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QSAR Studies on Keto Sulfones Derivatives as Inhibitors of 11β-Hydroxysteroid Dehydrogenase Type 1

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ABSTRACT

Metabolic disorders, such as obesity and type 2 diabetes, have assumed epidemic proportions and present major challenges for healthcare systems. The keto sulfones derivatives were discovered as potent and selective 11β-HSD1 inhibitors. The studies show that these compounds are not active against 11β-HSD2 and thus easily surpass the side effects of inhibition of 11β-HSD2 such as sodium retention, hypokalemia and hypertension. So here we have tried to explore the series of β- keto sulfones derivatives, to develop novel, selective and potent orally active compounds through QSAR analysis. The QSAR study carried out on 23 keto sulfones derivatives as inhibitors of 11β-HSD. Molecular modeling studies were performed using chemoffice 6.0 supplied by cambridgesoft. The sketched structures were subjected to energy minimization & the lowest energy structure was used to calculate the physiochemical properties. The regression analysis was carried out using a computer program called SYSTAT 10.2. The best models were selected from the various statistically significant equations. The study revealed that the LUMO, Dipole-dipole energy, NVDW contributed positively, and Heat of formation contributed negatively. The analysis resulted in 2-D equation, which suggests that, n=16, r=0.953, r^2=0.909, Standard error of estimate(s)=0.342 & validated $r^2(q^2)$ =0.7135. This study can help in rational drug design and synthesis of new selective 11β-HSD1 with predetermined affinity.

Keywords: HSD1; 11β-HSD1; Diabetes; Metabolic syndrome; Keto sulfones derivatives; QSAR.

INTRODUCTION

Glucocorticoids are well-known ubiquitous hormones playing a key role in modulating immune and inflammatory responses, regulating energy metabolism and cardiovascular homeostasis and the body's responses to stress. Opposing the action of insulin, glucocorticoids stimulate

production of glucose, switching the homeostatic balance towards catabolism. Thus, glucocorticoids promote gluconeogenesis but inhibit beta-cell insulin secretion and peripheral glucose uptake.[1,2] They also increase protein breakdown and lipolysis with consequent fatty acid mobilisation.[3] Recent investigations have implicated aberrant glucocorticoid receptor (GR) signalling in the development of several phenotypes associated with metabolic syndrome. Metabolic syndrome is characterized by abdominal obesity, impaired glucose tolerance, dyslipidemia, low levels of high density lipoprotein (HDL) cholesterol, and hypertension[4,5]. The major activator of the GR in humans is cortisol, and the adrenal cortex is the major source of circulating cortisol. Recent evidence suggests that GR signalling depends not only on the circulating cortisol levels, but also on the intracellular generation of cortisol through reduction of the inactive glucocorticoid, cortisone [6]. 11β-hydroxysteroid dehydrogenase type 1 is a key enzyme that acts as an NADPH-dependent reductase capable of converting the inactive 11β-glucocorticoids such as cortisone into their active form, (e.g., cortisol) in specific tissues, such as liver, adipose, and brain tissues (figure 1). Therefore, 11β-HSD1 regulates tissue specific glucocorticoid levels.[7-10] Conversely, 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2), a structurally related isoenzyme of 11β-HSD1, catalyzes the conversion of cortisol to cortisone utilizing NAD as a cofactor. 11β-HSD2 is expressed in cells that contain the mineralocorticoid receptor (MR) and protects the MR by converting cortisol to the inactive form, cortisone.[11]
Aberrant glucocorticoid action in the liver and adipose tissue has been linked to insulin resistance and dyslipidemia. Therefore, selective inhibition of 11β-HSD1 over 11β-HSD2 is a promising strategy to improve insulin sensitivity and treat type2 diabetes, and has attracted significant attention from the pharmaceutical research community. [12, 17-23]

