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Quantitative Structure–Cytotoxicity Relationship of Aurones

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Abstract. *Background/Aim: Seventeen aurones were subjected to quantitative structure–activity relationship (QSAR) analysis based on their cytotoxicity and tumor-specificity, in order to find their new biological activities. Materials and Methods: Cytotoxicity against three human oral squamous cell carcinoma cell lines and three oral mesenchymal cells was determined by the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) method. Tumor specificity (TS) was evaluated by the ratio of the mean 50% cytotoxic concentration (CC_{50}) against normal cells to that against tumor cell lines. Potency-selectivity expression (PSE) value was calculated by dividing TS by CC_{50} against tumor cells. Physicochemical, structural and quantum-chemical parameters were calculated based on the conformations optimized by force-field minimization. Results: Sixteen out of seventeen aurones showed relatively higher cytotoxicity and tumor specificity. Among them, (2Z)-2-[(4-hydroxyphenyl)methylene]-3(2H)-benzofuranone [7] showed the highest TS value and PSE values, comparable with those of doxorubicin and higher than 5-FU, respectively. TS values were correlated with molecular shape, size and polarizability rather than the types of substituted groups. Conclusion: Chemical modification of the lead compound may be a potential choice for designing a new type of anticancer drugs.*

Aurones are a sub-set of the flavone family that possess a number of biological activities, including anti-cancer (1-6), anti-microbial (7, 8), anti-parasitic (9), anti-inflammatory (8) and enzyme inhibitory activity (10-12). Due to their high availability, simple synthesis and generally low toxicity, aurones could be attractive candidates for safer cancer drugs.

However, as far as we know, only one paper has performed the rigorous antitumor investigation with normal cell lines or same type of cells (1). Based on these backgrounds, we have investigated here a total of 17 synthetic aurones (Figure 1) for their cytotoxicity activity and tumor-specificity, and then subjected to quantitative structure–activity relationship (QSAR) analysis.

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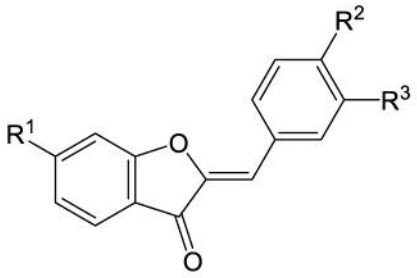
Key Words: Aurones, QSAR analysis, cytotoxicity, tumor selectivity.

Materials and Methods

Materials. The following chemicals and reagents were obtained from the indicated companies: Dulbecco's modified Eagle's medium (DMEM), from GIBCO BRL, Grand Island, NY, USA; fetal bovine serum (FBS), 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT), doxorubicin, from Sigma-Aldrich Inc., St. Louis, MO, USA; 5-fluorouracil (5-FU), dimethyl sulfoxide (DMSO) from Wako Pure Chem. Ind., Osaka, Japan. Culture plastic dishes and plates (96-well) were purchased from Becton Dickinson (Franklin Lakes, NJ, USA).

Synthesis of test compounds. (2*Z*)-2-(Phenylmethylene)-3(2*H*)-benzofuranone [**1**], (2*Z*)-2-[(4-methoxyphenyl)methylene]-3(2*H*)-benzofuranone [**2**], (2*Z*)-2-[(3,4-dimethoxyphenyl)methylene]-3(2*H*)-benzofuranone [**3**], (2*Z*)-2-[(4-fluorophenyl)methylene]-3(2*H*)-benzofuranone [**4**], (2*Z*)-2-[(4-chlorophenyl)methylene]-3(2*H*)-benzofuranone [**5**], (2*Z*)-2-[(4-bromophenyl)methylene]-3(2*H*)-benzofuranone [**6**], (2*Z*)-2-[(4-hydroxyphenyl)methylene]-3(2*H*)-benzofuranone [**7**], (2*Z*)-6-methoxy-2-(phenylmethylene)-3(2*H*)-benzofuranone [**8**], (2*Z*)-6-methoxy-2-[(4-methoxyphenyl)methylene]-3(2*H*)-benzofuranone [**9**], (2*Z*)-2-[(3,4-dimethoxyphenyl)methylene]-6-methoxy-3(2*H*)-benzofuranone [**10**] and (2*Z*)-2-[(4-bromophenyl)methylene]-6-methoxy-3(2*H*)-benzofuranone [**11**] were synthesized by the oxidative cyclization of 2'-hydroxychalcone derivatives, according to previous methods (13). Also, (2*Z*)-2-[(3,4-dimethoxyphenyl)methylene]-6-hydroxy-3(2*H*)-benzofuranone [**12**], (2*Z*)-2-[(4-fluorophenyl)methylene]-6-hydroxy-3(2*H*)-benzofuranone [**13**], (2*Z*)-2-[(4-chlorophenyl)



