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QSAR Studies of 3, 4-dihydropyrimidin-2(1H)-one Urea Derivatives as Antibacterial and Antifungal activity

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Abstract

The present study is aimed to elucidate the structural features of novel 3,4-dihydropyrimidin-2(1H)-one urea derivatives required for antibacterial and antifungal activity and to obtain predictive models to guide the rational synthesis of novel activity. The significant best 2D QSAR model (S.aureus) having correlation coefficient r2 = 0.7854 and cross-validated squared correlation coefficient q2 = 0.7563 with external predictive ability of pred_r2 = 0.7629 was developed. The main aimed to obtain predictive models which may guide the synthesis of more active antimicrobial agents.

Keywords: 3,4-dihydropyrimidin-2(1H)-one urea; 2D-QSAR; VLife MDS; Antimicrobial activity

Introduction

In recent years, the mounting threat of bacterial resistance has heightened the urgency to discover and develop anti-ineffective agents with novel mechanism of action and enhanced activity profile. Drug resistance develops as a result of gene mutations, rearrangements and genetic transfer between different bacteria [1]. These are serious problems to populations and to public health systems due to the morbidity and mortality they cause, and the costs related to the implementation of effective control measures, and led the World Health Organization to select 'antimicrobial resistance' as the theme for World Health Day 2011 [2]. Recent studies showed its potential for the treatment of multidrug-resistant including extended-spectrum β-lactamase (ESBL) producing Entero-bacteriaceae infections [3] like those caused by *Escherichia coli* and *Klebsiella pneumoniae*, and other Gram-negative species such as *Pseudomonas aeruginosa* and *Acinetobacter baumannii* [4,5]. Among the most common Gram-positive resistant pathogens are *Streptococcus pneumoniae*, resistant to penicillin and macrolides, methicillin-resistant *S. aureus* (MRSA), glycopeptides-intermediately resistant *S. aureus* (GISA), methicillin-resistant *S. epidermidis* [6]. Dihydropyrimidinones (DHPMs) are important biologically active materials, acting as calcium channel antagonists, anti-bacterial, anti-hypertensive, anti-inflammatory agents, cytotoxic activity, antihypertensive and antitubercular activity [7-9] and Quantitative structure–activity relationships (QSAR) have been employed, and continue to be developed and employed, both to correlate information in data sets and as a tool to facilitate the discovery of new molecules with increased biological potency [10]. QSAR models are mathematical equations relating chemical structure to a wide variety of physical, chemical and biological properties.

To our knowledge it is the first time the extensive QSAR has been studied on the 3, 4-dihydropyrimidin-2(1H)-one urea derivatives. With the above facts and in continuation of our research for newer antimicrobial agents in the present study, we reported 2D-QSAR studies on a series of 3,4-dihydropyrimidin-2(1H)-one urea derivatives to provide further insight into the key structural features required to design potential drug candidates of this class.

Materials and Method

Dataset for analysis

In the present study, a series of substituted 3, 4-dihydropyrimidin-2(1H)-one urea having antibacterial and antifungal activity from published result [11] was taken. The biological activity values represented as minimum inhibitory concentrations (MICs) were first converted to -log MIC (pIC_{50}) in micromolar (Table 1) and were used as the dependent variable for the QSAR model.

Molecular structure generation

The molecular structures of all the 23 molecules were built using the 2D draw application of V-Life MDS 3.5 software [12] with standard bond lengths and bond angles. Geometry optimization was carried out using the standard Merck Molecular Force Field (MMFF) followed by considering distance-dependent dielectric constant of 1.0, convergence criterion or root-mean-square (RMS) gradient at 0.01 kcal/mol Å and the iteration limit to 10,000 [13].

Selection of training and test tet

The dataset of 23 molecules was divided into training and test set by sphere exclusion (SE) method with pIC_{50} activity field as dependent variable and various 3D descriptors calculated for the compounds as independent variables. Selection of molecules in the training set and test is a key and important feature of any QSAR model. The sphere exclusion method [14] was adopted for division of training and test data set comprising of 18 and 5 (Table 1 marked with asterisk) molecules, respectively, with a dissimilarity value of 2.8.

