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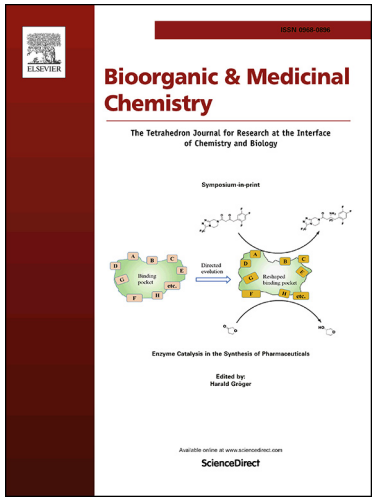

Anti-proliferative activity and structure-activity relationship of honokiol derivatives

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Anti-proliferative activity and structure-activity relationship of honokiol derivatives

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Abstract

As a known natural product with anti-tumor activity, honokiol has been widely researched and structural modified. Lots of honokiol derivatives have been found to possess good anti-proliferative activity and showed great potential in cancer therapy, but the SAR (structure-activity relationship) was still confused. Here in, the SAR were comprehensively researched by summary of reported derivatives and synthesis of novel derivatives. Amongst novel derivatives, the promising compounds **A6** and **A10** exhibited potent and selective anti-proliferative activities against K562 cell line with the IC_{50} values of 5.04 and 7.08 μM respectively. The SAR was discussed around honokiol and 79 derivatives by the means of CoMFA and theoretical calculation, which provided useful suggestion for further structural optimization of honokiol derivatives.

Keywords

Honokiol; Anti-proliferative; Structure-activity relationship; 3D-QASR; Theoretical calculations

Abbreviations

SAR	Structure-activity Relationship
3D-QASR	Three-dimensional Quantitative Structure-activity Relationship
CoMFA	Comparative Molecular Field Analysis
DFT	Density Functional Theory
HOMO	Highest Occupied Molecular Orbital

LUMO Lowest Unoccupied Molecular Orbital

1. Introduction

Honokiol is a pharmacologically active natural compound isolated from the root and stem bark of *Magnolia* species [1] which has been used as traditional herbal medicine for centuries [2]. A great number of studies showed honokiol could effectively inhibit the proliferation and growth of various tumor cell lines *in vitro* [3–6] and have visible anticancer activity *in vivo* [7–10]. In addition, the combination of honokiol with other anticancer therapies could generate better therapeutic effects [11–12]. And meanwhile, the anticancer mechanisms of honokiol have also been well researched and proved [13–19].

Inspired by the good anticancer effect of honokiol, a wide diversity of honokiol derivatives have been synthesized successively over the past 15 years [20–31]. Amongst them, some honokiol derivatives displayed better anti-proliferative activity than honokiol and showed good developing potential in anticancer field. However, the SAR (structure-activity relationship) of honokiol derivatives was still confused.