Compound	R^1	R^2	R^3
1	H	H	H
2	H	OMe	H
3	H	OMe	OMe
4	H	F	H
5	H	Cl	H
6	H	Br	H
7	H	OH	H
8	OMe	H	H
9	OMe	OMe	H
10	OMe	OMe	OMe
11	OMe	Br	H
12	OH	OMe	OMe
13	OH	F	H
14	OH	Cl	H
15	OH	Br	H
16	OH	OH	H
17	OH	OH	OH

Figure 1. *Structure of seventeen aurones.*

methylene]-6-hydroxy-3(2*H*)-benzofuranone [**14**], (2*Z*)-2-[(4-bromophenyl)methylene]-6-hydroxy-3(2*H*)-benzofuranone [**15**], (2*Z*)-6-hydroxy-2-[(4-hydroxyphenyl)methylene]-3(2*H*)-benzofuranone [**16**] and (2*Z*)-2-[(3,4-dihydroxyphenyl)methylene]-6-hydroxy-3(2*H*)-benzofuranone [**17**] were synthesized by the condensation of 6-hydroxy-3(2*H*)-benzofuranone with selected benzaldehyde derivatives, according to previous methods (14). All compounds were dissolved in DMSO at 40 mM and stored at –20˚C before use.

Cell culture. Human normal oral mesenchymal cells (gingival fibroblast, HGF; periodontal ligament fibroblast, HPLF; pulp cells, HPC) were established from the first premolar tooth extracted from the lower jaw of a 12-year-old girl (15), and cells at 10-18 population doubling levels were used in this study. Human OSCC cell lines [Ca9-22 (derived from gingival tissue); HSC-2, HSC-4 (derived from tongue)] were purchased from Riken Cell Bank (Tsukuba, Japan). All of these cells were cultured at 37˚C in DMEM supplemented with 10% heat-inactivated FBS, 100 units/ml, penicillin G and 100 μg/ml streptomycin sulfate under a humidified 5% CO_2 atmosphere.

Assay for cytotoxic activity. Cells were inoculated at 2.5×10^3 cells/0.1 ml in a 96-microwell plate. After 48 h, the medium was replaced with 0.1 ml of fresh medium containing different concentrations of single test compounds. Cells were incubated further for 48 h and the relative viable cell number was then determined by the MTT method (16). The relative viable cell number was determined by the absorbance of the cell lysate at 560 nm, using a microplate reader (Infinite F 50 R, TECAN, Kawasaki, Japan). Control cells were treated with the same amounts of DMSO and the cell damage induced by DMSO was subtracted from that induced by test agents. The concentration of compound that reduced the viable cell number by 50% (CC_{50}) was determined from the dose–response curve and the mean value of CC_{50} for each cell type was calculated from triplicate assays.

Calculation of tumor-selectivity index (TS). TS was calculated using the following equation:

TS=mean CC_{50} against normal cells/mean CC_{50} against tumor cells

[(D/B) in Table I]. Since both Ca9-22 and HGF cells were derived from the gingival tissue (17), the relative sensitivity of these cells was also compared [(C/A) in Table I]. We did not use human normal oral keratinocytes as controls, since many anticancer drugs showed potent cytotoxicity against normal keratinocytes by inducing apoptosis (16).

Calculation of potency-selectivity expression (PSE). PSE was calculated using the following equation:

PSE=TS/CC_{50} against tumor cells ×100 (18)

[that is, (D/B^2) ×100 (HGF, HPLF, HPC *vs*. Ca9-22, HSC-2, HSC-4) and (C/A^2) ×100 (HGF *vs*. Ca9-22) in Table I).

Estimation of CC_{50} values. Since the CC_{50} values had a distribution pattern close to a logarithmic normal distribution, we used the pCC_{50} (*i.e.*, the –log CC_{50}) for the comparison of the cytotoxicity between the compounds. The mean pCC_{50} values for normal cells and tumor cell lines were defined as N and T, respectively (18).

Calculation of chemical descriptors. The 3D-structure of each chemical structure (drawn by Marvin Sketch ver 16, ChemAxon, Budapest, Hungary, http://www.chemaxon.com) was optimized by CORINA Classic (Molecular Networks GmbH, Germany) and force-field calculations (amber-10: EHT) in Molecular Operating Environment (MOE) version 2015.1001 (Chemical Computing Group Inc., Quebec, Canada). The number of structural descriptors calculated from MOE and Dragon 7.0 (Kode srl., Pisa, Italy) after the elimination of overlapped descriptors were 265 and 2840, respectively.

The following 15 Dragon descriptors and 3 MOE descriptors were significantly correlated with T, N and T-N (Table II).

