CROATICA CHEMICA ACTA CCACAA **75** (2) 517–529 (2002)

ISSN-0011-1643
CCA-2814

Original Scientific Paper

QSAR of Flavonoids: 4. Differential Inhibition of Aldose Reductase and p56^{lck} Protein Tyrosine Kinase*

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Received May 7, 2001; revised October 4, 2001; accepted October 18, 2001

Flavonoids are a group of low molecular weight plant products, based on the parent compound, flavone (2-phenylchromone) and have shown potential for application in a variety of pharmacological targets. By using random screening techniques flavones have been proposed as inhibitors of aldose reductase, an enzyme crucial in the treatment of diabetic complications such as cataract formation. On the other hand, a large number of natural and synthetic flavonoids are being tested as specific inhibitors of protein tyrosine kinase (PTK). Kinetic analyses of the PTK inhibition indicate that flavonoids are competitive inhibitors with respect to the nucleotide ATP. A thorough investigation of the available experimental data base by using both classical and quantum chemical descriptors has been performed in order to develop quantitative structure-activity relationships for these enzyme systems. Relevance of the descriptors to binding properties of both enzyme receptors active site is proposed and the obtained results demonstrate in detail which specific electronic as well as the hydrophobic and steric properties of the substituents play a significant role in their differential binding.

Key words: QSAR, flavonoid derivatives, aldose reductase, protein tyrosine kinase.

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* This paper is dedicated to Professor Milan Randić (Des Moines) in honor of his 70th birthday.

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INTRODUCTION

Flavonoids are a group of low molecular weight plant products, analogs of flavone (2-phenylchromone) and have found wide interest as potential pharmacological agents. Their abundancy, relatively simple availability by synthetic means and interesting biological activity profiles in several enzymatic systems render them attractive for study. By application of random screening techniques flavones have been proposed as potential inhibitors of aldose reductase, an enzyme crucial in the treatment of diabetic complications such as cataract formation.[1–4] Using reduced nicotinamide-adenine-dinucleotide phosphate (NADPH) as a cofactor, aldose reductase (AR) reduces aldose sugars to their alcohols, *e.g.* glucose to sorbitol, while the second enzyme, sorbitol dehydrogenase (1-iditol dehydrogenase, EC 1.1.1.14), oxidizes sorbitol to fructose. Under diabetic conditions the glucose level in this pathway is increased and sorbitol is produced more rapidly than converted to fructose. The accumulation of sugar alcohols in lens, nerve or retina results in hyperosmotic effect which leads to lens swelling and subsequent cataract formation[5] as well as the pathologic changes in other tissues. A possible prevention or treatment of these effects is the inhibition of AR. The development of aldose reductase inhibitors (ARIs) enabled also the evaluation of role of AR in diabetic complications.

The inhibitory effect on aldose reductase was observed in structurally diverse compounds tetramethyleneglutaric acid, flavone, chinoline, coumarin, xanthone, naphthalene, quinazoline, phthalazine, benzoxazine or rhodanine derivatives,[6–10] which can be divided generally in two groups of ARIs, those containing a carboxylic acid moiety and those containing rigid spirohydantoins or related ring systems.[11]

Kador *et al.*[6,12] have shown that the structural requirements for the inhibitory activity consist of a generally planar structure with two aromatic hydrophobic regions and a common region susceptible to charge-transfer interactions. This observation lead to the proposed structure of AR with the inhibitor binding site with a hydrophobic (lipophilic) region and a region at which reversible charge transfer (nucleophilic substitution) can occur. Three distinct enzyme regions were proposed: a substrate site, nucleotide cofactor fold and inhibitor site.[12]

Flavonoids derivatives were found to be more potent than the previously known ARIs, tetramethyleneglutaric acid or isoquinoline analogs.[1] Some qualitative observations on structural requirements for the inhibitory activity like the ortho orientation of the hydroxyls in positions 3' and 4' of ring B were also determined. Further study[2] concentrated on the effect of number of hydroxyls in the flavonoid structure and glycosylation on the AR inhibi-

tory activity. Through the computer modelling and molecular orbital calculations the most important electronic and steric features were proposed.[6,12] ARIs reversibly interact with AR at an inhibitor site, which appears to be stereospecific and contains a nucleophilic residue. Kinetic studies[1,4,13] indicate that ARIs are not competitive with the substrate or NADPH cofactor. The presence of the selective lipophilic substituents or groups which could enhance charge transfer would be expected to result in ARI with better inhibitory potency. The presence of 7-OH and 3'-OH groups enhance the inhibitory activity of certain flavones. The substitution of 2-phenyl substituents with a carboxyl group retain the inhibitory activity, what lead to the conclusion that only 4-oxo-4*H*-chromone ring system appears to be necessary for the inhibitory activity.[6] However, further investigations[13] revealed that the presence of two hydroxyl groups in catechol orientation in ring B (3'-OH and 4'-OH) plays an important role in AR inhibitory activity.

On the other hand flavonoids are particularly interesting in their potential role as specific inhibitors of protein tyrosine kinase (PTK). Protein tyrosine kinases (PTKs) constitute a class of enzymes that provide a central switching mechanism in cellular signal transduction pathways by catalysing the transfer of the γ-phosphate of either ATP or GTP to specific tyrosine residues in certain protein substrates.[14,15] These enzymes are important mediators of normal cellular signal transduction, with PTKs being the intracellular effectors for many growth hormone receptors. The discovery of activated protein-tyrosine kinases as the product of dominant viral-transforming genes (oncogenes) first established the connection between protein-tyrosine phosphorylation and cell transformation. There is now substantial evidence accumulating to suggest that the inappropriate or elevated expression of these enzymes may also contribute to the transformed state of cells in many human malignancies.[16,17] The importance of PTKs in signal transduction and the association of aberrant PTK expression with proliferative disorders makes substances which modulate the activity of PTKs attractive therapeutic agents. Central to the function of all PTKs is the recognition and binding of a nucleoside triphosphate (usually ATP) and an appropriate tyrosyl-containing substrate, followed by the ensuing direct transfer of phosphate between the two.[18] Nucleoside-based analogs were among the first agents explored as potential inhibitors of ATP binding to PTKs. A variety of compounds have been shown to inhibit the function of PTKs in a manner which is competitive with respect to nucleotide binding, among them a large number of natural and synthetic flavonoids. Kinetic analyses of the PTK inhibition indicated that flavonoids were competitive inhibitors with respect to the nucleotide ATP.[19] Flavones and isoflavones differ in their inhibitory profiles both in their relative selectivity towards PTKs *versus* serine/threonine kinases and in their potencies among different PTKs.[19] Various syn-

thetic flavonoid analogs have been prepared[20–22] with the goal of the development of PTK inhibitors as chemotherapeutic agents.