Two-dimensional QSAR methodology

A large number of theoretical Two-dimensional individual descriptors (Individual, Chi, Path count, ChiChain, Cluster, element Count, estate number, estate contribution and Polar surface area). The invariable descriptors (descriptors that are constant for all the molecules) were removed, as they do not contribute to the QSAR, which resulted in total 157 descriptors was considered as independent variables in the present study. Alignment-independent descriptors can be generated by considering the topology of the molecule, atom type,

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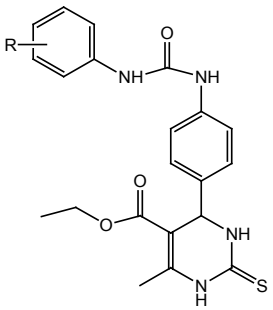
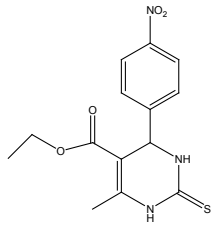
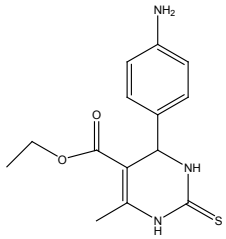


S.No	R	MIC_{50} [a]	pIC_{50}	MIC_{50} [b]	pIC_{50}	MIC_{50} [c]	pIC_{50}
1		35	4.4559	30	4.5228	30	4.5228
2		40	4.3979	40	4.3979	55	4.2596
3	2-F	10	5.0132	10	5.0132	10	5.0132
4	2-Cl	10	5.0132	10	5.0132	10	5.0132
5*	2-CF_3	25	4.6020	15	4.8239	25	4.6020
6	2-OCF_3	30	4.5228	25	4.6020	15	4.8239
7*	2-OC_6H_5	*40*	4.3979	35	4.4559	40	4.3979
8	2-F, 6-CH_3	60	4.2218	30	4.5228	50	4.3010
9	2-F, 6-CF_3	55	4.2596	40	4.3979	55	4.2596
10	2-Cl, 6-CH_3	40	4.3979	55	4.2596	40	4.3979
11*	2-Cl, 6-CF_3	40	4.3979	60	4.2218	60	4.2218
12	2-Cl, 5-CF_3	55	4.2596	80	4.0969	60	4.2218
13	2-Cl, 4-CF_3	35	4.4559	25	4.6020	35	4.4559
14*	2-Cl, 6-F	65	4.1870	85	4.0705	40	4.3979
15	3-CF_3	40	4.3979	20	4.6989	25	4.6020
16*	3-Cl, 4-F	60	4.2218	85	4.0705	80	4.0969
17	3,5-F	90	4.0457	-	-	95	4.0222
18	3,4-CH_3	90	4.0457	-	-	95	4.0222
19	4-F, 3-CH_3	65	4.1870	-	-	80	4.0969
20	4-isopropyl	85	4.0705	55	4.2596	90	4.0457
21	4-butyl	-	-	95	4.0222	-	
22	4-CF_3	20	4.6989	10	5.0132	15	4.8239
23	4-OCH_3	15	4.8239	15	4.8239	10	5.0132

*test set

[a] *Staphylococcus aureus;* [b] *Escherichia coli;*[c] *Candida albicans*

Table 1. The structures of 3,4-dihydropyrimidin-2(1H)-one urea derivatives with their activities.

and bond.

In this study to calculate AI descriptors, we have used following attributes, 2 (double bonded atom), 3 (triple bonded atom), C, N, O, S, H, F, Cl, Br and I and the distance range of 0-7. The preprocessing of the independent variables (descriptors) was done by removing invariable (constant column) and cross-correlated descriptors which resulted in total 218 descriptors to be used for QSAR analysis (Table 2).