Dragon descriptors (19): CATS3D_04_DL (CATS3D Donor-Lipophilic BIN 04), E1u (1st component accessibility directional WHIM index/unweighted), G3m (3rd component symmetry directional WHIM index/weighted by mass), GATS1e (Geary autocorrelation of lag 1 weighted by Sanderson electronegativity),

Table I. *Cytotoxic activity of 17 aurones against oral malignant and non-malignant cells. Each value represents the mean of triplicate determinations.*

	CC_{50} (μM)										TS value		PSE value	
	Human oral squamous cell carcinoma					Human normal oral cells								
	(A) Ca9-22	HSC-2	HSC-4	(B) mean	SD	(C) HGF	HPLF	HPC	(D) mean	SD	(D/B)	(C/A)	(D/B^2) ×100	(C/A^2) ×100
1	43	56	17	39	20	75	70	24	56	28	1.5	1.7	3.8	4.1
2	36	42	15	31	14	306	256	48	203	136	6.6	8.6	21.5	24.2
3	183	>354	78	>205		266	290	304	287	19	<1.4	1.5	<0.7	0.8
4	120	86	7	71	58	139	276	24	146	126	2.1	1.2	2.9	1.0
5	34	42	11	29	16	87	76	11	58	41	2.0	2.6	6.8	7.6
6	42	48	8	32	21	34	33	6	24	16	0.7	0.8	2.3	2.0
7	37	57	31	41	14	>400	>400	>400	>400		>9.7	>11.0	>23.3	>30.0
8	38	75	45	53	20	89	99	130	106	22	2.0	2.3	3.8	6.2
9	40	73	42	52	19	237	48	205	163	101	3.2	5.9	6.1	14.6
10	44	316	57	139	153	334	339	315	329	13	2.4	7.5	1.7	17.0
11	34	70	24	43	24	197	165	147	170	26	4.0	5.8	9.3	17.1
12	140	>385	300	>275		>360	324	>381	>355		><1.3	>2.6	><0.5	>1.8
13	47	59	66	58	10	143	109	89	114	28	2.0	3.0	3.4	6.4
14	37	41	41	40	2	113	107	95	105	9	2.6	3.0	6.6	8.2
15	39	48	49	45	6	154	123	105	128	25	2.8	4.0	6.2	10.3
16	183	>390	251	>275		303	>337	>386	>342		><1.2	1.7	>0.5	0.9
17	288	187	31	169	129	>392	>400	>356	>382		>2.3	>1.4	>1.3	>0.5
DXR	0.45	0.19	0.18	0.27	0.15	1.09	0.85	7.50	3.15	3.77	11.7	2.5	4329.4	552.1
5-FU	144	>1000	46	>397		>1000	>968	>1000	>989		><2.5	>7.0	><0.6	>4.8

HGF: Human gingival fibroblast; HPC: human pulp cells; HPLF: human periodontal ligament fibroblast; Ca9-22 (derived from gingival tissue), HSC-2 and HSC-4 (derived from tongue): oral squamous cell carcinoma cell lines; CC_{50}: 50% cytotoxic concentration; DXR: doxorubicin; 5-FU: 5-fluorouracil. TS: tumor-selectivity index; PSE: potency-selectivity expression.

Gm (Total symmetry index/weighted by mass), HATS2p (Leverage-weighted autocorrelation of lag 2/weighted by polarizability), HATS6p (Leverage-weighted autocorrelation of lag 6/weighted by polarizability), HATS6v (Leverage-weighted autocorrelation of lag 6/weighted by van der Waals volume), MLOGP (Moriguchi logP), MLOGP2 (Squared Moriguchi logP), Mor05i (Signal 05/weighted by ionization potential), O% (Percentage of O atoms), R6p (R autocorrelation of lag 6/weighted by polarizability), R6v (R autocorrelation of lag 6/weighted by van der Waals volume), RDF010s (Radial Distribution Function - 010/weighted by I-state).

MOE descriptors: vsurf_CW4 (apacity factor 4), vsurf_HB4 (H-bond donor capacity 4), vsurf_IW5 (Hydrophilic interaction energy moment 5) (20).

Statistical treatment. The relation among cytotoxicity, tumor specificity index and chemical descriptors was investigated using simple regression analyses by JMP Pro version 12.2.0 (SAS Institute Inc., Cary, NC, USA). The significance level was set at $p<0.05$.

Results

Cytotoxicity. Seventeen aurones generally showed higher cytotoxicity against three OSCC cell lines (Ca9-22, HSC-2, HSC-4) (average of mean CC_{50}=94±85 μM), compared to three normal cells (HGF, HPLF, HPC) (average of mean CC_{50}=198±125 μM).

Tumor-specificity. When three OSCC cell lines and three normal oral cells were used, [**7**] showed the highest TS value (>9.7), followed by [**2**] (6.6) and [**11**] (4.4) (D/B in Table I). [**7**] showed the highest PSE value (>23.3), followed by [**2**] (21.5) and [**11**] (9.3) (D/B^2×100 in Table I).

When Ca9-22 and HGF cells, both derived from gingival tissue, were used, [**7**] showed the highest TS value (>11.0), followed by [**2**] (8.6) (C/A in Table I). [**7**] showed the highest PSE value (>30.0), followed by [**2**] (24.2) (C/A^2×100 in Table I).

Computational analysis. We next performed the QSAR analysis of aurones in regards to their cytotoxicity against tumor cells and normal cells. Among a total of 3,105 descriptors, 18 descriptors described below correlated well with cytotoxicity and tumor specificity.

