Bioorganic & Medicinal Chemistry Letters 23 (2013) 4102–4106

Contents lists available at SciVerse ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

Structure–cytotoxic activity relationship of 3-arylideneflavanone and chromanone (*E,Z* isomers) and 3-arylflavones

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ARTICLE INFO

Article history:
Received 22 March 2013
Revised 13 May 2013
Accepted 14 May 2013
Available online 23 May 2013

Keywords:
Cytotoxicity
Arylideneflavanone
Arylidenechromanone
QSAR
X-ray

ABSTRACT

The *E,Z*-isomers of 3-arylidene substituted flavanone, chromanone and 3-aryl substituted flavone derivatives were tested in vitro for their cytotoxic activity against three cancer cell lines (HL-60, NALM-6, WM-115) and normal cell line (HUVEC). It was observed that substitution at C_3 position led to significant enhance in cytotoxicity. Isomeric configuration of 3-arylideneflavanones had an influence on the cytotoxic potential. Multiple regression analysis combined with variable selection by genetic algorithm was used to model relationships between molecular descriptors and the cytotoxic activity. The most accurate QSAR models were based on a combination between energy of LUMO, experimental value of log*P* and partial charge on carbonyl oxygen (δO_2).

Flavanone (2-phenyl-2,3-dihydrochromen-4-one) and flavone (2-phenyl-4*H*-chromen-4-one) derivatives, belonging to numerous flavonoids group, have recently gained increasing interest due to their activity as anticarcinogenic agents.[1–3] Chemoprevention, a relatively new and promising strategy in preventing cancer is defined as the use natural dietary compounds as well as synthetic substance to block, inhibit, reverse or retard the process of carcinogenesis. The role of flavonoids in this process is still widely discussed[4] but many newly isolated and structurally modified flavonoids could be a source of potential anticancer agents.[5,6] Flavanone derivatives possessing substituted benzyl moiety in position 3 exhibit biological activity as antioxidants[7] and inhibitors of aromatase.[8]

In this study, series (Table 1) of six 3-arylideneflavanones, two 3-arylidenechromanones and five 3-arylflavones were synthesized and examined in vitro for their cytotoxic efficacy. 3-Arylideneflavanones (**1a–f**) and 3-arylflavones (**3a–e**) were obtained by the three step synthesis in which the substituted flavanones and flavones were condensed with dedicated aldehydes in the presence of piperidine as catalyst.[7] 3-Arylidenechromanones (**2a**, **2b**) were also prepared by the condensation method using commercially available chromanone and appropriate aldehydes. The structure of the synthesized compounds were confirmed by elemental analysis, IR and ^{1}H and ^{13}C NMR spectroscopy and X-ray crystal structure analysis (compd **1e**—Fig. 1). NMR spectroscopy, HPLC analysis and X-ray structure determination, showed that only (*E*)-isomers were obtained. *Z*-Isomers were obtained by photoisomerization (Scheme 1). UV irradiation at 365 nm gave *Z*-isomer in a predominant amount (>95%) in mixture with *E*-isomer (less than 5%). The progress of isomerization was monitored by HPLC method.

X-ray structure determination of compound **1e** confirmed *E*-isomer. Crystal data and structural determination details are presented in Table S1 and in [9]. The dihedral angles C3–C2–C21–C22, O2–C3–C2–C21 and C3–C2–C21–H21 are: 177.7(2)°, 15.3(2)° and 3.1(2)°, respectively. Main chroman skeleton consists of two fused rings: benzene and pyran ring. The pyran ring adopts a distorted conformation between half-chair and half-boat with puckering parameters $Q = 0.34$ Å, $\varphi = 226.1°$, $\theta = 120.3°$. Two substituted benzene rings are planar and the angle between their best planes is 52.8(1)°. The full crystal packing analysis is described in Supplementary data (Fig. S2).