Results and Discussion

Some statistically significant 2D-QSAR models were chosen for discussion.

pIC_{50} (*S.aureus*) =0.5123(±0.0315) SssOE-index+0.1443(±0.0554) $SssCH_2E$-index-0.0221 (±0.0081) T_T_Cl_1 +0.1246 (±0.0520) Fluorines Count

N = 23, r^2 = 0.7854, q^2 = 0.7563, F test = 36.5431, pred_r^2 = 0.7629

Model 1 has a coefficient of correlation that explains 78.5 % variance in the activity. The model show that the descriptor SssOE-index electro topological state for number of oxygen atom connected with two single bonds indicated that the activity was increased with the presence of methoxy groups at R position. $SssCH_2E$-index topologic state for the number of CH_2 groups attached to two single bonds. T_T_Cl_1 showed that increase in the values of this descriptor would be beneficial for the antibacterial activity of dihydropyrimidin derivatives. The positive coefficient of the Fluorine Count descriptor suggests that dihydropyrimidin may be increased by increasing the number of fluorine atoms present in the nucleus. The activity contribution chart for 2DQSAR model is shown in Figure 1a and plots of observed vs. predicted values of pIC_{50} are shown in Figure 1b. The above model-1 is validated by predicting the biological activities of the training and test molecules, as indicated in Table 3.

pIC_{50} (*E.coli*) = 0.4170(± 0.0518) SsClE-index -0.2309(± 0.0908) T_C_O_3

N = 23, r^2 = 0.7729, q^2 = 0.7254, pred_r^2 = 0.7431

In 2D-QSAR model, r^2>0.5 suggests significant percentage of the total variance in biological activity is accounted by the model. The descriptor SsClE-index indicated by the high activity of molecules having chlorine atoms number of chlorine connected with one single bond beneficial for the activity. The descriptor T_C_O_3 carbon atoms (single double or triple bonded) separated from any oxygen atom (single or double bonded) by bond distance in a molecule plays most important role (~15%) in determining activity. Plots of observed vs. predicted values of pIC_{50} are shown in Figure 1c.

pIC_{50} (*C.albicans*) = 0.6168 (± 0.0322) SsssCHE-index + 0.2066(± 0.0464) T_2_N_2

N = 23, r^2 = 0.7498, q^2 = 0.6994, F test = 22.321, pred_r^2 = 0.6642

The descriptor SsssCHE positive correlation suggests that better antibacterial can be achieved by increasing the rings. The last independent descriptor T_2_N_2 (i.e., the number of double-bonded atoms separated from the nitrogen atom by 2 bonds) indicates to the activity. It suggests that the mono substituents with a nitrogen atom in the R position of the ring is detrimental to activity. The plots of observed vs. predicted values of pIC_{50} are shown in Figure 1d.

Parameter	SssOE-index	$SssCH_2E$-index	T_T_Cl_1	Fluorines Count
SssOE-index	1.0000			
$SssCH_2E$-index	0.4864	1.0000		
T_T_Cl_1	0.3741	0.5639	1.0000	
Fluorines Count	0.2198	0.5483	0.7632	1.0000

Table. 2. Correlation matrix between descriptors present in the best QSAR model -1.

Com	2D QSAR Model-1[a]		2D QSAR model-2[b]		2D QSAR model-3[c]	
	Pred.	Res.	Pred.	Res.	Pred.	Res.
1	4.4317	0.0242	4.3084	0.2144	4.7074	-0.1846
2	4.2281	0.1698	4.3695	0.0284	4.2976	-0.038
3	5.2154	-0.2022	4.9156	0.0976	5.1473	-0.1341
4	4.9122	0.101	4.9878	0.0254	4.9971	0.0161
5	4.7420	-0.14	4.6534	0.1705	4.6346	-0.0326
6	4.5393	-0.0165	4.7242	-0.1222	4.8488	-0.0249
7	4.4178	-0.0199	4.3472	0.1087	4.3908	0.0071
8	4.1160	0.1058	4.4364	0.0864	4.3515	-0.0505
9	4.0645	0.1951	4.3674	0.0305	4.2854	-0.0258
10	4.5678	-0.1699	4.0609	0.1987	4.3789	0.019
11	4.1782	0.2197	4.4698	-0.248	4.4133	-0.1915
12	4.3144	-0.0548	4.2951	-0.1982	4.1738	0.048
13	4.1818	0.2741	4.4439	0.1581	4.4317	0.0242
14	4.0928	0.0942	4.1987	-0.1282	4.3845	0.0134
15	4.4438	-0.0459	4.4543	0.2446	4.6173	-0.0153
16	4.1438	0.078	4.1587	-0.0882	4.1782	-0.0813
17	3.9326	0.1131	-	-	4.0092	0.013
18	4.2737	-0.228	-	-	4.1307	-0.1085
19	4.3597	-0.1727	-	-	4.0334	0.0635

