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QSAR Study of Quinolinediones with Inhibitory Activity of Endothelium-Dependent Vasorelaxation by CoMSIA

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Abstract—The 3D-QSAR study of quinolinediones which showed potent inhibitory effect on the acetylcholine induced vasorelaxation of rat aorta with the endothelium was conducted by CoMSIA. The statistical result, cross-validated q^2 (0.741) and r^2 (0.960) values, gave reliability to the prediction of inhibitory activity of this series.

Introduction

6-Anilino-5,8-quinolinedione (LY83583) has been widely used as an agent to reduce levels of nitric oxide (NO) dependent cGMP in tissues. This compound suppressed not only endothelium-dependent vasorelaxation, but also endothelium-independent relaxation induced by exogenuous NO generated from nitrovasodilator drugs.[1–3]

Quinones such as 1,4-naphthoquinones and 6-phenylamino-5,8-quinolindione showed the inhibition of the endothelium-dependent vasorelaxation.[4–7] 6-Phenylamino-5,8-quinolindiones also produced the inhibition of L-arginine-induced vasorelaxation in endotoxin-treated rats, indicating their inhibitory effects on inducible NO synthase. 6-Phenylamino-5,8-quinolindiones lowered intracellular cGMP in several tissues due to inhibition of endothelial nitric oxide synthase activity and decreased in NO formation.[3] Endogeneous formation of NO from L-arginine is catalyzed by NO synthase. Isozymes of NO synthase consisting of neuronal, endothelial and inducible form have in common a NADPH-cytochrome P450 reductase domain. Quinonoids compounds undergo one- or two-electron reduction by flavoenzymes such as cytochrome P450 and shunts electrons away from L-arginin oxidation.[4]

The bioisosteres of these quinones, 6/7-(substituted-phenyl)amino-5,8-quinolinediones, 7-(substituted-phenyl)amino-5,8-isoquinolinediones and 6/7-(substituted-phenyl)amino-5,8-quinazolinediones were synthesized and their inhibitory activities on the ACh-induced vasorelaxation of PE-precontracted rat aorta with the intact endothelium were reported.[8,9] In this series the presence of nitrogen on the heterocyclic quinones might be an important factor in the inhibitory activities. However, quantitative structure–activity relationship study for this series are not reported and here we report the QSAR of quinazolinediones on the inhibition of endothelium-dependent vasorelaxation.

Methods

Data set for analysis

The inhibitory activities of endothelium-dependent vasorelaxation of 6/7-(substituted-phenyl)amino-5,8-quinolinediones, 7-(substituted-phenyl)amino-5,8-isoquinolinediones, 6/7-(substituted-phenyl)amino-5,8-quinazolinediones of Ryu were used for this analysis.[8,9] Table 1 represents the structure and endothelium-dependent vasorelaxation inhibition activities (EC_{50}, μg/mL) of compounds employed in this study.

Computational methods

All molecular modeling and statistical analyses were performed using SYBYL 6.5 molecular modeling

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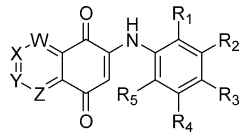
Table 1. Structure of quinolinedione derivatives



Compd	W	X	Y	Z	R_1	R_2	R_3	R_4	R_5	EC_{50} (μM)
1[a]	C	N	C	N	H	H	F	H	H	0.846
2	C	N	C	N	H	H	Br	H	H	0.534
3	C	N	C	N	H	I	H	H	H	0.664
4	C	C	C	N	H	H	F	H	H	0.541
5	C	C	C	N	H	H	Br	H	H	0.302
6	C	C	C	N	H	H	I	H	H	0.214
7	C	C	C	N	H	H	CF_3	H	H	0.607
8	C	N	C	C	H	F	F	H	H	0.640
9	C	N	C	C	H	F	H	F	H	0.290
10	C	N	C	C	F	H	F	H	H	0.430
11	C	C	C	C	H	H	H	H	H	0.239
12	C	C	C	C	H	H	F	H	H	0.362
13	C	C	C	C	F	F	F	H	H	0.330
14	N	C	N	C	H	H	Br	H	H	0.599
15	N	C	N	C	H	H	F	H	F	0.708
16	N	C	N	C	H	H	H	H	F	0.624
17	N	C	N	C	H	F	H	F	H	0.475
18	N	C	N	C	H	H	CH_3	H	H	0.503
19	N	C	N	C	H	H	CF_3	H	H	0.599
20	N	C	N	C	H	H	OCF_3	H	H	0.615
T1[b]	C	N	C	N	H	H	Cl	H	H	1.036
T2	C	N	C	N	H	F	H	H	H	0.437
T3	C	N	C	N	H	H	CF_3	H	H	1.269
T4	C	C	C	N	H	F	H	F	H	0.449
T5	C	C	C	N	H	H	OCF_3	H	H	0.603
T6	C	N	C	C	H	H	H	H	H	0.439
T7	C	N	C	C	H	F	H	H	H	0.562
T8	C	C	C	C	H	H	Cl	H	H	0.220
T9	N	C	N	C	H	H	H	H	H	0.340
T10	N	C	N	C	H	H	Cl	H	H	0.861
T11	N	C	N	C	H	H	F	F	F	0.919