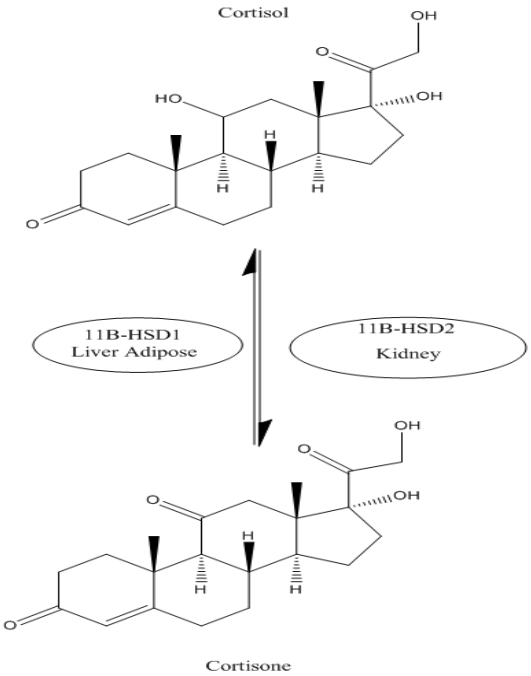


Figure 1: Interconversion of cortisone and cortisol by 11β-HSD type 1 and 2 enzymes

QSAR models are mathematical equations relating chemical structure to a wide variety of physical, chemical and biological properties. In view of above, and as a part our composite programme of rational drug design in the present study, we report the QSAR studies of keto sulfones derivatives as inhibitors of 11β-HSD1 enzyme.

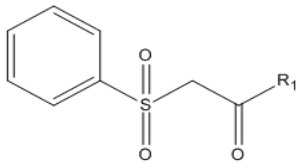
MATERIALS AND METHOD

2.1 Data Set for Analysis

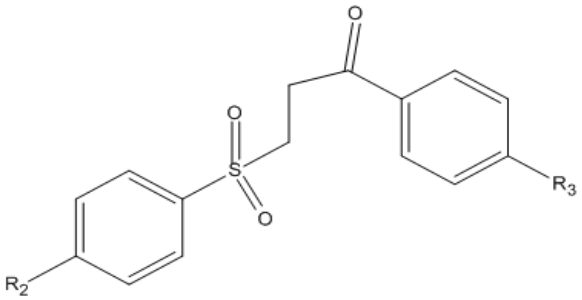
The in-vitro biological activity data reported as IC_{50} for inhibition of 11β-hydroxysteroid dehydrogenae type 1 by a series of keto sulfones derivatives [2] was used for the current study. A total of 23 compounds were selected for the study (Table 1). As biological activities are generally skewed, the reported IC_{50} values were converted into the corresponding pIC_{50} using the following formula:

$$pIC_{50} = -\log IC_{50}$$

Table 1: Biological activities of keto sulfones



COMPOUND	R_1	11 β-HSD1 IC_{50} (μm)	Biological Activity
1.	4-CF_3-Ph	0.187	0.72816
2. *	4-Me-Ph	0.102	-0.99139
3.	4-MeO-Ph	0.075	1.12494
4.	4-F-Ph	0.09	1.04576
5.	4-Cl-Ph	0.2	0.69897
6.	3-MeO-Ph	0.06	1.22185
7.	3,4-DiCl-Ph	0.101	0.995679
8. *	4-NO_2-Ph	1.31	-0.11727
9.	4-NEt_2-Ph	4.4	-0.64345
10.	2,4-DiMe-Ph	1.2	-0.07918
11.	2,5-DiMeO-Ph	9.3	-0.96848
12.	Benzhydryl	2.9	-0.46239
13. *	Et	15	-1.17609
14.	t-Bu	90	-1.95424
15.	$C(CH_3)_2CH_2CO_2Et$	5.0	-0.69897
16.	3-Thienyl	0.345	0.46218
17. *	2-(3-Me)Benzothiophene	0.525	0.27984
18.	2-(5-Phenyl)thiophene	0.134	0.87289
19.	2-(2,4-DiCl-phenyl)5-furan	0.169	0.77211



Compound	R_2	R_3	11 β-HSD1 IC_{50} (µm)	Biological Activity
20.	H	H	17.4	-1.24055
21.	H	F	19.6	-1.29226
22.*	H	Cl	24	-1.38021
23.	H	Br	25	-1.39794