A central question in application of molecular modelling techniques which include QSAR approach[23–26] is the intriguing possibility to elucidate the structural features in the given series of molecules which would define their selective activity towards various enzymatic protein systems. QSAR of flavonoids for inhibition of cAMP phosphodiesterase were determined[27] and new inhibitors of xantine oxidase were also developed using rational design approach.[28] In our continuing effort[29–31] towards this goal we have studied flavones as protein kinase inhibitors by using classical and quantum chemical QSAR approaches. A benchmark data set of 104 flavonoid derivatives as inhibitors of $p56^{lck}$ protein tyrosine kinase has been compiled and artificial neural network (ANN) approach has been applied[30] to find out the structural requirements of the hitherto unknown enzymatic receptor sites for optimal interaction with the flavonoid ligands.

In the present work we carried out a quantum chemical/classical QSAR study on a similarly exhaustive set of 75 flavonoids and closely related compounds tested as AR inhibitors[13,32,33] and the obtained structure-activity relationships of both enzyme systems were compared. We believe that such studies of enzymatic selectivity based on computed properties could become increasingly important in the current rapidly forthcoming era of genomics/proteomics drug discovery.

MATERIALS AND METHODS

Molecular structure and numbering of the substituents in the flavonoid derivatives are represented in Figure 1 and structures of the used flavone derivatives (natural and synthetic), are summarised in Tables IA and IB, for the AR and PTK enzyme systems respectively. The inhibitory effects on enzyme aldose reductase were measured spectrophotometrically. The reaction was initiated by addition of substrate

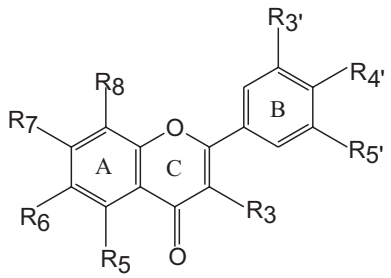

Figure 1. Molecular structure, numbering and list of the different substituents attached to the chromone moiety and phenyl ring of flavonoids in the present study.

TABLE IA

Molecular structures of flavonoids and analogs (isoflavonoids, coumarins) tested against AR and used in this study[a]

R_2	R_3	R_5	R_6	R_7	R_8	$R_{3'}$	$R_{4'}$
COOH	OCH_3	OH	OH	OH	OH	OH	OH
$COOCH_2CH_3$	OH	OCH_3	OCH_3	OCH_3	OCH_3	$OCOCH_3$	$OCOCH_3$
$COCH_2Ph$	ORh			OGlc	CH_2Ph		OGlc
$COOCH(CH_3)_2$	OGlc				COOH		
$COOCH_3$	Ph						
	CN						
	CH_3						
	COOH						

[a] Rh = rhamnose, Glc = glucose.

TABLE IB

List of substituents on the chromone (R_3-R_8) and phenyl ring ($R_{3'}$-$R_{5'}$) part of the flavonoid scaffold used in the study of inhibition of the enzyme PTK[a]

R_3	R_5	R_6	R_7	R_8	$R_{3'}$	$R_{4'}$	$R_{5'}$
OH	OH	OH	OH	OH	OH	OH	OH
$COOCH_3$	OCH_3	OCH_3	OCH_3	OCH_3	OCH_3	OCH_3	OCH_3
COOH	NH_2	NH_2	OAc	OAc	NH_2	OBn	
	NO_2	NO_2	OBn	NH_2		NH2	
			NH_2	NO_2		Br	
			NO_2			NO_2	
						NHAc	

[a] Bn = benzyl, Ac = acetyl.

and the rate of NADPH oxidation was followed by decrease in absorbance at 390 nm.[13,32,33] The biological assay data used in this study for the PTK system are results of *in vitro* tests for inhibitory activity against protein-tyrosine kinase $p56^{lck}$, a lymphoid cell lineage-specific PTK of the *src* family which is overexpressed in several lymphomas effort[20–22] and has been utilised by us previously.[29–31]

The descriptors set containing both classical parameters and quantum chemical computed descriptors (Table II) was chosen to describe the main physical forces that could be instrumental in inhibitor binding to the protein receptor: hydrophobicity, electronic effects and steric effects. Classical parameters were compiled by standard procedures from the literature.[23] In the asssignment of values of classical parameters on the chromone moiety 6 and 8 substituents were parameterized as »*ortho*« and »*para*« substituents, substituents 5 and 7 as »*meta*« to the pyrone oxygen, respectively.

TABLE II

Classical and quantum chemical parameters used in QSAR study

classical parameters	quantum chemical descriptors
Hansch hydrophobic constant (π)	net atomic charge on the nth atom (δ_n),
Hammett electronic constant for the *meta* and *para* position (σ_m and σ_p)	energies of the highest occupied molecular orbital (ε_{HOMO})
Molar refractivity (MR)	energies of the lowest unoccupied molecular orbital (ε_{LUMO}),
	total electron surface density ($\Sigma\delta$a)
	total electron surface HOMO density
	total electron surface LUMO density
	total dipole moment (μ)
	the energy barrier of the rotation of the phenyl ring (ε_{rot})

All quantum chemical parameters were calculated with semiempirical AM1 method,[34] available in the Spartan[35] program, using the fully optimised geometry of each compound in question.

Descriptor selections and corresponding models for quantitative structure-activity relationships were performed using multiple linear regression methods in the software package Axum 4.0 for Windows. Cross correlation coefficients were used to eliminate colinear descriptors. No colinearity greater that ~ 0.40 was permitted for descriptors in a specific QSAR.

RESULTS AND DISCUSSION

AR Inhibition

The classical and quantum chemical descriptors in the QSAR analysis were used separately in order to compare these two approaches and provide us with additional validation that our description of the interactions in the series of enzyme-inhibitor complexes is justified.

Classical Parameters

Monoparametric correlations were performed and good correlations were obtained with all three types of interactions of the substituents with the receptor site hydrophobic properties (π), the size of the substituents (MR) and charge at the phenyl ring region of the flavone molecule (σ_B) (Table IA). The overall correlation matrices for the selected parameters used in the multiple regression analyses are shown in Table IIIA.

TABLE IIIA

Correlation matrix of the classical parameters used in the study of AR inhibition

	σ_B	π_B	MR_B
σ_B	1.00		
π_B	–0.07	1.00	
MR_B	–0.11	0.21	1.00

TABLE IIIB

The same as in Table IIIA for the quantum chemical descriptors

	$\delta_{4'}$	$\Sigma\delta_{2'-4'}$	$\Sigma\delta a_{3'}$	$\Sigma\delta a_3$
$\delta_{4'}$	1.00			
$\Sigma\delta_{2'-4'}$	0.06	1.00		
$\Sigma\delta a_{3'}$	–0.04	0.10	1.00	
$\Sigma\delta a_3$	0.14	0.11	0.12	1.00

The results of regression analyses for the series of 75 inhibitors described above are given in Eq. (1) and could be shown in Table IV.*

$$\log 1/C = -3.04(\pm1.21)\sigma_B - 1.66(\pm0.23)\pi_B - 0.77(\pm0.23)MR_B + 4.3(\pm0.38) \quad (1)$$
$$n = 75,\ r = 0.83,\ p < 10\text{–}7,\ F = 34.667.$$

In Figure 2a plot of experimental inhibitory activity *versus* calculated activity (regression equation) is given.