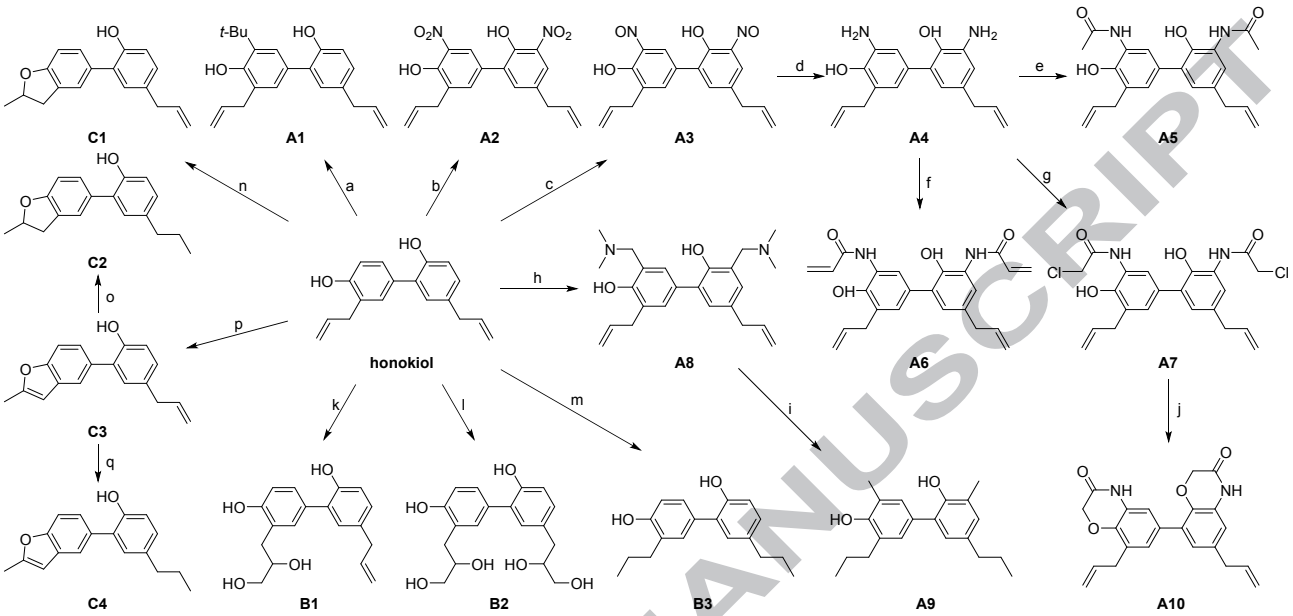
For improving the further development and application of honokiol derivatives on cancer therapy, we summarized the fragmentary and scattered researches. On this basis, a variety of honokiol derivatives (**A1**–**A10**, **B1**–**B3** and **C1**–**C4**) were designed and synthesized to fill in the blank of SAR. All the target compounds were evaluated for their anti-proliferative activities. The SAR were preliminarily analyzed with the honokiol derivatives from literature and further validated and investigated based on molecular modeling, CoMFA analysis and DFT calculation.

2. Results and Dicussion

2.1. Chemistry

Based on the existing research, seventeen honokiol derivatives were designed and synthesized (Scheme 1). Compounds **A1**–**A10** were designed to study the influence of the substituents on phenyls to anti-proliferative activity. Among them, compound **A1** was synthesized by Friedel-Crafts alkylation from honokiol. Compound **A2** and **A3** were prepared by nitration or nitrosation, respectively. Compound **A4** was produced by the reduction of **A3**. Compound **A5**–**A7** were generated by **A4**. Compound **A8** was synthesized via Mannich reaction. Compound **A9** was

synthesized through the hydrogenation of **A8**. And compound **A10** was provided by the intramolecular cyclisation of **A7**.



Scheme 1. Reagents and conditions: (a) t-BuOH, H_2SO_4(98%), 60°C, 29%; (b) HNO_3(65–68%), DCM/AcOH, 10°C, 52%; (c) $NaNO_2$, HCl(36–38%), MeCN/H_2O, r.t., 79%; (d) Zn, NH_4Cl, HOAc, EtOH/H_2O, r.t., 68%; (e) acetic anhydride, K_2CO_3, ethyl acetate, r.t., 95%; (f) acryloyl chloride, K_2CO_3, CH_2Cl_2, r.t., 48%; (g) chloroacetyl chloride, K_2CO_3, CH_2Cl_2, r.t., 53%; (h) dimethylamine(40%), HCHO(37%), MeOH, 60°C, 86%; (i) Pd/C, H_2, MeOH, reflux, 60%; (j) DMAP, NEt_3, THF, r.t., 63%; (k) i: m-CPBA (2.0 eq), CH_2Cl_2, r.t.; ii: NaOH, THF/H_2O, r.t. 38%; (l) i: m-CPBA (3.5 eq), CH_2Cl_2, r.t.; ii: NaOH, THF/H_2O, reflux. 66%; (m) Pd/C, H_2, MeOH, reflux, 94%; (n) H_2SO_4(98%), DCE, 50°C, 12%; (o) Pd/C, H_2, MeOH, reflux, 93%; (p) $PdCl_2$, NaOAc, O_2, DMA/H_2O, 60°C, 85%; (q) $NaBH_4$, $NiCl_2 \cdot 6H_2O$, EtOH, r.t., 81%.

Compounds **B1**–**B3** were designed to investigate the influence of side chains on anti-proliferative activity. Among them, compound **B1** and **B2** were prepared via the tandem process of epoxidation and hydrolyzation by controlling the dosage of m-chloroperoxybenzoic acid and the temperature of hydrolyzation according to our previous study [32]. Compound **B3** was produced through the hydrogenation of honokiol. In addition, four benzofuran-type derivatives **C1**–**C4** were synthesized respectively according to our previous research [33].