Cytotoxicity of aurones against human OSCC cell lines was correlated with E1u (topological shape) (r^2=0.791, $p<0.0001$), RDF010s (molecular shape) (r^2=0.722, $p<0.0001$), CATS3D_04_DL (lipophilicity) (r^2=0.694, $p<0.0001$), Mor05i (ionization potential) (r^2=0.690, $p<0.0001$), vsurf_HB4 (hydrogen bond donor capacity) (r^2=0.690, $p<0.0001$), vsurf_CW4 (molecular shape) (r^2=0.689, $p<0.0001$) (Figure 2).

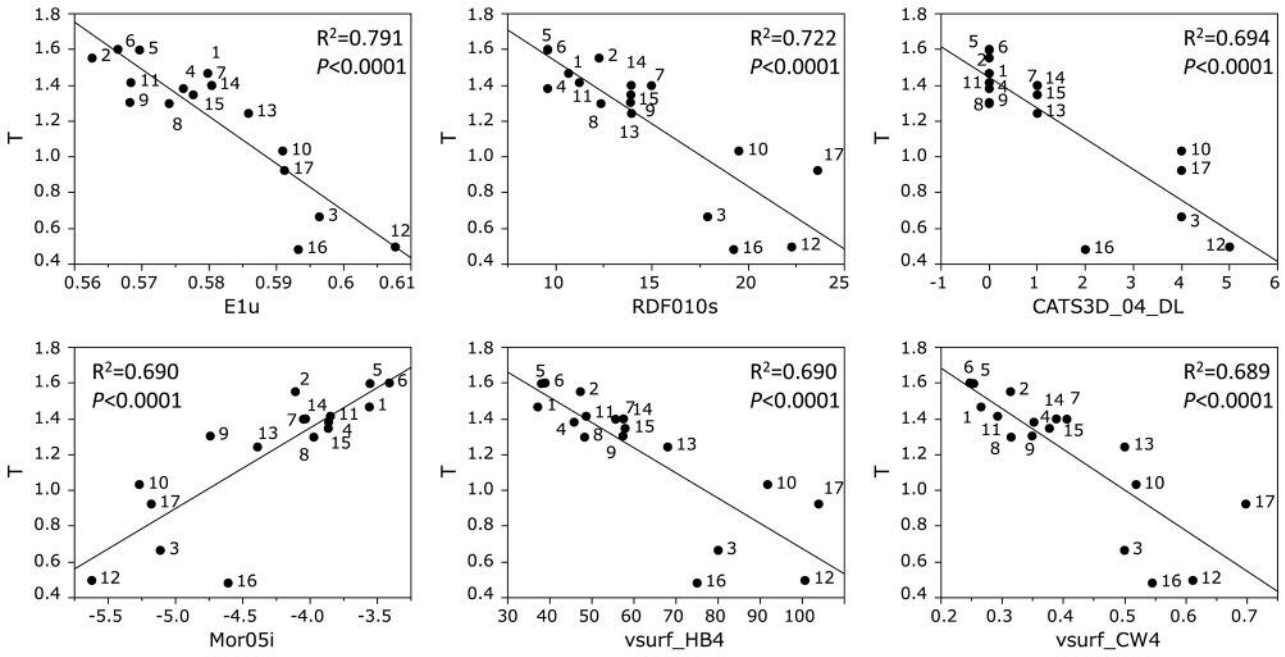


Figure 2. *Determination of coefficient between chemical descriptors and cytotoxicity of aurones against tumor cells (defined as T). The mean (pCC_{50} i.e., the $-log\ CC_{50}$) values for tumor cell lines were defined as T.*

Table II. *Descriptors that showed significant correlation with cytotoxicity against tumor cells (T) and normal cells (N), and tumor-specificity (T-N).*

	Descriptor	Explanation	Category	Source	Relevant property
N	vsurf_IW5	Hydrophilic interaction energy moment 5	vsurf descriptors	MOE	hydrophilicity
N	MLOGP2	Squared Moriguchi octanol-water partition coeff. (logP^2)	Molecular properties	Dragon	lipophilicity
N	MLOGP	Moriguchi octanol-water partition coeff. (logP)	Molecular properties	Dragon	lipophilicity
N	HATS2p	leverage-weighted autocorrelation of lag 2/weighted by polarizability	GETAWAY descriptors	Dragon	polarizability
N	GATS1e	Geary autocorrelation of lag 1 weighted by Sanderson electronegativity	2D autocorrelations	Dragon	electronegatibvity
N	O%	percentage of O atoms	Constitutional indices	Dragon	O atom
T	E1u	1st component accessibility directional WHIM index/unweighted	WHIM descriptors	Dragon	shape
T	RDF010s	Radial Distribution Function - 010/weighted by I-state	RDF descriptors	Dragon	shape
T	CATS3D_04_DL	CATS3D Donor-Lipophilic BIN 04 (4.000 - 5.000 Å)	CATS 3D	Dragon	lipophilicity
T	Mor05i	Signal 05/weighted by ionization potential	3D-MoRSE descriptors	Dragon	ionization potential
T	vsurf_HB4	H-bond donor capacity 4	vsurf descriptors	MOE	H-bond
T	vsurf_CW4	Capacity factor 4	vsurf descriptors	MOE	shape
T-N	HATS6p	Leverage-weighted autocorrelation of lag 6/ weighted by polarizability	GETAWAY descriptors	Dragon	polarizability
T-N	R6p	R autocorrelation of lag 6/weighted by polarizability	GETAWAY descriptors	Dragon	polarizability
T-N	R6v	R autocorrelation of lag 6/weighted by van der Waals volume	GETAWAY descriptors	Dragon	volume
T-N	Gm	Total symmetry index/weighted by mass	WHIM descriptors	Dragon	mass
T-N	G3m	3rd component symmetry directional WHIM Descriptors index/weighted by mass	WHIM	Dragon	mass
T-N	HATS6v	leverage-weighted autocorrelation of lag 6/ weighted by van der Waals volume	GETAWAY descriptors	Dragon	volume