***** Test Set

2.2 Software

A Core2duo personal computer (CPU at 1.83 GHz, HP) with the Windows Vista Home Premium operating system was used. Sketching of structures was performed with ChemDraw ultra 6.0 (Cambridgesoft, USA)[25]. Geometry optimisation was performed with Chem3D Ultra (Version 6.0, Cambridgesoft, USA)[25] and was utilized to calculate the molecular descriptors. The SYSTAT software (Version 10.2)[26] was employed for the Pearson Correlation Matrix and simple multiple linear regression model (MLR) analysis.[13]

2.3 Molecular Modelling

The structures were sketched using ChemDraw Ultra 6.0 and were exported to Chem3D software. The molecular mechanics (MM_2) method was applied to search for lower energy conformation for each molecule. The energy minimised molecules were subjected to re-optimization via the Austin model -1 method until the root mean square gradient attained a value smaller than 0.001 kcal/mol using Molecular Orbital Property Accompany Name (MOPAC).

2.4 Descriptors Generation

The thermodynamic, spatial and electronic parameters are shown in table 2 were calculated for QSAR analysis (The values of different descriptors calculated are given in supplementary data which can be downloaded from www.molinf.com). Thermodynamics parameters describe free energy change during drug receptor complex formation. Spatial parameters were quantified for steric features of drug molecules required for its complimentary fit with the receptor. Electronic parameters describe weak non-covalent bonding between drug molecules and the receptor.[14]

Table 2: List of descriptors used in QSAR Analysis

S.NO.	Abbr.	Descriptors	Type
1.	CSA	Connolly Solvent Accessible Surface Area (Angstroms2)	Steric
2.	CMA	Connolly Molecular Surface Area (Angstroms2)	Steric
3.	CSE	Connolly Solvent- Excluded Volume (Angstroms3)	Steric
4.	EM	Exact Mass (g/mole)	Steric
5.	MW	Molecular Weight (atomic mass units)	Steric
6.	OV	Ovality	Steric

7.	PMX	Principal Moments of Inertia, X	Steric
8.	PMY	Principal Moments of Inertia, Y	Steric
9.	PMZ	Principal Moments of Inertia, Z	Steric
10.	BP	Boiling Point (Kelvin)	Thermodynamic
11.	HOF	Heat of Formation(kcals/mole)	Thermodynamic
12.	HR	Henry's Law Constant	Thermodynamic
13.	LogP	LogP	Thermodynamic
14.	MRCM	Molar Refractivity (cm3/mole)	Thermodynamic
15.	BE	Bending Energy (kcal/mol)	Thermodynamic
16.	CCE	Charge-Charge Energy (kcal/mol)	Thermodynamic
17.	CDE	Charge-Dipole Energy (kcal/mol)	Thermodynamic
18.	DM	Dipole Moment (Debye)	Thermodynamic
19.	DDE	Dipole-Dipole Energy (kcal/mol)	Thermodynamic
20.	NVDW	Non-1,4 van der Waals Energy (kcal/mol)	Thermodynamic
21.	SBE	Stretch-Bend Energy(kcal/mol)	Thermodynamic
22.	TRE	Torsion Energy(kcal/mol)	Thermodynamic
23.	TE	Total Energy (kcal/mol)	Thermodynamic
24.	VDW	van der Waals Energy (kcal/mol)	Thermodynamic
25.	AP	Alpha Coefficients	Electronic
26.	BC	Beta Coefficients	Electronic
27.	GP	Gamma Coefficients	Electronic
28.	EE	Electronic Energy	Electronic
29.	HOMO	HOMO Energy(eV)	Electronic
30.	LUMO	LUMO Energy (eV)	Electronic
31.	RE	Repulsion Energy (eV)	Electronic
32.	E	Total Energy (eV)	Electronic
33.	STR	Stretch	Steric
34.	MR	Molar Refractivity	Steric
35.	D	Dipole	Steric
36.	PR	Probe Radius	Steric

2.5 Division of Test and Training Set

It is proven that the only way to estimate the true predictive power of a model is to test it on a sufficiently large collection of compounds from an external test set. The test set must include not less than five compounds, whose activities and structure must cover the range of activities and structures of compounds from the training set. This application is necessary for obtaining trustful statistics for comparison between the observed and predictive activities for these compounds. In this series 5 compounds were selected as a test set and remaining 18 compounds were used as training set. The test set used for the validation of model.