Cytotoxicity of compounds was determined by the MTT (3-(4,5-dimethylthiazol-2-yl)2,5-diphenyltetrazolium bromide) assay.[10] The compounds were evaluated for their ability to cytotoxic effect on three cancer cell lines: human skin melanoma (WM-115),

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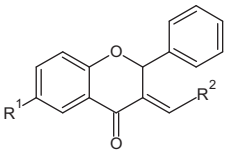
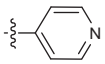
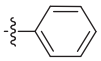
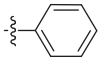
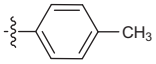
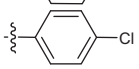
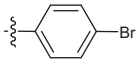
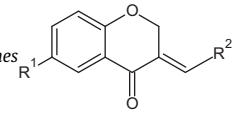
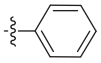
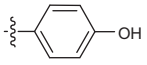
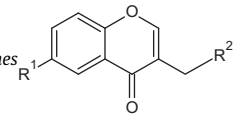
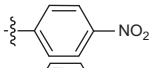
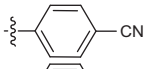
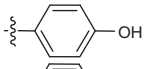
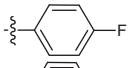
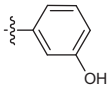
http://dx.doi.org/10.1016/j.bmcl.2013.05.044

Table 1
Structure of 3-arylideneflavanones, 3-arylidenechromanones and 3-arylflavones



Compd	R^1	R^2
1a	H	
1b	H	
1c	6-OH	
1d	H	
1e	H	
1f	H	
3-Arylidenechromanones		
2a	H	
2b	H	
3-Arylflavones		
3a	H	
3b	H	
3c	H	
3d	H	
3e	H	

human leukaemia promyelocytic (HL-60) and lymphoblastic (NALM-6). In the further study cytotoxicity against normal cells (HUVEC—human umbilical vein endothelial cells) for five selected compounds were examined.

The results of cytotoxicity against cancer cell lines for compounds **1a**–**f**, **2a**–**b** and **3a**–**e** are shown as IC_{50} values in Table 2. Chromanone, flavanone, naringenin, quercetin and cisplatin were used as reference compounds. The statistical significance (*p*-values of unpaired *t*-test) between cytotoxicity of the tested and reference compounds has been placed in Table S6 (see Supplementary data).

As can be seen, the tested compounds demonstrate extremely different activity from very high cytotoxicity (IC_{50} = 0.9 μM) to lack of such activity (IC_{50} >1000 μM). The unsubstituted 3-arylideneflavanone (**1b**) appeared to be a weak cytotoxic agent against all the three cancer cells as well as flavanone. Addition of hydroxyl group at C6 position (R^1) resulted in significantly enhanced cyto-

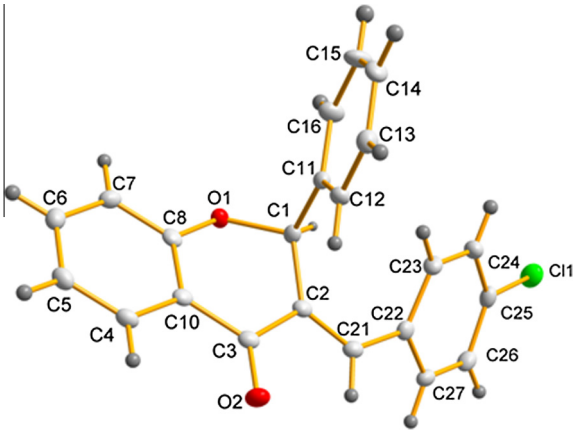
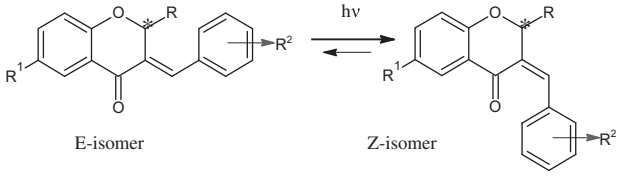


Figure 1. Molecular structure of **1e** and atom numbering scheme. Displacement ellipsoids are drawn at 50% probability level.