20	4.2587	-0.1882	4.3569	-0.0973	4.1527	-0.107
21	-	-	4.1491	-0.1269	-	-
22	4.6611	0.0378	4.9714	0.0418	4.8108	0.0131
23	4.9910	-0.1671	4.7679	0.056	5.0979	-0.0847

Table 3: Observed and Predicted activities with residue according to 2D QSAR models.

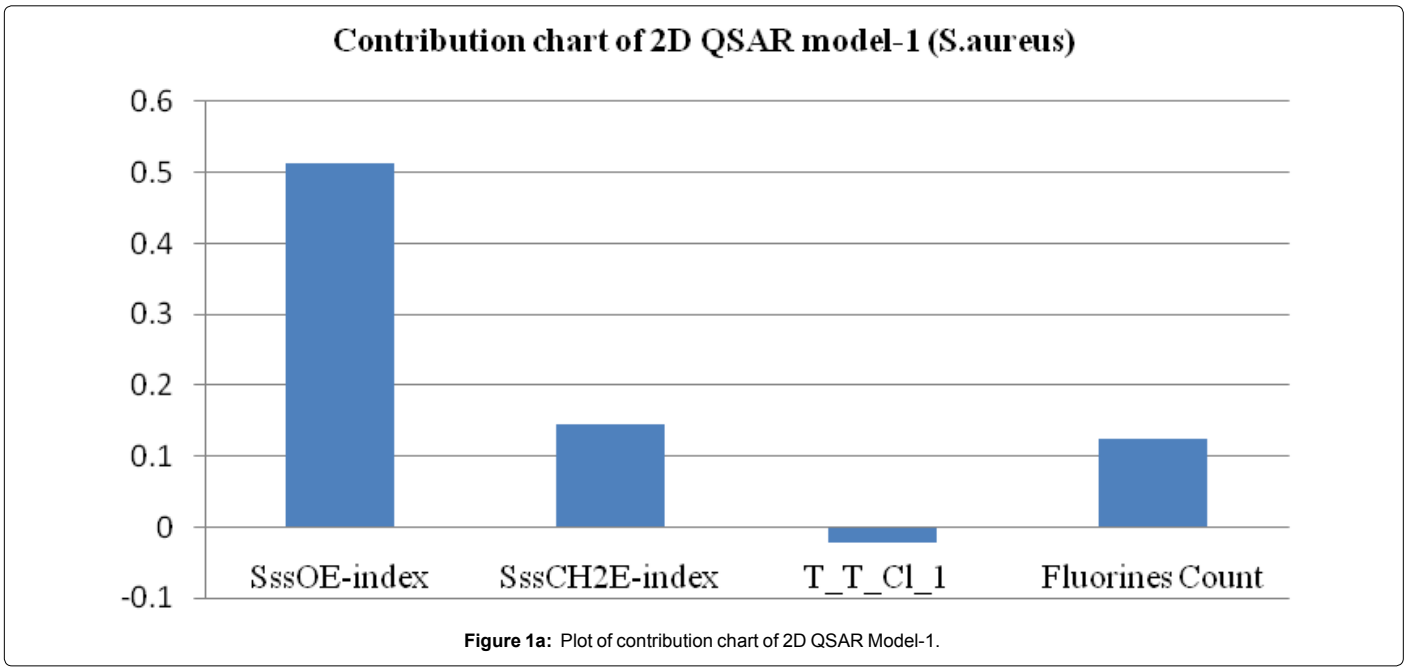


Figure 1a: Plot of contribution chart of 2D QSAR Model-1.