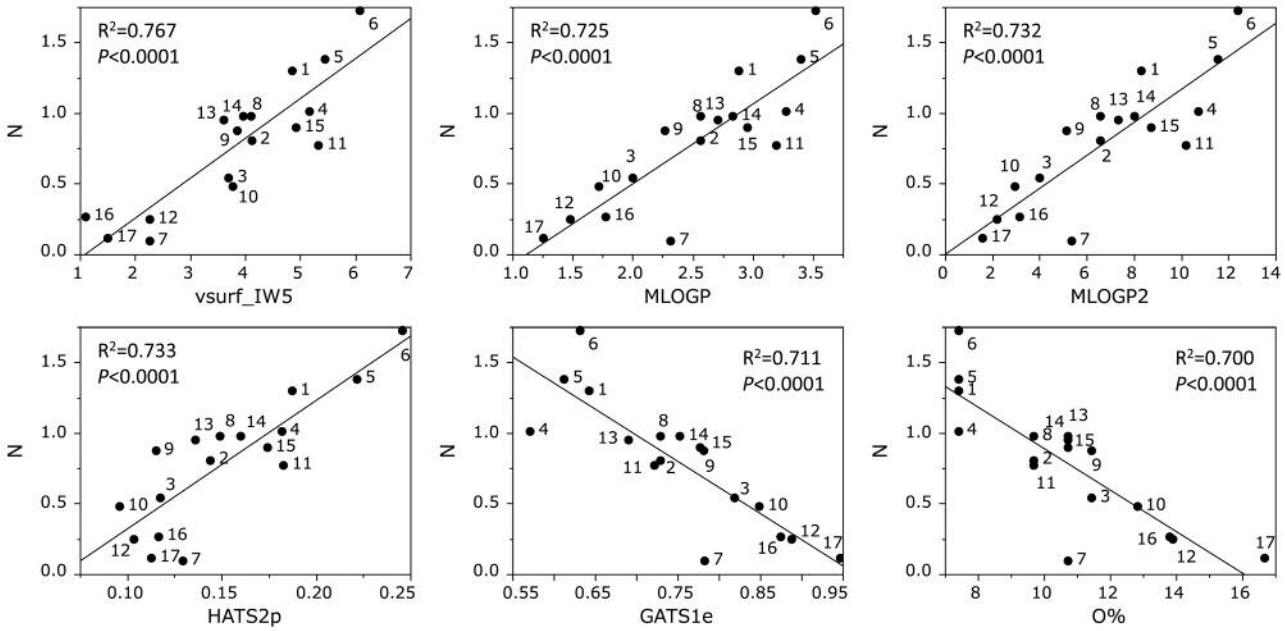


Figure 3. *Determination of coefficient between chemical descriptors and cytotoxicity of aurones against normal cells (defined as N). The mean (pCC_{50} i.e., the $-log\ CC_{50}$) values for normal cells were defined as N.*