2.6 Statistical Analysis

First, the descriptors were checked for constant or near constant values and those detected were discarded from the original data matrix. Then, the descriptors were correlated with each other and with the activity data. Among the collinear descriptors detected, the one most highly correlated with activity was retained and the rest were omitted. The contribution of descriptors to biological activity was studied using simple linear regression analysis by SYSTAT 10.2 Software and, due to the problem of collinearity among descriptors, different combinations of descriptors were subjected to sequential and stepwise multiple regression analysis. The

intercorrelation matrix of the descriptors of QSAR Equations, (1) to (3) is given in Table 3. Descriptors having intercorrelation above |r|>0.5 were not considered while deriving the QSAR model. The predictor variables with p value >0.05 were eliminated whilst deriving the QSAR models in order to assure their statistical reliability. Statistical quality of the models was evaluated by using the parameters; number of compounds (n), correlation coefficient (r), coefficient of determination (r^2), standard error of estimate (s), variance, Fischer F-test for quality of fit, and Student's t-test for test of significance . Figures within parentheses indicate the confidence interval (95% significant) of the regression coefficient and the intercept. The level of significance of each regression term was assessed using t-test and is reflected through the minimum value of the standard error term. Residual plots derived by plotting residuals, i.e., the difference between the predicted and the observed response as a function of the dependent variable, are used to identify outliers from the QSAR models. A compound is considered as an outlier when the residual value exceeds twice the standard error of the estimate of the model.

Table 3: Pearson Correlation Matrix of the descriptors used in model 1 to 3

Parameters	LUMO	NVDW	DDE	HOF
LUMO	1.000			
NVDW	0.247	1.000		
DDE	-0.330	-0.247	1.000	
HOF	0.362	0.227	0.121	1.000

In order to validate the derived QSAR models, the leave-one-out (LOO) method, also known as the jack-knife validation test, was used. Once a model was derived, each compound was eliminated from the remaining compounds and the eliminated compound was predicted from this model. The same procedure was repeated after elimination of another compound, until all the compounds had been eliminated once. The predictability of each model was evaluated by using cross validated correlation coefficient (q^2).[15]

RESULT AND DISCUSSION

The correlation between the different physicochemical descriptors and indicator variables as independent variable and the negative log of the observed activity as dependent variable was determined using SYSTAT while exploring the statistically significant relationships to study the selectivity requisites among these compounds. The intercorrelation between all the descriptors was also checked and good orthogonality was ensured during quantitative model building. Some of the statistically significant models are discussed below:

Model 1:

$$BA = -2.183(\pm0.711) + 0.393(\pm0.130)NVDW + 0.345(\pm0.075)DDE - 0.004(\pm0.004)HOF + 0.322(\pm0.763)LUMO$$

$n = 18, r = 0.818, r^2 = 0.669, s = 0.685, F = 6.577, P = 0.004,$

Where n represents the number of data points, r is the multiple correlation coefficient, s is the standard error of the estimate, and F is the F-statistic ratio. Compound 14 behave as an outlier which has a t-butyl group at R position. Its outlier behaviour may be due to its bulky nature, having high heat of formation, it indicates that the more rigid compounds will have a smaller chance of adapting to the preferred conformation than conformationally flexible compounds.[16]

SAR studies also shows that the presence of bulky groups decreases the enzyme inhibition activity significantly. The LUMO energy is the crucial indicator of molecular reactivity and properties, a high value of LUMO for the compounds to improve its activity. The significance of LUMO indicates, high electrophilicity of the compounds, and there by accepting electrons to its lowest unoccupied molecular orbital, would help them to improve the biological activity.[24] The negative contribution of HOF indicates the substituent should have low heat of formation, it indicates that the more rigid compounds will have a smaller chance of adapting to the preferred conformation than conformationally flexible compounds.[16] The positive contribution of Dipole-Dipole energy suggests that the moiety which increases the charge distribution over the molecule is favourable for the activity and it is due to the sulfonyl group present in the nucleus. The compounds might be involved in making fruitful binding interactions with the amino acids present at the catalytic site of the enzyme, through a hydrogen type of bonding. The molecular properties like LUMO and dipole-dipole energy play a critical role in modulating the activity profile for these classes of compounds. The positive contribution of Non-1,4 van der Waals Energy also important for the biological activity.