2.2. Anti-proliferative activity of target compounds

The anti-proliferative activities of honokiol derivatives against K562 (human myelogenous

leukemia cells), HepG2 (human hepatoblastoma cells) and A549 (human lung carcinoma cells) tumor cell lines were evaluated by MTT assay. The results were described in IC_{50} (concentration required for 50% inhibition) and presented in Table 1.

Table 1. IC_{50} values of honokiol and its derivatives against HepG2, A549 and K562 cell lines

Compd.	IC_{50} (μM)		
	K562	A549	HepG2
honokiol	23.91 ± 4.0	35.41 ± 5.2	34.30 ± 3.4
A1	32.55 ± 1.4	25.71 ± 4.5	31.10 ± 3.5
A2	>128	>128	>128
A3	>128	>128	>128
A4	>128	>128	>128
A5	>128	>128	>128
A6	5.04 ± 1.7	16.57 ± 3.7	19.13 ± 2.4
A7	21.55 ± 1.7	29.32 ± 7.2	19.11 ± 1.3
A8	31.57 ± 7.1	60.80 ± 9.8	47.46 ± 5.9
A9	26.25 ± 2.1	29.23 ± 4.2	34.54 ± 6.2
A10	7.08 ± 1.6	37.00 ± 2.2	27.39 ± 6.9
B1	99.96 ± 3.4	90.37 ± 4.7	25.33 ± 3.5
B2	>128	>128	>128
B3	18.19 ± 5.5	30.35 ± 0.4	30.76 ± 2.9
C1	126.2 ± 12.5	115.5 ± 2.0	125.6 ± 2.2
C2	72.86 ± 4.9	96.11 ± 7.1	121.6 ± 2.5
C3	67.87 ± 4.3	71.55 ± 1.9	107.2 ± 12.7
C4	73.92 ± 3.3	61.93 ± 2.7	88.27 ± 8.0

It is observed that the substituents on phenyls had a significant influence on the anti-proliferative activity. Several compounds exhibited more potent anti-proliferative activity than honokiol. Among them, compound **A6** and **A10** showed excellent inhibitory effect against K562 cell line with the IC_{50} values of 5.04 and 7.08 μM, respectively. The side chains also made a difference, as compound **B3** exhibited higher activity than those of honokiol, **B1** and **B2**. After change the skeleton, benzofuran-type derivatives **C1–C4** showed low anti-proliferative activity. The structure-activity relationship will be detailedly discussed below with reported honokiol derivatives.

Low selectivity was a common and severe problem for cancer chemotherapy. To some traditional anticancer drugs, human normal cells were even more sensitive than tumor cells [34]. For evaluate

the potential clinical value of promising compounds, we studied the selectivity of promising compounds between tumor cells and normal cells by testing the anti-proliferative activities against human umbilical vein endothelial cell (HUVEC). As shown in Table 2, the selectivities of promising compounds **A6** and **A10** were 11.47 and 11.59 respectively, which were much higher than that of honokiol. It meant that compounds **A6** and **A10** were relatively less toxic for normal cells and could specifically inhibited the proliferation of K562 tumor cells. It's also indicated that derivatives may have different mechanisms of action in comparison to honokiol. For example, honokiol is a Sirt3 activator and NFkB inhibitor [35–37], but the derivatives may have different effect on Sirt3 and NFkB, or act through other pathways, in order to selectively inhibit the proliferation of tumor cells. Further studies about mechanisms of derivatives are ongoing.

Table 2. The selectivity of anti-proliferative activity of promising compounds.

Compd.	IC_{50} (μM)		Selectivity [a]
	K562	HUVEC	
honokiol	23.91	52.6 [b]	2.20
A6	5.04	57.79	11.47
A10	7.08	82.06	11.59

[a] Selectivity is defined as IC_{50} (HUVEC) / IC_{50} (K562)

[b] Data was cited from ref. 23

2.3. Preliminary SAR of honokiol derivatives

The Preliminary SAR of anti-proliferative activity of honokiol derivatives was summarized and discussed in Table S1-S5 of Supporting Information, including 17 compounds of this article (**A1**–**A10**, **B1**–**B3** & **C1**–**C4**) and 62 reported honokiol derivatives (**1**–**62**) (Fig. 1) [20–30]. It's suggested that the hydrophobic side chain and free phenolic hydroxyl were essential for anti-proliferative activity, while the positions of phenolic hydroxyls had little influence. The substituents on phenyl will adjust the activity, and the restructuring of skeleton may cause surprising results. In addition, we found the log*P* value could be used as a significant parameter to predict the activity and design new compounds.