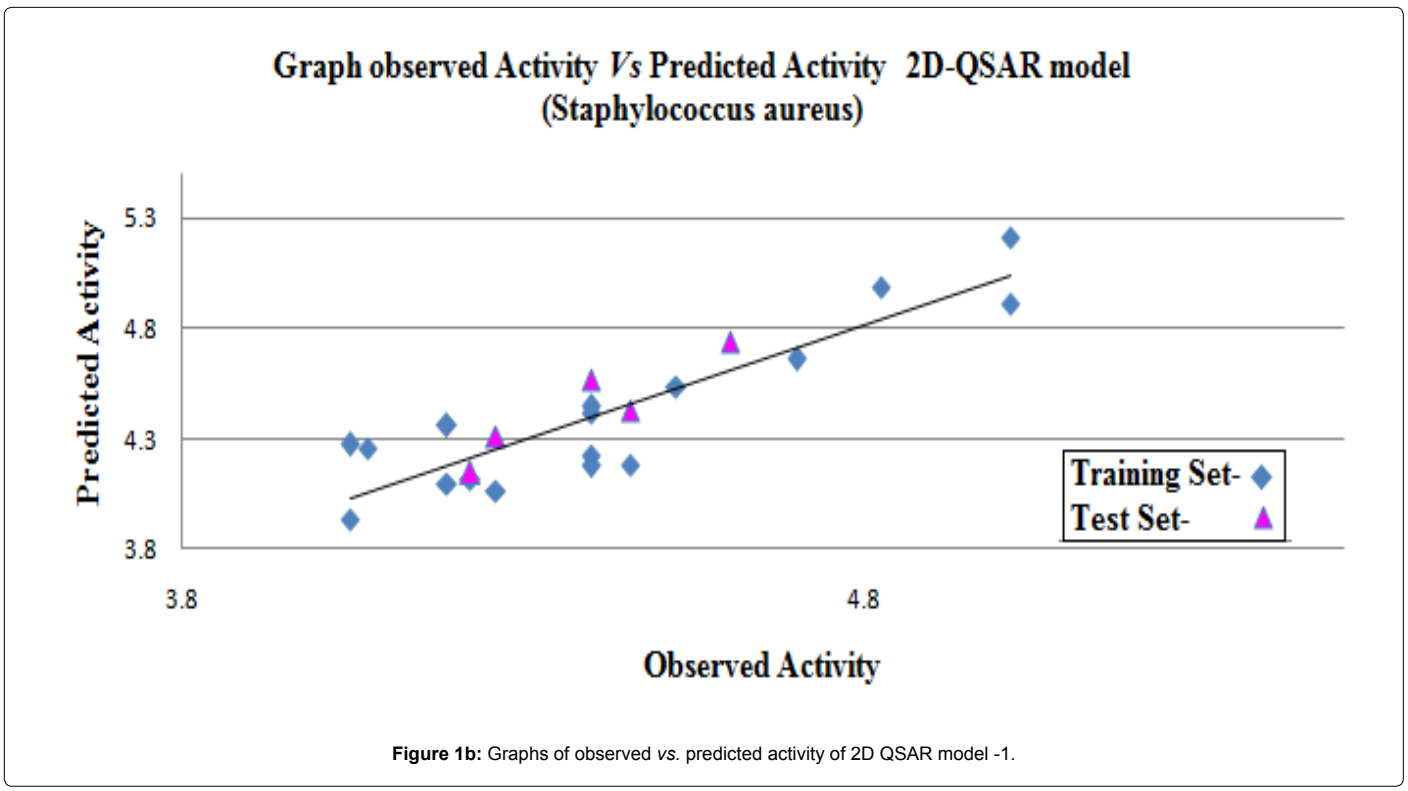


Figure 1b: Graphs of observed *vs.* predicted activity of 2D QSAR model -1.