Quantum Chemical Descriptors

QSAR studies by using quantum chemical parameters are an attractive alternative to the classical approach. The topography of all nuclei and electrons in a drug molecule is explicitly involved as well as the energy of their interaction in a drug-receptor complex and is thus suitable for more detailed analysis of the partitioning of enzyme-inhibitor interactions. The overall correlation matrices for the selected parameters used in the multiple regression analyses are shown in Table IIIB.

* Due to large volume of the data in the Table IV it is given in the Supplementary material deposited at the Editorial office. This material may be found on the www under http://pubwww.srce.hr/ccacaa or will be aviable on request from the Editorial office.

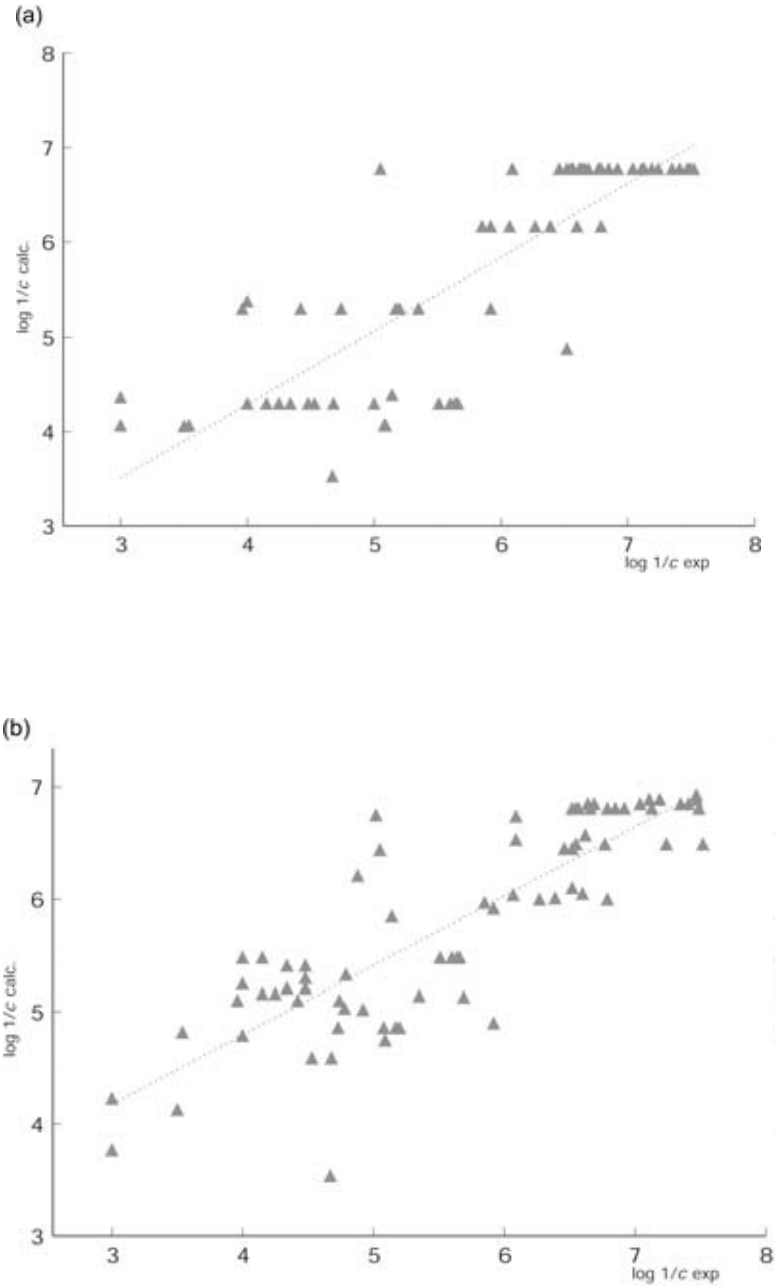

Figure 2. Observed *versus* calculated inhibitory activity for the data base of 75 flavonoid analogs as inhibitors of AR: a) with classical parameters (Eq. (1)): $n = 75$, $r = 0.83$, $F = 34.667$; b) with quantum chemical descriptors (Eq. (2)): $n = 75$, $r = 0.79$, $F_{(2,74)} = 21.687$.

In Eq. (2) the quantitative structure-activity relationship for the quantum chemical descriptors is given.

$$\log 1/C = -4.21(\pm 1.35)\delta_{4'} + 3.94(\pm 0.61)\Sigma\delta_{2',-4'} - 6.92(\pm 0.9)\Sigma\delta a_{3'} - 1.74(\pm 0.34)\Sigma\delta a_{3'} + 14.05(\pm 1.31) \quad (2)$$

$$n = 75,\ r = 0.79\ ,\ p < 10\text{–}7,\ F = 21.687.$$

In Figure 2b this relationship is given as a plot of calculated *versus* experimental inhibitory activity.*

PTK Inhibition by Flavonoids

Activity-structure relationships of flavonoids inhibiton of PTK has been studied in our laboratory previously[29–31] using multiple linear regression, artificial neural network as well as CODESSA approach with ortogonalisation of descriptors, respectively. Thus, we briefly summarise the main conclusions here.

The substituents at the 3' and 4' position of the phenyl ring B should have electron-donating properties and most probably this part of the flavonoid molecule interacts with the catalytic domain of the enzyme, through hydrogen bonds. The chromone moiety shows the dependence on hydrophobic (π) and electronic parameters such as sum of charges at the chromone ring atoms $\Sigma\delta_{C3–C8}$. The steric hindrance of the substituent at C_3 position in the chromone moiety is also a potency determining factor and a bulky group in this position has an adverse effect on the bioactivity in the series.

The dependence of inhibitory activity on the parameter $\Sigma\delta_{C3–C8}$ in our case is in accordance with QSAR investigation of flavonoids as inhibitors of cyclic AMP phosphodiesterase by J. E. Ferrell *et al.*[36] On the basis of quantum-chemical calculations, they found that there is a resemblance between the charge distribution of the pyranone ring of the inhibitor molecule and the pyrimidine ring of cAMP. The fact that flavonoids are competitive inhibitors of ATP binding site can now be rationalised by extending this analogy to the benzo-γ-pyrone part of flavones and the pyrimidine ring of ATP.

The high activity of inhibitors containing amino groups seems to reinforce the proposition that hydrogen bonding plays an important role in the mechanism of action of these compounds within the catalytic domain. Significantly, all derivatives with 4'-NO_2 substituent are inactive. These results

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* Due to large volume of the data in the Table V it is given in the Supplementary material deposited at the Editorial office. This material may be found on the www under http://pubwww.srce.hr/ccacaa or will be aviable on request from the Editorial office.

can be further correlated to investigation of J. C. Wallet *et al.*,[37] who in order to study mechanisms of action of flavones at the molecular level, prepare a complex between a 2',6'-dimethoxyflavone and orthophosphoric acid. This was considered to be a simple model of interaction between a flavone and a more complex biological phosphate such as nucleotide, coenzyme or DNA and the authors concluded that complexes with phosphate groups involve strong hydrogen bonds.