2.4. 3D-QSAR analysis

As the target compounds had more prominent activity and developing potential against K562 tumor cell lines, the 3D-QSAR of the anti-proliferative activity against K562 was investigated by

using CoMFA. For increasing sample size and obtaining a more credible model, compounds with related IC_{50} values against K562 cell lines in the reference [27] were also selected to establish the CoMFA. The predictive biological activity versus the experimental biological activity were plotted in Fig. S1 of Supporting Information.

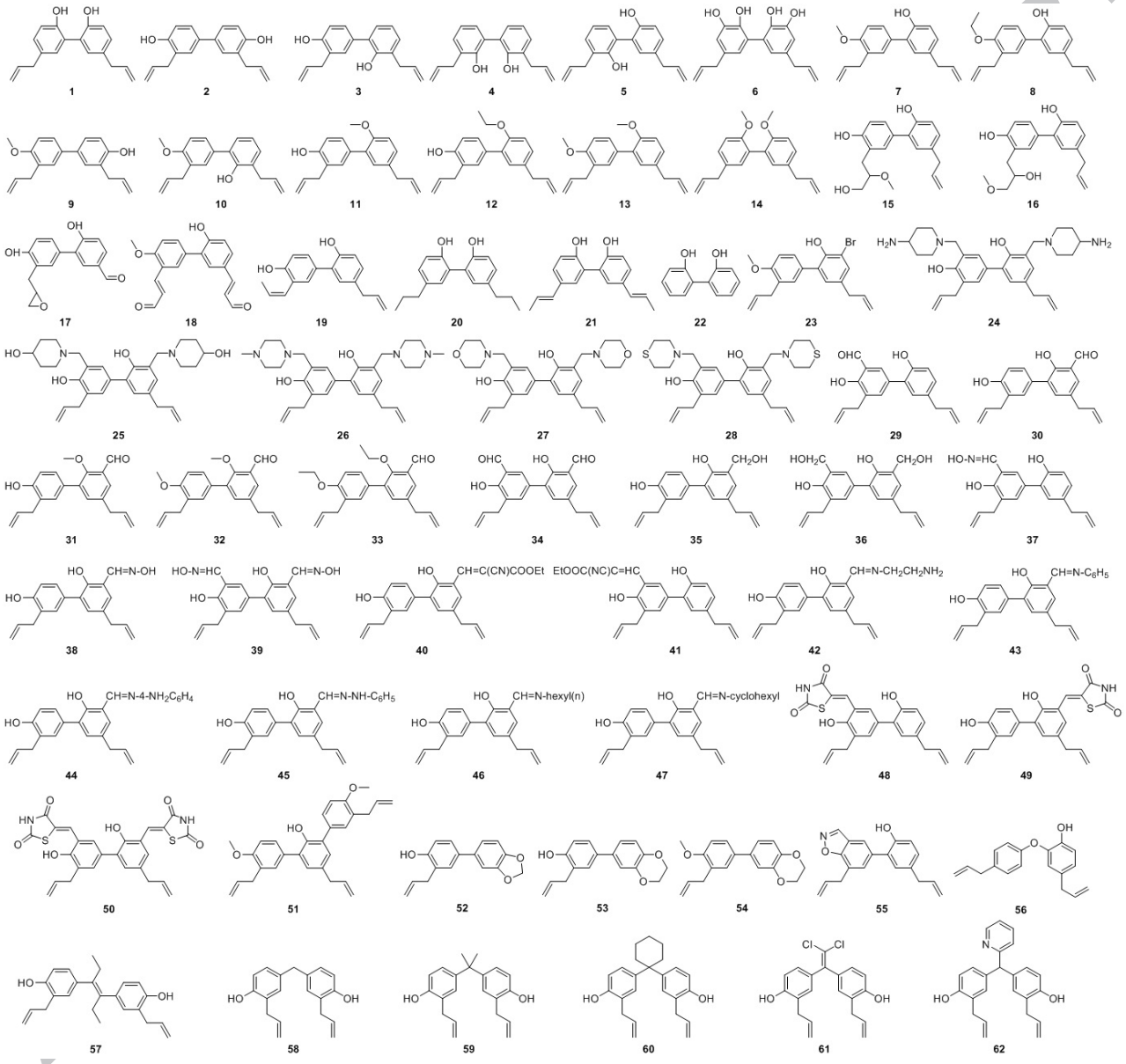


Fig. 1. Reported honokiol derivatives with anti-proliferative activity

The alignment of compounds in the training set and 3D contour maps for CoMFA were shown in Fig. 2a, in which the biphenyl structure in the target compounds was selected as a common skeletal structure for alignment. Compound **A6**, the most active compound, was used as the template to illustrate the structure-activity relationships (Fig. 2b). The 3D contour maps for CoMFA were shown in Fig. 2c and Fig. 2d, respectively. In Fig. 2c, the steric field contours are represented with different