Scheme 1. Photoisomerization of 3-arylideneflavanone (R = phenyl) and 3-arylidenechromanone (R = H).

toxic activity of **1c**. The substitution by pirydyl (**1a**) instead of phenyl (R^2) dramatically increased antiproliferative activity especially against human leukemia cells (HL-60 and NALM-6). The IC_{50} values of **1a** (*E* and *Z* isomers) are comparable to that of cisplatin (Table 2). The compound **1a** exhibit similar activity as cytotoxic agent and as aromatase inhibitor.[8] *E*-Isomers of compounds containing halogen atom (chloride or bromide) in *para*-position of the aryl substituent (**1e** and **1f**) have high activity against human leukemia cells; therefore *Z*-isomers show no cytotoxicity against these cancer cells. 3-arylideneflavon with halogen atom (fluoride) (**3d**) exhibit less cytotoxic activity. Replacement of the halogen group on flavanone derivatives (**1e**, **1f**) with the methyl group (compound **1d**) led also to approximately fivefold decrease of cytotoxic activity of *E*-isomer. Both geometric isomers of all flavanone derivatives (except of **1a)** showed moderate activity against human skin melanoma (WM 115) cells, whereas *Z*-isomers of 3-arylidenechromanone were fourfold more active than *E*-isomers.

In order to find similar compounds among *E*, *Z*-isomers with regard to cytotoxic activity against all the three cancer cell lines a hierarchical cluster analysis using Ward's method applying squared Euclidean Distance was carried out (Fig. 2). Results indicate three clusters, two of them homogenous (only one type of isomers) and third mixed. Six *E*-isomer compounds are classified to group A and four *Z*-isomers to group B. Third group C consists both isomers. Then one-way ANOVA with NIR *post-hoc* test has been conducted to determine which variables ($\log IC_{50}$) are significantly different between the groups. Compounds in group C demonstrate the highest cytotoxic activity against all the three cancer cell lines. *Z*-Isomers from group B exhibit the least cytotoxic activity against leukemia cell lines whereas *E*-isomers from group A have weak cytotoxicity against WM-115.

The studies of cytotoxic activity of flavones and flavanones demonstrated that the presence of C_2–C_3 double bond in molecule is an important feature for enhancing cytotoxicity against different cancer cells.[11–13] In our studies, addition of aryl substituent at C3

Table 2
Cytotoxic activity of 3-arylidene-flavanones (**1a**–**f**), 3-arylidene-chromanones (**2a**–**b**) and 3-arylflavones (**3a**–**e**) against HL-60, NALM-6 and WM115 cancer cell lines. In parenthesis: *p*-value from *t*-test for comparison of cytotoxicity of selected compounds against cancer cell line and against normal cell line (HUVEC).

Compound	IC_{50}[a] (μM)					
	HL-60		NALM-6		WM-115	
	E-Isomer	*Z*-Isomer	*E*-Isomer	*Z*-Isomer	*E*-Isomer	*Z*-Isomer
1a	0.9 ± 0.2 (p <0.001)[b]	1.1 ± 0.2 (p <0.001)	1.6 ± 0.3(p <0.001)	0.7 ± 0.03 (p <0.001)	6.3 ± 0.5 (p = 0.055)	4.6 ± 0.4 (p = 0.023)
1b	33.3 ± 3.0	27.3 ± 3.2	29.5 ± 4.7	>1000	59.4 ± 0.9	52.6 ± 4.5
1c	5.8 ± 0.2	7.3 ± 0.7	8.7 ± 0.5	58.8 ± 1.4	44.5 ± 3.2	9.1 ± 0.2
1d	40.9 ± 6.1	40.8 ± 7.3	51.4 ± 3.8	>1000	60.1 ± 2.4	57.0 ± 6.6
1e	5.8 ± 0.5	>1000	7.4 ± 0.6	>1000	52.0 ± 3.5	27.4 ± 5.9
1f	5.7 ± 0.2 (p <0.001)	>1000 (p <0.001)	6.9 ± 0.1 (p = 0.071)	>1000 (p <0.001)	25.9 ± 2.3 (p <0.001)	32.6 ± 10.9 (p = 0.581)
2a	5.4 ± 0.6	6.7 ± 0.8	6.2 ± 0.2	5.5 ± 0.4	53.7 ± 4.3	13.5 ± 2.6
2b	5.7 ± 0.4	6.5 ± 0.7	32.3 ± 3.1	466.4 ± 49.6	69.0 ± 2.7	12.1 ± 2.9
3a	2.4 ± 0.4 (p <0.001)		5.0 ± 0.3 (p = 0.040)		6.1 ± 0.4 (p = 0.008)	
3b	3.8 ± 0.4		4.8 ± 0.2		6.3 ± 0.3	
3c	46.7 ± 2.5		49.8 ± 2.2		57.2 ± 4.2	
3d	19.1 ± 4.7		8.2 ± 0.5		53.2 ± 2.8	
3e	6.3 ± 0.3		7.3 ± 0.4		17.6 ± 2.7	
Chromanone	676.7 ± 32.6		673.7 ± 22.5		>1000	
Flavanone	51.1 ± 1.7		57.6 ± 8.6		71.2 ± 3.2	
Naringenin	413.7 ± 33.8		426.3 ± 20.5		524.8 ± 37.8	
Quercetin	58.0 ± 4.0		77.1 ± 7.8		177.5 ± 37.8	
Cisplatin	0.8 ± 0.1		0.7 ± 0.3		18.2 ± 4.3	