More recently[38] crystal structures of aldose reductase with bound citrate, cacodylate and the substrate glucose-6-phosphate were reported. The location of negative charges within the active site suggests that the active site contains an anion binding site which interacts with hydroxyl of the Tyr 48 side chain and Nε of His 110. Additionally,[39] the solved crystal structure of human aldose reductase complexed with potent (IC_{50} = 3nM) inhibitor zopolrestat: 3,4-dihydro-4-oxo-3-{[5-(trifluoromethyl)-2-benzothiazolyl]methyl} -1-phtalazineacetic acid provides a picture of multiple hydrophobic contacts of phtalazineacetic acid moiety lining the active site pocket. By superposition of chromone ring onto the phtalazineacetic acid part of zopolrestat structure similar interactions with the enzyme could be achieved. In particular, our finding that position 3 of the chromone ring requires a bulky hydrophobic substituent matches nicely with zopolrestat complex crystal structure in which trifluoromethyl-2-benzothiazolyl is present at position 3.

In summary, the agreement in description of QSAR in terms of classical and quantum chemical parameters is good. Flavonoids are in general good inhibitors of both enzymes, with their inhibitory potency spreading over 5 orders of magnitude. However, there are specific differences in requirements for their binding to the enzyme sites AR and PTK. For the binding to the enzyme site AR (i) a hydrogen bond donor should be present at position 4' (ii) larger substituent in 4' than OH is not favourable (iii) position 3 requires a bulky hydrophobic substituent .

To the contrary, in PTK (iv) a hydrogen bond donor at position 3' or 4' in the phenyl ring is required and (v) specific orientation of hydrophobic substituent at position 8 is required and steric hindrance at position 3 in the chromone ring is decreasing the inhibitiory potency of flavonoids.

CONCLUSIONS

Results of our QSAR study in which we applied both classical and quantum chemical computed descriptors could be consistently explained in terms of physico-chemical nature: hydrophobicity, electronic structure and steric factors.

Differences in QSAR of flavonoids between two enzymes PTK and AR could be translated into specific substituent structural requirements. Specific differences in inhibition ability towards PTK and aldose reductase for a large data set of flavonoids comprising a broad variety of substituents provide one with incentives for rational drug design of novel flavonoid analogues. Work along these lines is in progress in this laboratory.

Acknowledgment. – The Ministry of Science and Technology of Slovenia is thanked for financial suppport through grant No. J1-7374 to T. Š.

ABBREVIATIONS

AR – aldose reductase
PTK – protein tyrosine kinase
ARI – aldose reductase inhibitors
ATP – adenosine triphosphate
MR – molecular refractivity
MLR – multiple linear regression
NADPH – nicotinamide-adenine-dinucleotide phosphate.

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SAŽETAK

QSAR za flavonoide: 4. Diferencijalna inhibicija aldoza-reduktaze i p56 proteina tirozin-kinaze

Alenka Štefanič-Petek, Aleš Krbavčič i Tom Šolmajer

Flavonoidi su grupa biljnih produkata niske molekularne težine, sa zajedničkim temeljnim spojem flavonom (2-fenilkromonon), a pokazali su se vrlo dobrima u raznim farmakologijskim primjenama. Uporabom tehnike slučajnog odabira uočeno je da su flavoni inhibitori aldoza-reduktaze, enzima važnog pri liječenju diabetičkih komplikacija kao što je stvaranje katarakte. S druge strane, velik broj prirodnih i umjetnih flavonoida testirani su kao specifični inhibitori proteina tirozin-kinaze (PTK). Kinetičke analize inhibicije PTK pokazuju da su flavonoidi usporedivi inhibitori s nukleotidom ATP. U svrhu razvoja kvantitativnog odnosa strukture i aktivnosti za te enzimske sustave uporabom klasičnih i kvantnokemijskih deskriptora provedena je iscrpna analiza dostupnih eksperimentalnih podataka. Ukazano je na važnost deskriptora za opis svojstava vezivanja obiju enzimskih receptorskih aktivnih mjesta, a dobiveni rezultati pokazuju koja elektronska kao i hidrofobna i sterička svojstva supstituenata imaju važnu ulogu u njihovim pogodovnim vezivanjima.

Supplementary Material

TABLE IV

AR inhibitors used in QSAR with listed classical parameters and calculated IC_{50}