Model 2:

BA = -1.763(±0.463) + 0.876(±0.502)LUMO + 0.379(±0.083)NVDW + 0.357(±0.048)DDE – 0.006(±0.002)HOF

n = 17, r = 0.918, r^2 = 0.843, s = 0.437, F = 16.120, P = 0.000

Outlier: R = 2-(2, 4-DiCl-phenyl)-5-furan

In model 2, removing the outlier compound 14 increases the value of r^2 significantly from 0.669 to 0.843. Compound 19 behave as an outlier which have a 2-(2, 4-DiCl-phenyl)-5-furan at R position. The outlier behaviour of this compound may be due to its rigidity in its structure which may make the compound conformationally unfavourable for the binding of the enzyme.

Model 3:

BA = -1.656(±0.364) + 1.199(±0.408)LUMO + 0.399(±0.065)NVDW + 0.363(±0.038)DDE – 0.007(±0.002)HOF

n = 16, r = 0.953, r^2 = 0.909, s = 0.342, F = 27.330, P = 0.000, q^2=0.7135

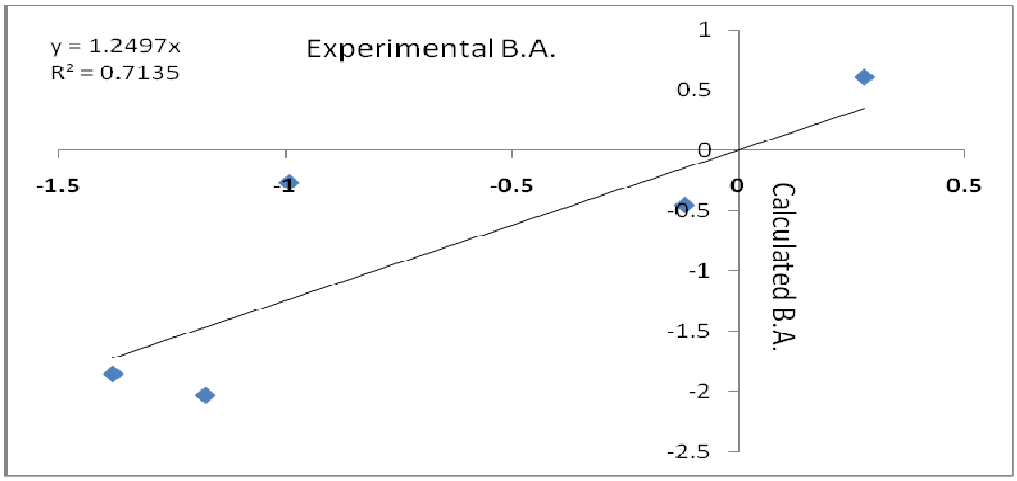


Figure 2: Calculated B.A. vs Experimental B.A. for Best Multiple Linear Regression model

In model 3, removing the outlier compound 19, increases the value of r^2 significantly from 0.843 to 0.909. The r^2 value accounts for 90% variance in observed activity value. Model 3 is the best model for the inhibition of 11β-HSD1 enzyme. As the r^2 value can be easily increased by increasing the number of descriptors in the model, so cross validated correlation coefficient (q^2) was used as a parameter to select the optimum number of descriptors. The variation in cross validation correlation coefficient (q^2) as a function of number of descriptors is shown in Figure 2.

To conclude, all types of descriptors like electronic, thermodynamic, and steric must be fully optimized for better 11β-HSD1 inhibitory activity. The findings suggests that the presence of bulky group decreases the enzyme inhibition activity, the presence of conformationally rigid structure is unfavourable for the binding of compounds with the enzyme and the presence of high electrophilicity groups such as methoxy group in the phenyl ring increases the activity of the compound towards the enzyme. The moiety which increases the charge distribution over the molecule is favourable for the activity. The similar result has been given in the SAR study of this series of compounds by Xiang et al. (2007), without any physicochemical relevance. Our study supplements this by QSAR analysis of the substituent position for better biological activity. The present study provides better insight into designing more potent 11β-HSD 1 inhibitors in future prior to their synthesis.

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