[a] IC_{50}-concentration of a test compound required to reduce the fraction of surviving cells to 50% of that observed in the control, non-treated cells. Mean values of IC_{50} (in μM) ± standard deviation from 3 experiments each performed in quintuple are presented.
[b] *p*-Value from unpaired *t*-test (each mean IC_{50} value against cancer cell line was compared with IC_{50} against normal cells HUVEC (from Table 3)).

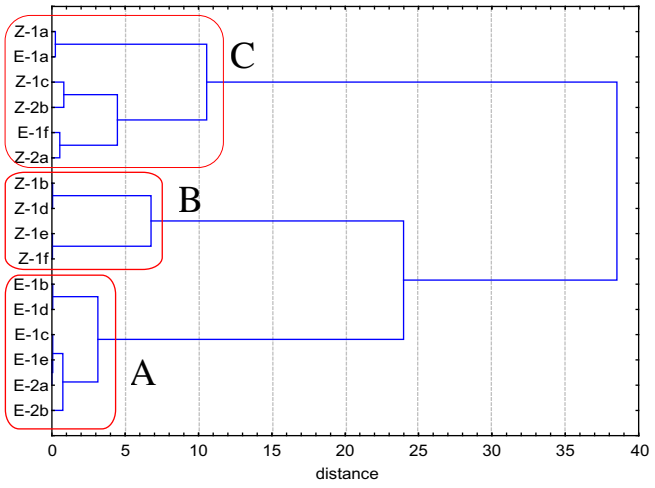


Figure 2. Dendrogram based on cytotoxic activity (expressed as IC50 in μM) against Hl-60, NALM-6 and WM-115 cancer cell lines.

Table 3
Cytotoxic activity of selected compounds against normal cells (HUVEC)

Compound	IC_{50} (μM)	
	E-Isomer	*Z*-Isomer
1a	5.77 ± 0.17	5.14 ± 0.15
1f	7.23 ± 0.34	29.12 ± 8.03
3a	5.40 ± 0.21	

position resulted in similar diversification of antiproliferative activity between flavone and flavanone derivatives. Thus, the presence of C_2–C_3 double in 3-substituted moiety seemed less important. Table 3 contains results of cytotoxicity for selected compounds: **3a** and *E*,*Z*-isomers of **1a** and **1f** against normal human cells HUVEC. As can be seen, **1a** exhibit statistically significant (p <0.001) better cytotoxic activity against human leukaemia than

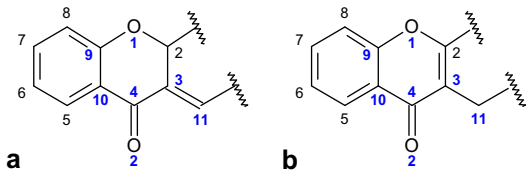


Figure 3. The basic molecular structure of flavanone and chromanone (a) and flavone (b) derivatives. Partial charges for atoms denoted by blue bold numbers were calculated and used in QSAR study.

Table 4
Parameters of GA-MLR models

Cancer cell line	RMSEC	RMSECV	RMSEP	R^2model	R^2test
HL-60	0.343	0.628	0.595	0.720	0.848
NALM-6	0.409	0.561	0.822	0.745	0.863
WM-115	0.183	0.309	0.157	0.785	0.913

RMSE—Root mean square error of calibration (C), cross-validation (CV) and prediction (P).

normal cells. Unfortunately, against WM-115 cancer cell line and HUVEC, **1a** is toxic in similar manner.

