Quantitative structure activity relationship (QSAR) approach employed to understand the affinity and selectivity of a novel series of 6-arylaminobenzoxazinones derivatives towards progesterone receptor. The generated correlations were found to be statistically significant and exhibited good predictive power. The results obtained from the QSAR study revealed that substituents indicate the importance of aromatic ring, hydrogen bond donor, molecular hydrophobicity and steric influence for receptor binding. The QSAR models suggest that hydrophobic character is crucial for the Progesterone receptor inhibitory activity exhibited by these compounds and inclusion of hydrophobic substituents will enhance the inhibitory activity. The findings of the QSAR study provide a set of guidelines for designing compounds with better PR inhibitory potency.

Keywords: 6-arylaminobenzoxazinones, PR receptor, QSAR

Introduction

Estrogen and progesterone are two prime female reproductive hormones, have effects on multiple organs beyond reproductive system and their actions are mediated through receptor-based gene stimulation [1]. The progesterone receptor (PR) is a member of the intracellular receptor (IR) superfamily that includes the androgen (AR), estrogen (ER), glucocorticoid (GR) and mineralocorticoid (MR) receptors. Two different isoforms, A and B of PR are present in various target organs of progesterone. It is observed that PR-B acts mainly as progesterone-responsive gene activator, whereas PR-A functions as modulator of PR-B activity and repressor for other IRs, suggesting PR-A to be an important modulator for steroid hormone receptor actions. Primary uses of PR agonist and antagonist combined with estrogen are for the purpose of birth control, hormone replacement therapy, endometriosis, dysfunctional uterine bleeding, dysmenorrhea, endometrial cancer, uterine leiomyomas, breast cancer, meningiomas and others.

Focus on development of more selective and efficacious PR antagonists, have increased to a great extent considering the unwanted effects due to cross-reactivities with other IRs (AR, GR, ER, MR) and GABA (γ-amino butyric acid) receptor.

Experimental Methods

The computing tools used for the present study were the Chemdraw Ultra (Version 8.0) software & energy minimized via MOPAC with energy tolerance value of root mean square gradient 0.001 kcal/mol & maximum number of iteration set to 1000. Conformational search of each energy-minimized structure was performed using the stochastic approach which is similar to the RIPS Method and validation program VALSTAT (VALSTAT, 2004). The progesterone receptor inhibitor activity data of 6-arylaminobenzoxazinones derivatives were taken from the reported work of Jeffery C et al. The molecular structures of all 25 compounds were sketched using the Chemdraw Ultra (Version 8.0) software & energy minimized via MOPAC with energy tolerance value of root mean square gradient 0.001 kcal/mol & maximum number of iteration set to 1000.

The series was divided into a training set of 21 compounds & a test set of 4 compounds carried out automatically by the (VALSTAT software,2004). The sequential multiple linear regression analysis method was employed. The best model was selected from the various statistically significant equations on the basis of the observed squared correlation coefficient (r2), standard deviation (std.) the sequential Fischer test (F), the Bootstrapping r2, chance, Q2 value, Spress value, standard deviation of error prediction (SDEP) & the predictive squared correlation coefficient of the test set (r2 pred.).

Results and Discussion:

The computing tools used for the present study were the Chemdraw Ultra (Version 8.0) software & energy minimized via MOPAC with energy tolerance value of root mean square gradient 0.001 kcal/mol & maximum number of iteration set to 1000. Conformational search of each energy-minimized structure was performed using the stochastic approach which is similar to the RIPS Method and validation program VALSTAT (VALSTAT, 2004).

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The progesterone receptor inhibitor activity data of 6-arylaminobenzoxazinones derivatives were taken from the reported work of Kern JC et al. The molecular structures of all 25 compounds were sketched using the Chemdraw Ultra (Version 8.0) software & energy minimized via MOPAC with energy tolerance value of root mean square gradient 0.001 kcal/mol & maximum number of iteration set to 1000. All conformers generated for each structure were analyzed in conformational geometrics panels with great care, and the lowest energy conformation of each structure was selected & added to a molecular database to compute various physicochemical properties. The series was divided into a training set of 21 compounds & a test set of 4 compounds carried out automatically by the (VALSTAT software,2004). The sequential multiple linear regression analysis method was employed. The best model was selected from the various statistically significant equations on the basis of the observed squared correlation coefficient ($r^2$), standard deviation (std.) the sequential Fischer test (F), the Bootstrapping $r^2$, chance, $Q^2$ value, $S_{\text{PRESS}}$ value, standard deviation of error prediction (SDEP) & the predictive squared correlation coefficient of the test set (Table 1).

**Table 1: Comparison of cross validation parameters for generated QSAR models**

<table>
<thead>
<tr>
<th>Model No.</th>
<th>$r^2$</th>
<th>$S_{\text{PRESS}}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.821324</td>
<td>0.238603</td>
</tr>
<tr>
<td>2</td>
<td>0.783425</td>
<td>0.347219</td>
</tr>
<tr>
<td>3</td>
<td>0.857453</td>
<td>0.305647</td>
</tr>
</tbody>
</table>

$^a$ = Squared correlation coefficient of prediction. $^b$ = Standard deviation of prediction. $^c$ = Standard error of prediction

**Conclusion:**
The QSAR analysis of 25 6-arylaminobenzoxazinones derivatives using a novel set of QSAR descriptors resulted in quantitative models of good statistical significance. The generated QSAR models also showed good predictive potential as established by their high $r^2(>0.7)$ and hence can be used in the prediction of biological activity of novel molecules prior to their synthesis.

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**Conflict of interest:** Nil  
**Acknowledgement:** None

**References:**

3. VALSTAT, 2004. A statistical program developed by DR Arun Kumar, SGSITS, Indore

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