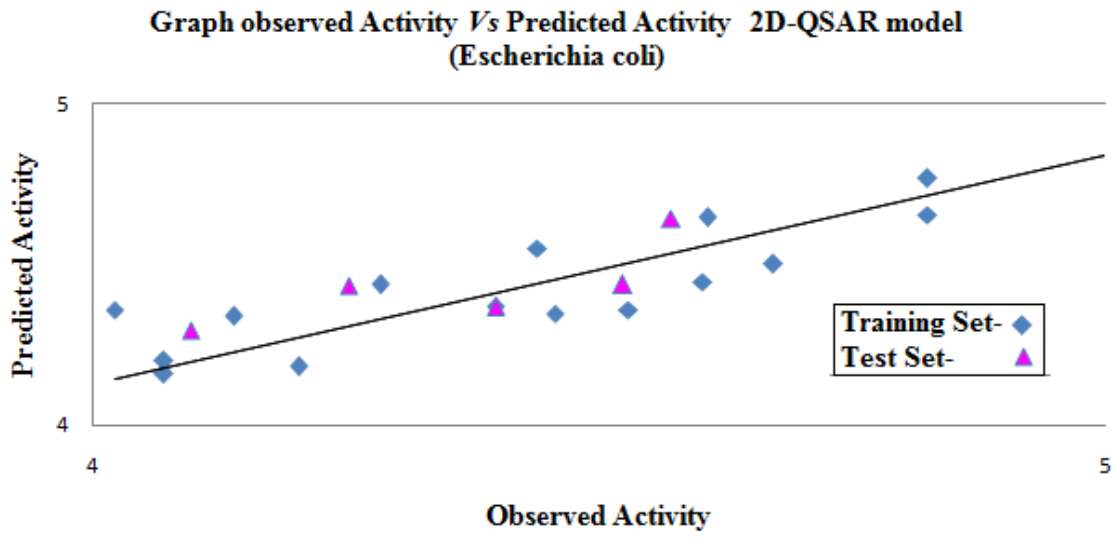


Figure1c: Graphs of observed *vs.* predicted activity of 2D QSAR model -2.

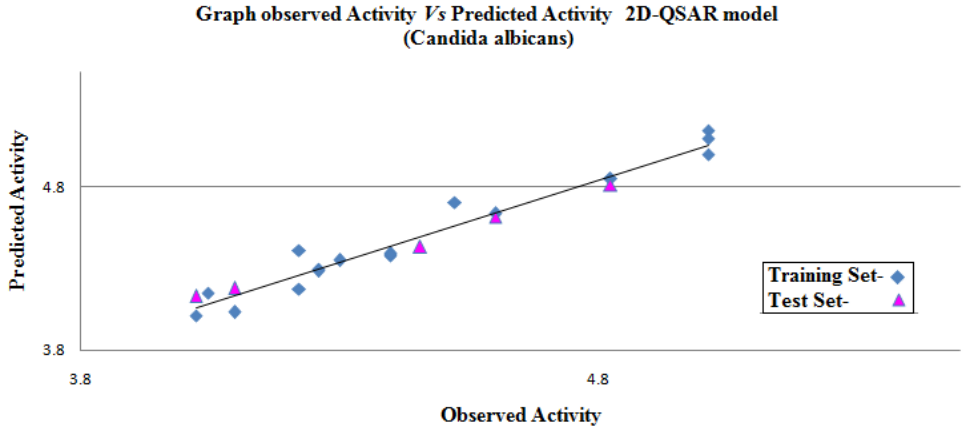


Figure1d: Graphs of observed *vs.* predicted activity of 2D QSAR model -3.

Conclusion

Two dimensional quantitative structure activity relationship study by means of partial least square method was performed on a series of 3,4-dihydropyrimidin-2(1H)-one urea as antibacterial and antifungal using molecular design. However Models by partial least square could be considered as best one in terms of excellent internal and external predictive abilities. In conclusion, the model developed to predict the structural features of 3,4-dihydropyrimidin-2(1H)-one urea to inhibit antibacterial and antifungal, reveals useful information about the structural features requirement for the molecule.

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