The compound **1f** was selected to test on normal cells due to the extremely different cytotoxicity between *E* and *Z*-isomer. Unexpectedly, *Z*-isomer of **1f** inactive against HL-60 shows moderate toxicity against normal cells. The compound **3a** (chosen as the most cytotoxic among flavone derivatives) demonstrate higher cytotoxic activity against cancer than normal cells for HL-60 only.

The structures of compounds were optimized using Gaussian software[14] by semi-empirical parametrization method RM1[15] and continuum solvation model SMD.[16] After optimization Mulliken[17] charges on both O and selected C atoms (Fig. 3) were calculated. Other molecular descriptors for the compound dataset were obtained using QSAR properties utility of HYPERCHEM v.7.03.[18] The values of the significant descriptors for all 21 compounds were given

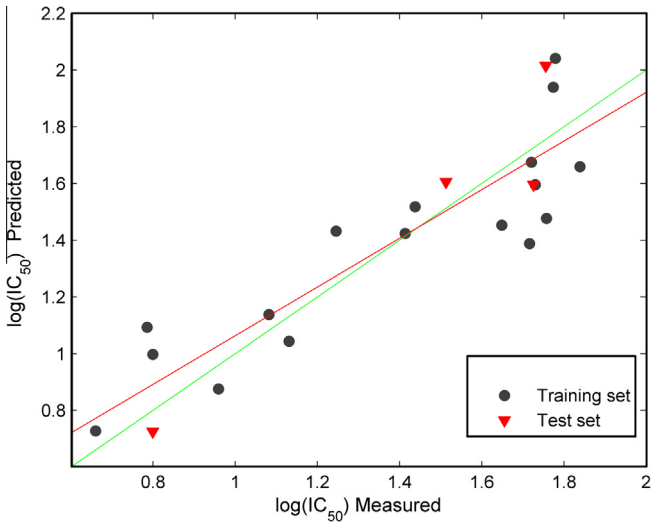


Figure 4. MLR model for cytotoxicity against WM-115 cancer cell line for training set and test set.

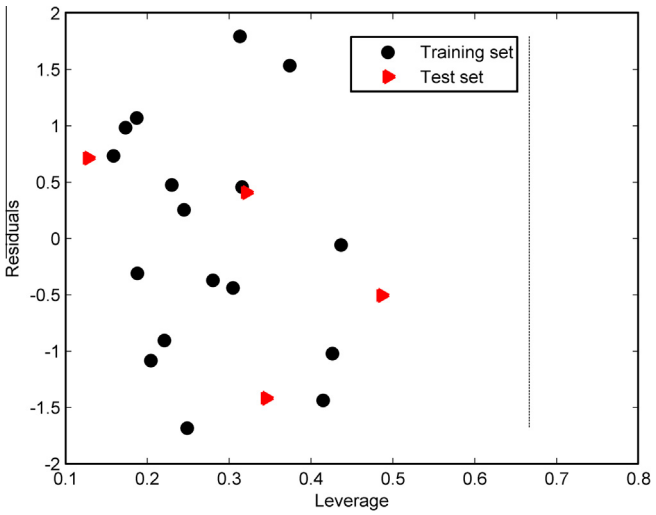


Figure 5. Williams plot, plot of standardized residuals versus leverages for each compound in training and test set for WM-115 cancer cell line.

in Supplementary data (Tables S3 and S4). Moreover, experimentally (with the use of HPLC method) obtained log*P* values were added to computational descriptors (Table S4).

The correlation between cytotoxic activity and structural properties was obtained using the multiple linear regression method (MLR). Genetic algorithms (GA) was applied for modeling descriptors subset selection. The calculation were made with the MATLAB® software.

A set of 17 compounds was used as a training set for a QSAR modeling. Then the model was applied to a set of four new compounds. The goodness of fit of each model, for both internal and external validation was checked by determination coefficient (R^2) and root mean square errors of: calibration (RMSEC), cross-validation (RMSECV) and prediction (RMSEP). The results of statistical parameters obtained for GA-MLR modeling of cytotoxic activity can be found in Table 4.