colors: the green color on the substituted group of 5-position and 5'-position means a bulky group here would be favorable for higher anti-proliferative activity, while the yellow color on the substituted group of 3-position and 5'-position means oppositely. This is in agreement with the actual experimental data: For example, compounds **A6** and **A10** have higher anti-proliferative activity with a bulky group at 5-position while compounds **B1** and **47** have lower anti-proliferative activity with a small-sized group at 5-position. The electrostatic contour plot is shown in Fig. 1d and displayed in distinguishable colors: Blue means an increase in the positive charge will lead to an increase in the activity, while the red contour defines in the opposite. Hence, the target compounds bearing an electron-withdrawing group on the biphenyls ring or an electron-donating group near the 5'-position displayed higher activity. These results provided useful information for further optimization of honokiol derivatives.

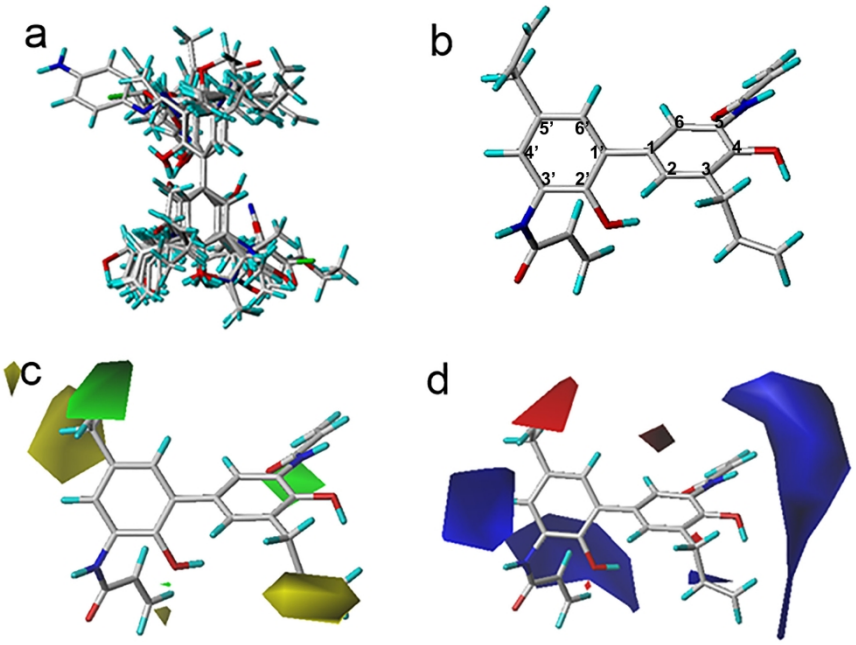


Fig. 2. (a) Superposition modes of compounds. (b) The structure of template molecule **A6**. (c) Steric map from the CoMFA model. (d) Electrostatic map from the CoMFA model.