[a]1–20: Training set.
[b]Test set.

software (Tripos Inc.) and Silicon Graphics Indy workstation (IRIX 6.2). The 2D structure of each compound was built using SYBYL Build program with the default SYBYL settings. The 2D structure was converted to a 3D structure using Concord 4.0 program. The structural energy minimization was performed using the SYBYL energy minimizer (Tripos Force Field) and Gasteiger–Huckel charge or AM1 semiempirical quantum mechanical charge, with a 0.005 kcal/mol energy gradient convergence criterion. Low energy conformation was searched by geometry optimization after rotating every 30° of single bond from 1 to 330° of tortional angle. All of the structures generated were aligned into lattice box by fitting with 2-aryl amino quinone group as a common structure.

Calculation of CoMSIA descriptors

The CoMSIA of the QSAR module of SYBYL was used for the analysis. Similarity indices between a compound and a probe atom were calculated. The common probe atom with charge +1, radius 1 Å, and hydrophobicity +1 was placed at the intersections of a regularly spaced lattice. The attenuation factor (α) was set at 0.3. To determine the similarity, the mutual distance between probe atom and the atoms of the molecules in the data set was considered. In this study physicochemical properties such as steric and electrostatic feature, hydrogen bond donors and acceptors, and hydrophobic fields were considered.

The equation used to calculate the similarity indices is as follows.

$$A^{q}_{F,K,(j)} = -\Sigma W_{\text{probe},k} W_{ik} \mathrm{e}^{-\alpha\gamma iq2}$$

A is the similarity index at grid point q, summed over all atoms i of the molecule j under investigation. $W_{\text{probe},k}$ is the probe atom with radius 1 Å charge +1, hydrophobicity +1, hydrogen bond donating +1, and hydrogen bond accepting +1. W_{ik} is the actual value of the physicochemical property k of atom i. The mutual distance between the probe atom at grid point q and atom i of the test molecule is represented by r_{iq}. α Is the attenuation factor, with a default value of 0.3, and an optimal value normally between 0.2 and 0.4, larger values of which result in a steeper Gaussian function curves and a strong attenuation of the distance-dependent effects of molecular similarity.

The partial least squares (PLS) method was used for fitting the 3D structural features and their biological activities. The optimum number of components in the final PLS model was determined by the q^2 value, obtained from the leave-one-out cross validation technique.

Molecular alignment

Using compound **6** as template molecule, superposition of all quinolinediones was performed with common 2-phenylamino quinone containing in all compounds. Figure 1 shows the results of such alignment.

Results and Discussion

Firstly, CoMFA, the most commonly used QSAR program, was employed for the analysis with the training set composed of 20 various analogues, which biological activities are known. All three models showed low correlation (q^2 values: 0.405–0.563) and overstated ONC values (8–10) with steric, electrostatic fields,

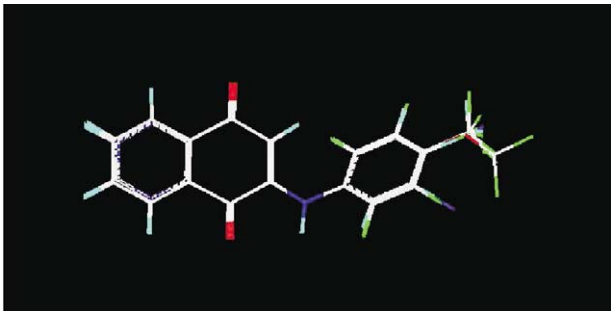


Figure 1. Stereoview of the 20 compounds aligned.