No.	Case	Substituents	π_{AC}	π_B	$\Sigma\pi$	$(\Sigma\pi)^2$	σ_{AC}	σ_B	$\Sigma\sigma$	MR_{AC}	MR_B	ΣMR	log 1/*c*
1	bp-1	5,7,3',4'-OH; 3,6-OCH_3	–1.38	–1.34	–2.72	7.39	0.09	–0.25	–0.16	2.24	0.66	2.90	7.52
2	cp-26	3',4'-OH; 5,6,7,8-OCH_3	–0.08	–1.34	–1.42	2.02	0.09	–0.25	–0.16	3.26	0.66	3.29	7.49
3	bp-25	6,3',4'-OH; 5,7,8-OCH_3	–0.73	–1.34	–2.07	4.28	–0.01	–0.25	–0.26	2.75	0.66	3.41	7.47
4	cp-23	5,7,3',4'-OH; 6-OCH_3; 8-CH_2Ph	0.65	–1.34	–0.69	0.48	–0.11	–0.25	–0.36	4.45	0.66	5.11	7.47
5	cp-24	5,3',4'-OH; 6,7,8-OCH_3	–0.73	–1.34	–2.07	4.28	0.09	–0.25	–0.16	2.75	0.66	3.41	7.41
6	cp-17	3',4'-OH; 5,7,8-OCH_3	–0.06	–1.34	–1.40	1.96	0.36	–0.25	0.11	2.57	0.66	3.23	7.35
7	cp-6	5,6,7,3',4'-OH; 3-OCH_3	–2.03	–1.34	–3.37	11.35	–0.01	–0.25	–0.26	1.73	0.66	2.39	7.24
8	cp-22	5,6,3',4'-OH; 7,8-OCH_3	–1.38	–1.34	–2.72	7.39	–0.01	–0.25	–0.26	2.24	0.66	2.90	7.19
9	cp-16	7,3',4'-OH; 5,8-OCH_3	–0.71	–1.34	–2.05	4.20	0.36	–0.25	0.11	2.06	0.66	2.72	7.13
10	cp-14	5,3',4'-OH; 7,8-OCH_3	–0.71	–1.34	–2.05	4.20	0.36	–0.25	0.11	2.06	0.66	2.72	7.11
11	cp-5	3',4'-OH; 5,6,7-OCH_3	–0.06	–1.34	–1.40	1.96	–0.03	–0.25	–0.28	2.57	0.66	3.23	7.04
12	cp-21	5,6,7,3',4'-OH; 8-OCH_3	–2.03	–1.34	–3.37	11.36	–0.01	–0.25	–0.26	1.73	0.66	2.39	6.92
13	cp-4	6,3',4'-OH; 5,7-OCH_3	–0.71	–1.34	–2.05	4.20	–0.13	–0.25	–0.38	2.06	0.66	2.72	6.85
14	bp–29	4'-OH; 5,6,7,8-OCH_3	–0.08	–0.67	–0.75	0.56	0.09	–0.37	–0.28	3.26	0.48	3.74	6.79
15	cp-15	8,3',4'-OH; 5,7-OCH_3	–0.71	–1.34	–2.05	4.20	0.36	–0.25	0.11	2.06	0.66	2.72	6.79
16	cp-20	3',4'-OH; 3,5,7,8-OCH_3	–0.08	–1.34	–1.42	2.02	0.48	–0.25	0.23	3.26	0.66	3.92	6.77
17	cp-1	5,6,7,3',4'-OH	–2.01	–1.34	–3.35	11.22	–0.13	–0.25	–0.38	1.04	0.66	1.70	6.69
18	bp-3	5,3',4'-OH; 6,7-OCH_3	–0.71	–1.34	–2.05	4.20	–0.03	–0.25	–0.28	2.06	0.66	2.72	6.66
19	cp-13	5,8,3',4'-OH; 7-OCH_3	–1.36	–1.34	–2.70	7.29	0.36	–0.25	0.11	1.55	0.66	2.21	6.64
20	cp-18	5,7,3',4'-OH; 3,8-OCH_3	–1.38	–1.34	–2.72	7.39	0.48	–0.25	0.23	2.24	0.66	2.90	6.62
21	bp-24	6,4'-OH; 5,7,8-OCH_3	–0.73	–0.67	–1.40	1.96	–0.01	–0.37	–0.38	2.75	0.48	3.23	6.60
22	cp-11	3',4'-OH; 5,6,7-OCH_3	–0.08	–1.34	–1.42	2.02	–0.03	–0.25	–0.28	3.26	0.66	3.92	6.57
23	cp-12	5,7,3',4'-OH; 8-OCH_3	–1.36	–1.34	–2.70	7.29	0.36	–0.25	0.11	1.55	0.66	2.21	6.55

TABLE IV (cont.)

No.	Case	Substituents	π_{AC}	π_B	$\Sigma\pi$	$(\Sigma\pi)^2$	σ_{AC}	σ_B	$\Sigma\sigma$	MR_{AC}	MR_B	ΣMR	log 1/*c*
24	cp-19	7,3',4'-OH; 3,5,8-OCH_3	–0.73	–1.34	–2.07	4.28	0.48	–0.25	0.23	2.75	0.66	3.41	6.55
25	bp-13	8-OCH_3; 5,6,7,3',4'-$OCOCH_3$	–1.94	–1.28	–3.22	10.37	1.21	0.70	1.91	4.64	2.60	7.24	6.52
26	cp-2	5,6,3',4'-OH; 7-OCH_3	–1.36	–1.34	–2.70	7.29	–0.13	–0.25	–0.38	1.55	0.66	2.21	6.52
27	cp-10	6,3',4'-OH; 3,5,7-OCH_3	–0.73	–1.34	–2.07	4.28	–0.01	–0.25	–0.26	2.75	0.66	3.41	6.52
28	bp-4	5,3',4'-OH; 3,6,7-OCH_3	–0.73	–1.34	–2.07	4.28	0.09	–0.25	–0.16	2.75	0.66	3.41	6.46
29	bp-17	5,7,4'-OH; 6,8-OCH_3	–1.38	–0.67	–2.05	4.20	0.09	–0.37	–0.28	2.24	0.48	2.72	6.39
30	bp-27	5,4'-OH; 6,7,8-OCH_3	–0.73	–0.67	–1.40	1.96	0.09	–0.37	–0.28	2.75	0.48	3.23	6.27
31	cp-7	5,6,3',4'-OH; 3,7-OCH_3	–1.38	–1.34	–2.72	7.39	–0.01	–0.25	–0.26	2.24	0.66	2.90	6.09
32	quercetin	3,5,7,3',4'-OH	–2.01	–1.34	–3.35	11.22	0.36	–0.25	0.11	1.04	0.66	1.70	6.09
33	bp-15	5,6,4'-OH; 7,8-OCH_3	–1.38	–0.67	–2.05	4.20	–0.01	–0.37	–0.38	2.24	0.48	2.72	6.07
34	bp-11	5,6,7,4'-OH; 8-OCH_3	–2.03	–0.67	–2.70	7.29	–0.01	–0.37	–0.38	1.73	0.48	2.21	5.92
35	bp-12	5,6,7,4'-OH; 8,3'-OCH_3	–2.03	–0.69	–2.72	7.39	–0.01	–0.25	–0.26	1.73	1.17	2.90	5.92
36	bp-2	5,4'-OH; 6,7-OCH_3	–0.71	–0.67	–1.38	1.91	–0.03	–0.37	–0.40	2.06	0.48	2.54	5.85
37	quercitrin	5,7,3',4'-OH; 3-O-Rh	–4.18	–1.34	–5.52	30.47	0.28	–0.25	0.03	4.41	0.66	5.07	5.69
38	mc-12	2-COOH; 7-OH	–0.67	–0.32	–0.99	0.98	0.12	0.37	0.49	0.68	0.69	1.37	5.66
39	mc-12Et	2-$COOCH_2CH_3$; 7-OH	–0.67	0.51	–0.16	0.03	0.12	0.37	0.49	0.68	1.75	2.43	5.64
40	mc-12Bzl	2-$COOCH_2Ph$; 7-OH	–0.67	1.84	1.17	1.37	0.12	0.86	0.98	0.68	3.72	4.40	5.60
41	mc-12*i*Pr	2-$COOCH(CH_3)_2$; 7-OH	–0.67	0.36	–0.31	0.10	0.12	0.38	0.50	0.68	1.71	2.39	5.51
42	bp-19	5,7,4'-OH; 6,8,3'-OCH_3	–1.38	–0.69	–2.07	4.28	0.09	–0.25	–0.16	2.24	1.17	3.41	5.35
43	bp-26	6,4'-OH; 5,7,8,3'-OCH_3	–0.73	–0.69	–1.42	2.02	–0.01	–0.25	–0.26	2.75	1.17	3.92	5.20
44	bp-5	5,4'-OH; 6,7,3'-OCH_3	–0.71	–0.69	–1.40	1.96	–0.03	–0.25	–0.28	2.06	1.17	3.23	5.17
45	bp-18	5,7-OH; 6,8,4'-OCH_3	–1.38	–0.02	–1.40	1.96	0.09	–0.27	–0.18	2.24	0.99	3.23	5.14
46	bp-10	5,6,7-OH; 8-OCH_3	–2.03	0.00	–2.03	4.12	–0.01	0.00	–0.01	1.73	0.30	2.03	5.09
47	bp-14	5,6-OH; 7,8-OCH_3	–1.38	0.00	–1.38	1.91	–0.01	0.00	–0.01	2.24	0.30	2.54	5.08
48	bp-9	3',4'-OH; 5,6,7-OCH_3; 3-$COCH_3$	–0.61	–1.34	–1.95	3.80	0.35	–0.25	0.10	3.59	0.66	4.25	5.05
49	bp-7	5,3'-OH; 6,7-OCH_3; 4'-O-Glc	–0.71	–3.51	–4.22	17.81	–0.03	0.16	0.13	2.06	4.03	6.09	5.02

TABLE IV (cont.)