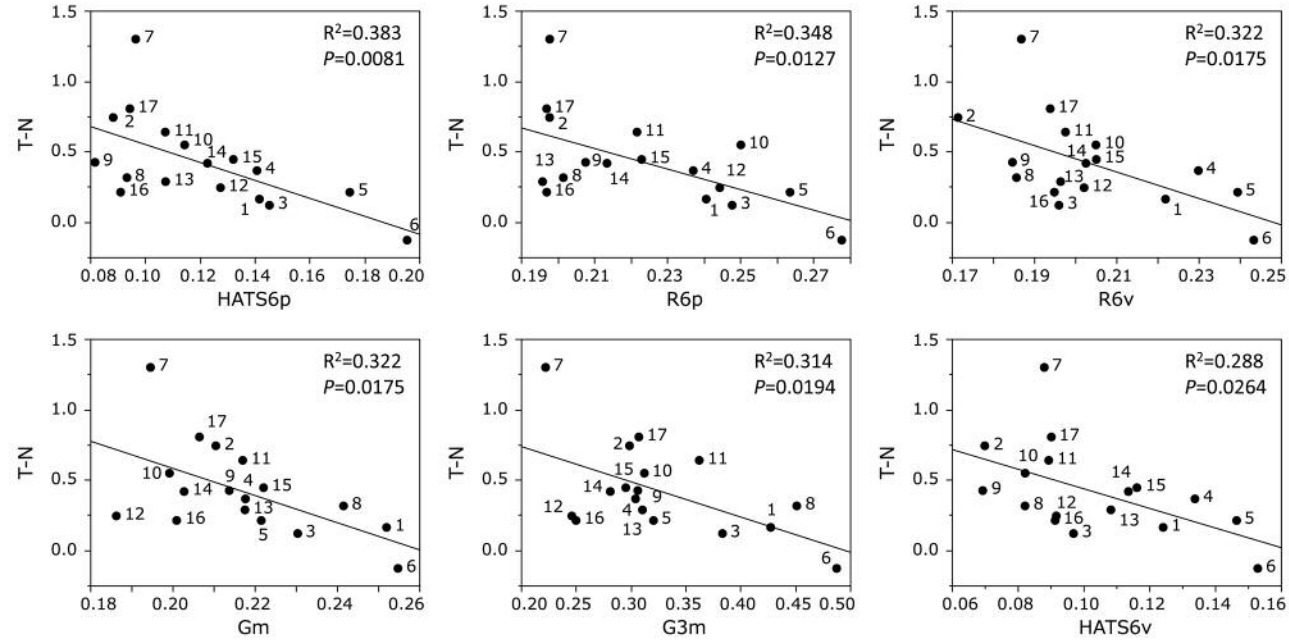


Figure 4. *Determination of coefficient between chemical descriptors and tumor specificity of aurones (defined as T−N).*

Cytotoxicity of aurones against human normal oral mesenchymal cells was correlated with vsurf_IW5 (hydrophilicity) (r^2=0.767, p<0.0001), MLOGP (lipophilicity) (r^2=0.725, p<0.0001), MLOGP2 (lipophilicity) (r^2=0.732, p<0.0001), HATS2p (polarizability) (r^2=0.733, p<0.0001), GATS1e (electronegatibvity) (r^2=0.711, p<0.0001), O % (percentage of O atoms) (r^2=0.700, p<0.0001) (Figure 3).

Tumor specificity of piperic acid esters was correlated with HATS6p (polarizability) (r^2=0.383, p=0.0081), R6p (polarizability) (r^2=0.348, p=0.0127), R6v (molecular

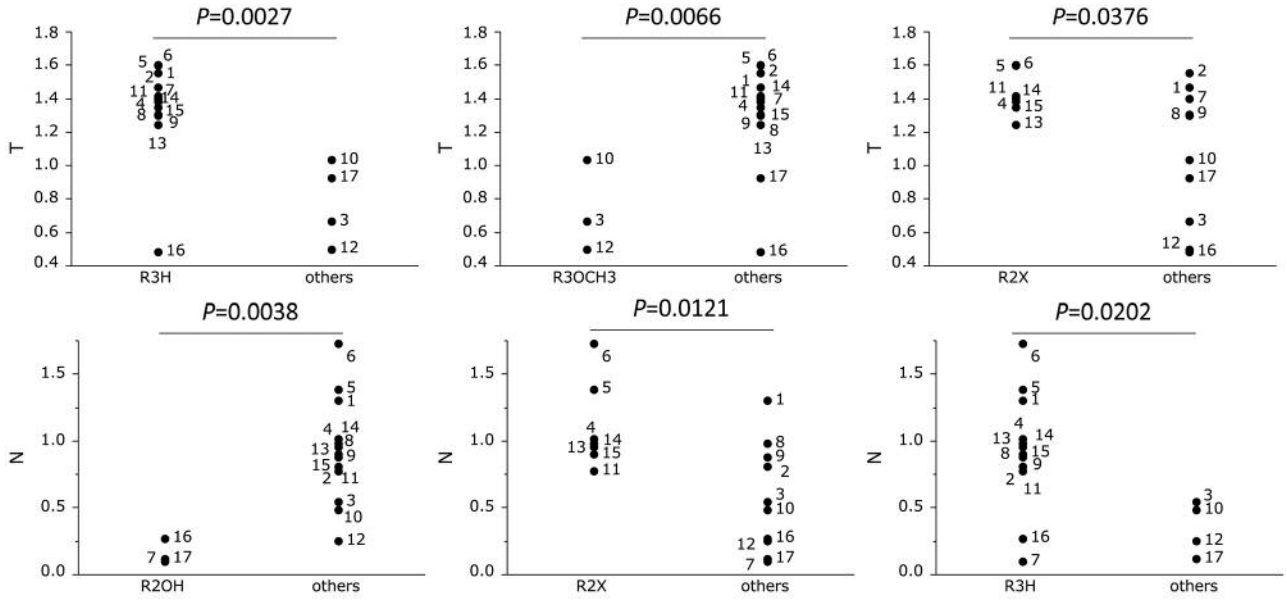


Figure 5. *Substituted groups that significantly affected the cytotoxicity against OSCC cell lines (T) and normal oral mesenchymal cells (N) and tumor specificity (T-N).*

volume) (r^2=0.322, p=0.0175), Gm (mass) (r^2=0.322, p=0.0175), G3m (mass) (r^2=0.314, p=0.0194), HATS6v (molecular volume) (r^2=0.288, p=0.0264) (Figure 4).

