted activity.

($r^2 = 0.843$) and predictability ($q^2 = 0.754$) could be used in optimizing this newly identified lead structure 6-amino-4-phenyltetrahydroquinoline for its improved FSH receptor antagonistic activity.

In conclusion, our attempt to find a good correlation between the chosen physico-chemical and structural variables with the recently identified novel 6-amino-4-phenyltetrahydroquinoline scaffold resulted in some interesting and useful information to optimize the FSH receptor antagonistic activity. The derived QSAR model not only provides information about the hydrophobic interactions between these ligands and the large lipophilic pocket of the FSH receptor active site but also supplements the ideal type of linker required at the 6-position and the substitutional requirements at the 4-phenyl ring of the tetrahydroquinoline scaffold for improved FSH receptor antagonistic activity.

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