No.	Case	Substituents	π_{AC}	π_B	$\Sigma\pi$	$(\Sigma\pi)^2$	σ_{AC}	σ_B	$\Sigma\sigma$	MR_{AC}	MR_B	ΣMR	log 1/*c*
50	bp-42c	4-OH	–0.72	0.00	–0.72	0.52	–0.53	0.00	–0.53	1.48	0.00	1.48	5.00
51	bp-8	5-OH; 6,7,3'-OCH_3; 4'-O-Glc	–0.71	–2.86	–3.57	12.75	–0.03	0.16	0.13	2.06	4.54	6.60	4.92
52	bp-6	5-OH; 6,7-OCH_3; 4'-O-Glc	–0.71	–2.84	–3.55	12.60	–0.03	0.04	0.01	2.06	3.85	5.91	4.88
53	jnp-8	5,7,3',4'-OH; 3-O-Glc	–4.18	–1.34	–5.52	30.47	0.28	–0.25	0.03	4.41	0.66	5.07	4.79
54	bp-21	5,7-OH; 6,8,3'-OCH_3; 4'-O-Glc	–1.38	–2.86	–4.24	17.98	0.09	0.16	0.25	2.24	4.54	6.78	4.78
55	bp-30	4'-OH; 5,6,7,8,3'-OCH_3	–0.08	–0.69	–0.77	0.59	0.09	–0.25	–0.16	3.26	1.17	4.43	4.74
56	bp-22	5,4'-OH; 6,8,3'-OCH_3; 7-O-Glc	–3.55	–0.69	–4.24	17.98	0.01	–0.25	–0.24	5.61	1.07	6.68	4.73
57	bp-39c	4-OH; 7-OCH_3; 3-Ph	1.27	0.00	1.27	1.60	–0.19	0.00	–0.19	3.91	0.00	3.91	4.68
58	bp-20	5,7-OH; 6,8,3',4'-OCH_3	–1.38	–0.04	–1.42	2.02	0.09	–0.15	–0.06	2.24	1.68	3.92	4.67
59	bp-46c	3-Ph; 4-OH	1.24	0.00	1.24	1.54	–0.47	0.00	–0.47	3.92	0.00	3.92	4.53
60	bp-36c	3-OH; 6-OCH_3	–0.69	0.00	–0.69	0.48	–0.15	0.00	–0.15	1.47	0.00	1.47	4.48
61	bp-44c	3-CN	–0.62	0.00	–0.62	0.38	0.40	0.00	0.40	1.83	0.00	1.83	4.48
62	bp-45c	3-COOH	–0.37	0.00	–0.37	0.14	0.21	0.00	0.21	1.89	0.00	1.89	4.48
63	bp-28	5,4'-OH; 6,7,8,3'-OCH_3	–0.73	–0.69	–1.42	2.02	0.09	–0.25	–0.16	2.75	1.17	3.92	4.42
64	bp-35c	3-OH	–0.67	0.00	–0.67	0.45	0.12	0.00	0.12	0.78	0.00	0.78	4.34
65	bp-40c	3,8-COOH; 5-OCH_3	–0.66	0.00	–0.66	0.44	0.86	0.00	0.86	2.47	0.00	2.47	4.34
66	bp-37c	4-OH; 3,7-OCH_3	–0.71	0.00	–0.71	0.51	–0.13	0.00	–0.13	2.16	0.00	2.16	4.25
67	bp-38c	7-OCH_3; 4-CH_3	0.54	0.00	0.54	0.29	–0.05	0.00	–0.05	1.76	0.00	1.76	4.15
68	jnp-3	3,5,7,4'-OH; 3'-OCH_3	–2.01	–0.69	–2.70	7.29	0.36	–0.25	0.11	1.04	1.07	2.11	4.00
69	bp-43c	4-CH_3	0.51	0.00	0.51	0.26	–0.33	0.00	–0.33	1.76	0.00	1.76	4.00
70	bp-47c	3-CH_3; 4-OH	–0.16	0.00	–0.16	0.03	–0.60	0.00	–0.60	1.95	0.00	1.95	4.00
71	bp-16	5,6,4'-OH; 7,8,3'-OCH_3	–1.38	–0.69	–2.07	4.28	–0.01	–0.25	–0.26	2.24	1.17	3.41	3.96
72	bp-23	6-OH; 5,7,8-OCH_3	–0.73	0.00	–0.73	0.53	–0.01	0.00	–0.01	2.75	0.30	3.05	3.54
73	bp-33i	5,5'-OH; 7,2',4'-OCH_3	–0.69	–0.71	–1.40	1.96	–0.15	–0.03	–0.18	1.37	1.96	3.33	3.50
74	bp-31i	7-OH; 5-OCH_3	–0.69	0.00	–0.69	0.48	–0.25	0.00	–0.25	1.37	0.30	1.67	3.00
75	bp-32i	5,4'-OH; 7,2',5'-OCH_3	–0.69	–0.71	–1.40	1.96	–0.15	–0.13	–0.28	1.37	1.96	3.33	3.00

TABLE V

AR inhibitors used in QSAR with listed quantum chemical descriptors and calculated IC_{50}