Discussion

The present study demonstrated that sixteen out of seventeen aurones showed relatively higher cytotoxicity and tumor specificity. Among them, [**7**] showed the highest TS value (D/B=>9.7, C/A=>11.0) and PSE values (D/B^2×100=>23.3, C/A^2×100=>30.0) (Table I). It should be noted that TS values of [**7**] was comparable with those of doxorubicin (D/B=11.7, C/A=2.5) and higher than 5-FU (D/B=><2.5, C/A=>7.0). PSE value of [**7**] was also higher than that of 5-FU (D/B^2×100=><0.6, C/A^2×100=>4.8) albeit much lower than those of doxorubicin (D/B^2×100=4329.4, C/A^2×100=552.1) (Table I).

QSAR analysis demonstrated that tumor specificity of aurones were rather correlated with HATS6p, R6p, R6v, Gm, G3m, HATS6v that reflects molecular shape, size and polarizability (Figure 4). However, chemical descriptors that were correlated with cytotoxicity against normal cells (vsurf_IW5, MLOGP, MLOGP2, HATS2p, CATS1e, O% (Figure 3) and tumor cells (E1u, RDF10s, CATS3D_04_DL, Mor05i, vsurf, vsurf_CW4) (Figure 2) were quite different with each other. This suggests that modification of the backbone structure of aurones can produce more selective compounds.

We calculated the possible contribution of substituted groups to the expression of cytotoxicity against OSCC cell lines and normal oral mesenchymal cells and tumor-specificity (Table III). Most of the substituents listed did not affect these activities (p=0.0503-0.9838) except for hydrogen (p=0.0027), OCH_3 (p=0.0066) at R3, or X at R2 (p=0.0376) in determining cytotoxicity against tumor cells (upper panel in Figure 5), and OH (p=0.0038) and X (p=0.0121) at R2 and H (p=0.0202) at R3 in determining cytotoxicity against normal cells (lower panel in Figure 5). From these data, tumor specificity of aurones was rather correlated with molecular shape, size and polarizability (Figure 5).

In conclusion, compound **7** is a potential lead compound for synthesizing more potent compounds targeted to OSCC cells.

Conflicts of Interest

The Authors wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

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Table III. *Substituted groups that affect the cytotoxicity against OSCC cell lines (T) and normal oral mesenchymal cells (N) and tumor specificity (T-N).*

	Factor	*p*-Value
T	R1H	0.1123
T	R1OCH3	0.7623
T	R1OH	0.0503
T	R2H	0.4986
T	R2OCH3	0.1444
T	R2OH	0.1511
T	R2F	0.6918
T	R2Cl	0.2475
T	R2Br	0.2135
T	R2X	0.0371
T	R3H	0.0027
T	R3OCH3	0.0066
N	R1H	0.1547
N	R1OCH3	0.9503
N	R1OH	0.1593
N	R2H	0.2608
N	R2OCH3	0.2567
N	R2OH	0.0038
N	R2F	0.5423
N	R2Cl	0.2066
N	R2Br	0.1575
N	R2X	0.0121
N	R3H	0.0202
N	R3OCH3	0.1283
T-N	R1H	0.8231
T-N	R1OCH3	0.6704
T-N	R1OH	0.8835
T-N	R2H	0.4253
T-N	R2OCH3	0.9838
T-N	R2OH	0.0329
T-N	R2F	0.6847
T-N	R2Cl	0.6472
T-N	R2Br	0.5755
T-N	R2X	0.3112
T-N	R3H	0.9423
T-N	R3OCH3	0.5199

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References

1 Alsaif G, Almosnid N, Hawkins I, Taylor Z, Knott DLT, Handy S, Altman E and Gao Y: Evaluation of fourteen aurone derivatives as potential anti-cancer agents. Curr Pharm Biotechnol *18*: 384-390, 2017.

2 Priyadarshani G, Nayak A, Amrutkar SM, Das S, Guchhait SK, Kundu CN and Banerjee UC: Scaffold-Hopping of aurones: 2-arylideneimidazo[1,2-a]pyridinones as topoisomerase IIα-inhibiting anticancer agents. ACS Med Chem Lett *7(12)*: 1056-1061, 2016.