As it can be seen the proposed models have potential for predictive application (R^2 test >0.84) although the fitting power verified by R^2 model not exceed 0.8. It might be related with relatively small training set (17 compounds). In further study some new compounds would have been helpful for the better validation of the models. The predicted values of logIC_{50} for WM-115 cancer cell line for the compounds in the training and test sets are plotted against the measured values in Figure 4.

The equations of GA-MLR models were obtained as follows:

$$\log IC_{50}(HL60) = 7.33 - 7.37 \log P_{exp} - 31.91E_{LUMO} + 0.80(\log P_{exp})^2 - 40.95E_{LUMO}^2 - 2.39 log P_{exp} E_{LUMO}$$

$$\log IC_{50}(NALM6) = -54.33 + 15.8 \log P_{exp} + 4.8E_{LUMO} - 184.56\delta O_2 + 50.27 log P_{exp}\delta O_2$$

$$\log IC_{50}(WM115) = -29.12 + 6.53 \log P_{exp} + 2.91E_{LUMO} - 89.39\delta O_2 - 0.20(\log P_{exp})^2 + 14.54 log P_{exp}\delta O_2$$

For HL-60 and WM-115 polynomial regression models with interaction effect of the two variables were performed. All models include two the same descriptors: energy of LUMO and logP_{exp}, additionally equations for NALM-6 and WM-115 cell lines contain partial charge on carbonyl oxygen (δO_2). Electronic descriptor (E_{LUMO}) and hydrophobicity/lipophilicity (log*P*) are important descriptors in the modelling of different (covalent and non-covalent) mechanisms of toxicity.[20–22] Covalent mechanism of cytotoxicity requires electrophilic properties of active compounds. Electrophilicity (ω) of a molecule can be derived from energies of frontier orbitals (HOMO, LUMO) as follows: $\omega = (E_{LUMO} + E_{HOMO})^2/4\,(E_{LUMO} - E_{HOMO})$.[22] The high values of ω for tested compounds correlated with the high cytotoxic activity. On the other hand the efficient cytotoxic agent needs optimal lipophilicity that allows it to get the reactive site (DNA, protein). Increase of log*P* value of tested compounds leads to a reduction of cytotoxic activity. The both isomers of **1a** are characterized by relatively low logP_{exp} (2.85 and 2.98) and relatively high electrophilicity which result in very good potential as cytotoxic agent. Whereas, the loss of cytotoxic activity of *Z*-isomers of **1d**, **1e** and **1f** might be partially explained by concurrent factors, very high lipophilicity (logP_{exp} >4.4) and low electrophilicity.

QSAR models are generally limited to query chemicals structurally similar to the training compounds, therefore the chemical applicability domain (AD), defined as theoretical space of the data set of the model, was verified by the Williams plot. From plot in Figure 5, the applicability domain was established inside an area within ±2 standard deviations and a leverage threshold h^* ($h^* = 3(p + 1)/n$, where p is the number of model parameters and n the number of compounds in training set).[19] The plot indicate that leverage values for the compounds from training and test sets are lower than the critical value (the dotted line) and the residuals are not greater than two standard deviation units. For the future, predicted cytotoxic activity data must be considered reliable only for those chemicals that fall within the applicability domain on which the model was constructed.

In summary, the study of the relationship between the configuration and cytotoxic activity against cancer cell lines of flavanone derivatives, revealed that either both isomers exhibit very similar cytotoxic activity or only *Z*-isomer is cytotoxic whilst *E*-isomer is entirely inactive. The most promising compound is **1a**, due to the very high and independent of isomeric form cytotoxic activity especially against human leukaemia cancer cell lines. Both leukaemia cancer cells are more sensitive than normal cells to the toxic effect of **1a**, therefore it is good candidate for anticancer lead compound. However, further experiments are needed to understand mechanism of cytotoxic action of these compounds.

Statistically significant equations describing structure–cytotoxic activity relationships in flavanone, chromanone and flavone group were obtained. Models posses good regression statistics indicating mechanistic importance of lipophilicity, electrophilicity (E_{LUMO}) and partial charge on carbonyl oxygen for prediction of cytotoxic activity of tested compounds.

Acknowledgment

We are thankful for funding support from Nicolaus Copernicus University, Collegium Medicum, Grant No. 411.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmcl.2013.05.044.

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