No.	Case	Substituents	C2'	C4'	C3'	ΣC2'-C4'	Dip. m.	S.D.A./Ph.	ΔS.D.A. (Chr.-(Fl.-Ph.)	S.L.A.	HOMO	Sd3	Sd3'	log 1/*c*
1	bp-1	5,7,3',4'-OH; 3,6-OCH_3	0.19	–0.23	0.25	0.21	3.92	120.98	34.97	113.57	–0.082	1.055	1,182	7.52
2	cp-26	3',4'-OH; 5,6,7,8-OCH_3	0.19	–0.25	0.25	0.19	2.39	120.98	30.92	118.34	–0.172	1.055	1.000	7.49
3	bp-25	6,3',4'-OH; 5,7,8-OCH_3	0.23	–0.25	0.24	0.22	1.91	120.98	32.34	123.18	–0.156	1.055	1.000	7.47
4	cp-23	5,7,3',4'-OH; 6-OCH_3; 8-CH_2Ph	0.23	–0.25	0.23	0.21	3.62	120.98	37.49	113.15	–0.067	1.055	1.000	7.47
5	cp-24	5,3',4'-OH; 6,7,8-OCH_3	0.21	–0.26	0.24	0.19	2.29	120.98	31.04	116.06	–0.002	1.055	1.000	7.41
6	cp-17	3',4'-OH; 5,7,8-OCH_3	0.22	–0.23	0.23	0.22	1.54	120.98	31.09	118.79	–0.098	1.055	1.000	7.35
7	cp-6	5,6,7,3',4'-OH; 3-OCH_3	0.23	–0.25	0.21	0.19	2.63	120.98	30.96	116.81	–0.08	1.055	1,182	7.24
8	cp-22	5,6,3',4'-OH; 7,8-OCH_3	0.22	–0.25	0.24	0.21	2.54	120.98	30.93	117.35	–0.013	1.055	1.000	7.19
9	cp-16	7,3',4'-OH; 5,8-OCH_3	0.21	–0.25	0.23	0.19	1.65	120.98	31.21	119.96	–0.166	1.055	1.000	7.13
10	cp-14	5,3',4'-OH; 7,8-OCH_3	0.23	–0.26	0.23	0.20	2.06	120.98	30.99	114.8	–0.009	1.055	1.000	7.11
11	cp-5	3',4'-OH; 5,6,7-OCH_3	0.21	–0.26	0.24	0.19	2.06	120.98	30.84	116.69	–0.06	1.055	1.000	7.04
12	cp-21	5,6,7,3',4'-OH; 8-OCH_3	0.19	–0.26	0.25	0.18	3.43	120.98	31.03	117.65	–0.024	1.055	1.000	6.92
13	cp-4	6,3',4'-OH; 5,7-OCH_3	0.21	–0.22	0.23	0.22	2.37	120.98	30.96	121.79	–0.071	1.055	1.000	6.85
14	bp-29	4'-OH; 5,6,7,8-OCH_3	–0.28	–0.32	0.42	–0.18	1.87	113.51	29.62	118.33	–0.157	1.000	1.000	6.79
15	cp-15	8,3',4'-OH; 5,7-OCH_3	0.19	–0.25	0.25	0.19	2.04	120.98	31.07	121.04	–0.039	1.055	1.000	6.79
16	cp-20	3',4'-OH; 3,5,7,8-OCH_3	0.22	–0.26	0.22	0.18	0.81	120.98	30.93	119.45	–0.124	1.055	1,182	6.77
17	cp-1	5,6,7,3',4'-OH	0.19	–0.26	0.26	0.19	3.56	120.98	30.86	115.96	–0.043	1.055	1.000	6.69
18	bp-3	5,3',4'-OH; 6,7-OCH_3	0.20	–0.25	0.24	0.19	3.18	120.98	30.91	113.97	–0.047	1.055	1.000	6.66
19	cp-13	5,8,3',4'-OH; 7-OCH_3	0.20	–0.26	0.25	0.19	1.83	120.98	31.10	115.72	–0.465	1.055	1.000	6.64
20	cp-18	5,7,3',4'-OH; 3,8-OCH_3	0.23	–0.23	0.23	0.23	1.71	120.98	34.90	114.37	–0.073	1.055	1,182	6.62
21	bp-24	6,4'-OH; 5,7,8-OCH_3	–0.25	–0.29	0.40	–0.14	1.24	113.51	29.64	120.99	–0.149	1.000	1.000	6.60
22	cp-11	3',4'-OH; 5,6,7-OCH_3	0.19	–0.25	0.25	0.19	1.75	120.98	25.93	117.9	-0.118	1.055	1.000	6.57
23	cp-12	5,7,3',4'-OH; 8-OCH_3	0.19	–0.25	0.25	0.19	3.13	120.98	31.04	115.45	-0.061	1.055	1.000	6.55
24	cp-19	7,3',4'-OH; 3,5,8-OCH_3	0.22	–0.25	0.22	0.19	0.55	120.98	31.11	119.47	-0.187	1.055	1,182	6.55

No.	Case	Substituents	C2'	C4'	C3'	ΣC2'-C4'	Dip. m.	S.D.A./Ph.	ΔS.D.A. (Chr.-(Fl.-Ph.)	S.L.A.	HOMO	Sd3	Sd3'	log 1/*c*
25	bp-13	8-OCH_3; 5,6,7,3',4'-$OCOCH_3$	0.05	-0.31	0.42	0.16	3.45	209.35	35.21	120.7	-0.054	1.294	1.000	6.52
26	cp-2	5,6,3',4'-OH; 7-OCH_3	0.21	-0.25	0.23	0.19	2.91	120.98	30.92	115.89	-0.049	1.055	1.000	6.52
27	cp-10	6,3',4'-OH; 3,5,7-OCH_3	0.21	-0.22	0.22	0.21	2.69	120.98	35.13	120.59	-0.11	1.055	1,182	6.52
28	bp-4	5,3',4'-OH; 3,6,7-OCH_3	0.19	-0.22	0.24	0.21	3.31	120.98	34.91	113.59	-0.019	1.055	1,182	6.46
29	bp-17	5,7,4'-OH; 6,8-OCH_3	-0.27	-0.30	0.41	-0.16	1.98	113.51	29.64	114.39	-0.118	1.000	1.000	6.39
30	bp-27	5,4'-OH; 6,7,8-OCH_3	-0.29	-0.32	0.43	-0.18	1.75	113.51	29.65	114.64	-0.061	1.000	1.000	6.27
31	cp-7	5,6,3',4'-OH; 3,7-OCH_3	0.19	-0.25	0.26	0.20	2.65	120.98	34.88	115.66	-0.003	1.055	1,182	6.09
32	quercetin	3,5,7,3',4'-OH	0.20	-0.26	0.24	0.18	1.21	120.98	31.63	119.63	-0.02	1.055	1,039	6.09
33	bp-15	5,6,4'-OH; 7,8-OCH_3	-0.27	-0.31	0.42	-0.16	2.42	113.51	28.46	119.8	-0.006	1.000	1.000	6.07
34	bp-11	5,6,7,4'-OH; 8-OCH_3	-0.29	-0.31	0.41	-0.19	2.52	113.51	29.53	117.55	-0.127	1.000	1.000	5.92
35	bp-12	5,6,7,4'-OH; 8,3'-OCH_3	0.12	-0.27	0.28	0.13	3.03	148.01	34.77	116.6	-0.059	1.294	1.000	5.92
36	bp-2	5,4'-OH; 6,7-OCH_3	-0.27	-0.29	0.40	-0.16	3.37	113.51	29.42	113.31	-0.012	1.000	1.000	5.85
37	qcitrin	5,7,3',4'-OH; 3-O-Rh	0.23	-0.15	0.18	0.26	2.27	120.98	93.61	115.19	-0.518	1.055	1,896	5.69
38	mc-12	2-COOH; 7-OH	0.00	0.00	0.00	0.00	5.74		-24.51	101.13	-0.306		1.000	5.66
39	mc-12Et	2-$COOCH_3CH_3$; 7-OH	0.00	0.00	0.00	0.00	5.67		-73.94	103.6	-0.18		1.000	5.64
40	mc-12Bzl	2-$COOCH_3$Ph; 7-OH	0.00	0.00	0.00	0.00	5.42		-131.52	102.3	-0.212		1.000	5.60
41	mc-12iPr	2-$COOCH(CH_3)_3$; 7-OH	0.00	0.00	0.00	0.00	5.27		-90.65	101.4	-0.095		1.000	5.51
42	bp-19	5,7,4'-OH; 6,8,3'-OCH_3	0.21	-0.26	0.25	0.20	3.09	148.01	35.28	115.91	-0.014	1.294	1.000	5.35
43	bp-26	6,4'-OH; 5,7,8,3'-OCH_3	0.10	-0.27	0.29	0.12	1.26	148.01	33.93	121.74	-0.034	1.294	1.000	5.20
44	bp-5	5,4'-OH; 6,7,3'-OCH_3	0.12	-0.26	0.27	0.13	3.67	148.01	34.13	113.93	-0.106	1.294	1.000	5.17
45	bp-18	5,7-OH; 6,8,4'-OCH_3	-0.32	-0.27	0.42	-0.17	3.88	141.89	35.45	114.62	-0.091	1.000	1.000	5.14
46	bp-10	5,6,7-OH; 8-OCH_3	-0.12	-0.11	-0.06	-0.29	2.52	105.28	27.28	118.23	-0.124	1.000	1.000	5.09
47	bp-14	5,6-OH; 7,8-OCH_3	-0.10	-0.12	-0.05	-0.27	2.43	105.28	27.24	117.45	-0.059	1.000	1.000	5.08
48	bp-9	3',4'-OH; 5,6,7-OCH_3; 3-$COCH_3$	0.20	-0.27	0.25	0.18	2.56	120.98	32.48	117.79	-0.18	1.055	1,234	5.05
49	bp-7	5,3'-OH; 6,7-OCH_3; 4'-O-Glc	0.28	-0.08	0.14	0.34	5.42	255.77	20.13	117.47	-0.045	1.055	1.000	5.02
50	bp-8	5-OH; 6,7,3'-OCH_3; 4'-O-Glc	0.11	-0.24	0.32	0.19	5.67	277.34	26.93	122.1	-0.148	1.294	1.000	4.92