3 de Mendonça IC, Porto IC, do Nascimento TG, de Souza NS, Oliveira JM, Arruda RE, Mousinho KC, dos Santos AF, Basílio-Júnior ID, Parolia A and Barreto FS: Brazilian red propolis: phytochemical screening, antioxidant activity and effect against cancer cells. BMC Complement Altern Med *15*: 357, 2015.

4 Václavíková R, Boumendjel A, Ehrlichová M, Kovár J and Gut I: Modulation of paclitaxel transport by flavonoid derivatives in human breast cancer cells. Is there a correlation between binding affinity to NBD of P-gp and modulation of transport? Bioorg Med Chem *14(13)*: 4519-4525, 2006.

5 Lawrence NJ, Rennison D, McGown AT and Hadfield JA: The total synthesis of an aurone isolated from Uvaria hamiltonii: aurones and flavones as anticancer agents. Bioorg Med Chem Lett *13(21)*: 3759-3763, 2003.

6 Jacobson KA, Moro S, Manthey JA, West PL and Ji XD: Interactions of flavones and other phytochemicals with adenosine receptors. Adv Exp Med Biol *505*: 163-171, 2002.

7 Sutton CL, Taylor ZE, Farone MB and Handy ST: Antifungal activity of substituted aurones. Bioorg Med Chem Lett *27(4)*: 901-903, 2017.

8 Bandgar BP, Patil SA, Korbad BL, Biradar SC, Nile SN and Khobragade CN: Synthesis and biological evaluation of a novel series of 2,2-bisaminomethylated aurone analogues as anti-inflammatory and antimicrobial agents. Eur J Med Chem *45(7)*: 3223-3227, 2010.

9 Roussaki M, Costa Lima S, Kypreou AM, Kefalas P, Cordeiro da Silva A and Detsi A: Aurones: a promising heterocyclic scaffold for the development of potent antileishmanial agents. Int J Med Chem *2012*: 196921, 2012.

10 Mughal EU, Sadiq A, Murtaza S, Rafique H, Zafar MN, Riaz T, Khan BA, Hameed A and Khan KM: Synthesis, structure-activity relationship and molecular docking of 3-oxoaurones and 3-thioaurones as acetylcholinesterase and butyrylcholinesterase inhibitors. Bioorg Med Chem *25(1)*: 100-106, 2017.

11 Siah M, Farzaei MH, Ashrafi-Kooshk MR, Adibi H, Arab SS, Rashidi MR and Khodarahmi R: Inhibition of guinea pig aldehyde oxidase activity by different flavonoid compounds: An *in vitro* study. Bioorg Chem *64*: 74-84, 2016.

12 Morales-Camilo N, Salas CO, Sanhueza C, Espinosa-Bustos C, Sepúlveda-Boza S, Reyes-Parada M, Gonzalez-Nilo F, Caroli-Rezende M and Fierro A: Synthesis, biological evaluation, and molecular simulation of chalcones and aurones as selective MAO-B inhibitors. Chem Biol Drug Des *85(6)*: 685-695, 2015.

13 Detsi A, Majdalani M, Kontogiorgis CA, Hadjipavlou-Litina D and Kefalas P: Natural and synthetic 2'-hydroxy-chalcones and aurones: Synthesis, characterization and evaluation of the antioxidant and soybean lipoxygenase inhibitory activity. Bioorg Med Chem *17*: 8073-8085, 2009.

14 Okombi S, Rival D, Bonnet S, Mariotte AM, Perrier E and Boumendjel A: Discovery of benzylidenebenzofuran-3(2*H*)-one (aurone) as inhibitors of tyrosinase derived from human melanocytes. J Med Chem *49*: 329-333, 2006.

15 Kantoh K, Ono M, Nakamura Y, Nakamura Y, Hashimoto K, Sakagami H and Wakabayashi H: Hormetic and anti-radiation effects of tropolone-related compounds. In Vivo *24*: 843-852, 2010.

16 Sakagami H, Okudaira N, Masuda Y, Amano O, Yokose S, Kanda Y, Suguro M, Natori T, Oizumi H and Oizumi T: Induction of apoptosis in human oral keratinocyte by doxorubicin. Anticancer Res *37(3)*: 1023-1029, 2017.

17 Horikoshi M, Kimura Y, Nagura H, Ono T and Ito H: A new human cell line derived from human carcinoma of the gingiva. I. Its establishment and morphological studies. Jpn J Oral Maxillofac Surg *20*: 100-106, 1974 (in Japanese).

18 Sakagami H, Masuda Y, Tomomura M, Yokose S, Uesawa Y, Ikezoe N, Asahara D, Takao K, Kanamoto T, Terakubo S, Kagaya H, Nakashima H and Sugita Y: Quantitative structure-cytotoxicity relationship of chalcones. Anticancer Res *37*: 1091-1098, 2017.

19 Calculate Descriptors", MOE2015.10 on-line help manual, Chemical Computing Group.

20 Cruciani G, Crivori P, Carrupt P-A and Testa B: Molecular fields in quantitative structure-permeation relationships: the VolSurf Approach; J Mol Struct *1-2*: 17-30, 2000.

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