No.	Case	Substituents	C2'	C4'	C3'	ΣC2'-C4'	Dip. m.	S.D.A./Ph.	ΔS.D.A. (Chr.-(Fl.-Ph.)	S.L.A.	HOMO	Sd3	Sd3'	log 1/*c*
51	bp-6	5-OH; 6,7-OCH_3; 4'-O-Glc	–0.22	-0.27	0.41	-0.08	3.41	244.58	35.27	113.39	-0.049	1.000	1.000	4.88
52	jnp-8	5,7,3',4'-OH; 3-O-Glc	0.18	-0.28	0.27	0.17	4.45	120.98	44.63	113.17	-0.023	1.055	1,864	4.79
53	bp-21	5,7-OH; 6,8,3'-OCH_3; 4'-O-Glc	0.25	-0.18	0.18	0.25	5.80	277.34	36.97	117.01	-0.052	1.294	1.000	4.78
54	bp-30	4'-OH; 5,6,7,8,3'-OCH_3	0.19	-0.26	0.26	0.19	2.18	148.01	35.17	118.75	-0.145	1.294	1.000	4.74
55	bp-22	5,4'-OH; 6,8,3'-OCH_3; 7-O-Glc	0.11	-0.28	0.28	0.11	3.11	148.01	34.16	119.18	-0.143	1.294	1.000	4.73
56	bp-39c	4-OH; 7-OCH_3; 3-Ph	0.00	0.00	0.00	0.00	5.57		-74.67	110.96	-0.078		1,506	4.68
57	bp-20	5,7-OH; 6,8,3',4'-OCH_3	–0.31	0.09	0.36	0.14	2.82	169.35	36.12	114.68	-0.044	1.294	1.000	4.67
58	bp-46c	3-Ph; 4-OH	0.00	0.00	0.00	0.00	5.27		-75.54	107.3	-0.46		1,506	4.53
59	bp-36c	3-OH; 6-OCH_3	0.00	0.00	0.00	0.00	4.00			100.63	-0.12		1,039	4.48
60	bp-44c	3-CN	0.00	0.00	0.00	0.00	6.62			102.69	–0.175		1,104	4.48
61	bp-45c	3-COOH	0.00	0.00	0.00	0.00	4.85			104.18	–0.112		1,156	4.48
62	bp-28	5,4'-OH; 6,7,8,3'-OCH_3	0.20	-0.25	0.25	0.20	2.53	148.01	35.29	115.72	-0.053	1.294	1.000	4.42
63	bp-35c	3-OH	0.00	0.00	0.00	0.00	5.38			99.31	-0.075		1,039	4.34
64	bp-40c	3,8-COOH; 5-OCH_3	0.00	0.00	0.00	0.00	7.30			103.76	-0.61		1,156	4.34
65	bp-37c	4-OH; 3,7-OCH_3	0.00	0.00	0.00	0.00	5.36			101.43	-0.141		1,182	4.25
66	bp-38c	7-OCH_3; 4-CH_3	0.00	0.00	0.00	0.00	4.14			99.17	-0.025		1.000	4.15
67	bp-41c	8,9-OH; 3-OCH_3	0.00	0.00	0.00	0.00	7.51			117.86	-0.054		1,182	4.15
68	bp-43c	4-CH_3	0.00	0.00	0.00	0.00	4.98			99.41	-0.255		1.000	4.00
69	bp-47c	3-CH_3; 4-OH	0.00	0.00	0.00	0.00	3.99			100.07	-0.261		1,130	4.00
70	jnp-3	3,5,7,4'-OH; 3'-OCH_3	0.14	-0.26	0.25	0.13	1.90	148.01	34.80	119.57	-0.011	1.294	1,039	4.00
71	bp-16	5,6,4'-OH; 7,8,3'-OCH_3	0.20	-0.25	0.25	0.20	2.82	148.01	35.19	117.36	-0.054	1.294	1.000	3.96
72	bp-23	6-OH; 5,7,8-OCH_3	–0.12	-0.12	-0.04	-0.28	2.37	105.28	27.30	119.39	-0.169	1.000	1.000	3.54
73	bp-33i	5,5'-OH; 7,2',4'-OCH_3	–0.38	0.15	0.26	0.03	1.41	176.02	38.35	101.77	-0.355		1,506	3.50
74	bp-31i	7-OH; 5-OCH_3	–0.13	-0.11	-0.07	-0.31	1.95	0.00	-75.72	99.59	-0.417		1,506	3.00
75	bp32i	5,4'-OH; 7, 2',5'-OCH_3	–0.42	0.05	0.33	-0.04	3.17	177.34	38.47	102.54	-0.353		1,506	3.00