2.5. Theoretical calculation

According to the frontier molecular orbital theory and our recent study [38], HOMO has the priority to provide electrons, while LUMO accept electrons in the first place [39]. These two frontier orbitals are the most important quantum-chemical descriptors that affect the bioactivity of compounds [40]. Therefore, by means of DFT/B3LYP, we calculated the frontier molecular orbitals

of representative compounds **A6**, **A10**, **B3** and honokiol that have different biological activities, respectively. From Fig. 3, it was observed that the HOMO of honokiol was mainly located on the benzene ring α while the HOMO of the most active compound **A6** was mainly located on the oxygen atoms of the amide group attached to the ring α; The LUMO of honokiol was mainly located on the benzene ring β while the LUMO of the compound **A6** was mainly located on the carbon-oxygen double bond of the amide group attached to the ring β. Hence, there were striking differences between the frontier molecular orbitals of honokiol and compound **A6** and this may help to explain the difference in the activity of them.

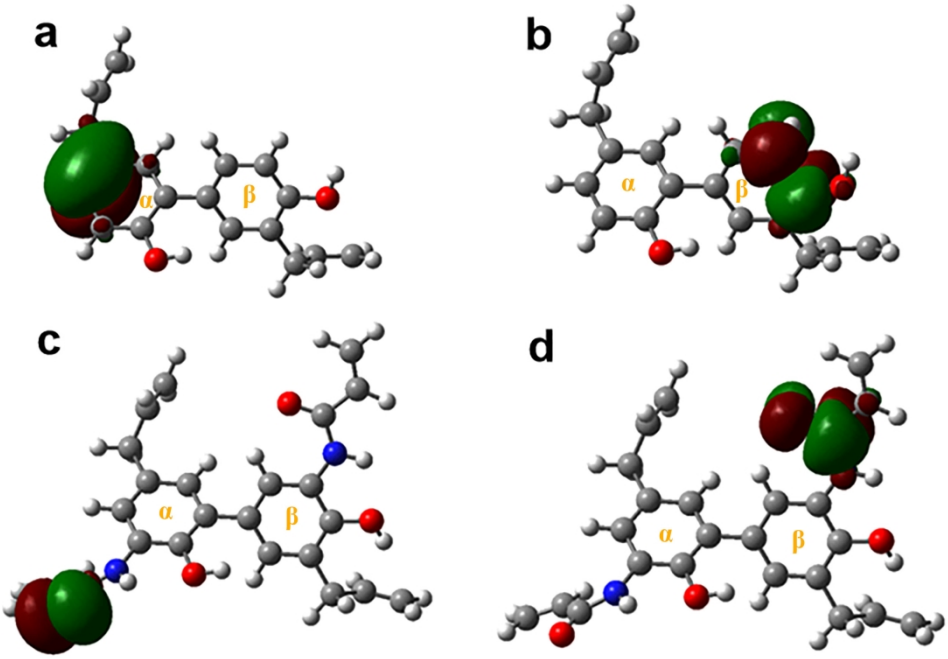


Fig. 3. Frontier molecular orbitals of honokiol: (a) HOMO; (b) LUMO, and compound **A6**: (c) HOMO; (d) LUMO.

In addition, compounds **B3** was obtained by reducing the double bonds of two allyl groups of honokiol. As shown in Table 3, comparing to the orbital energy of the honokiol, we found that the existence of a double bond helped to decrease the LUMO orbital energy level. A similar phenomenon was also clearly seen in the orbital energy levels of compounds **A10** and **A6**, that is, the introduction of double bonds or the addition of conjugate system in 3-position and 4-position can reduce the LUMO orbital energy level of the target compounds, which may cause the improvement of corresponding biological activity. Therefore, considering both Table 3 and Fig. 2, it's not hard to draw a conclusion that increasing the volume of the substituent at 5'-position and meanwhile increasing the conjugate architecture to a certain degree may play a key role in further optimization

of honokiol derivatives. According to Fig. 4, the charges for both oxygen atoms of the amide groups in ESP mapping are found to be negative, which indicates the oxygen atoms may have some interactions with the receptor. Hence, it is quite valuable to improve anti-proliferative activity against K562 by introducing amide groups into the structure of honokiol.

Table 3. The molecular frontier orbital energy of some representative compounds.

DFT	**B3**	**honokiol**	**A10**	**A6**
E_{HOMO} / Hartree [α]	−0.22593	−0.23055	−0.24585	−0.22459
E_{LUMO} / Hartree	0.03426	0.02768	0.01949	0.01579
ΔE [β] / Hartree	0.26019	0.25823	0.26534	0.24038

[α] $\Delta E = E_{LUMO}-E_{HOMO}$; [β] 1 Hartree = 4.35974417×10^{-18} J = 27.2113845 eV.

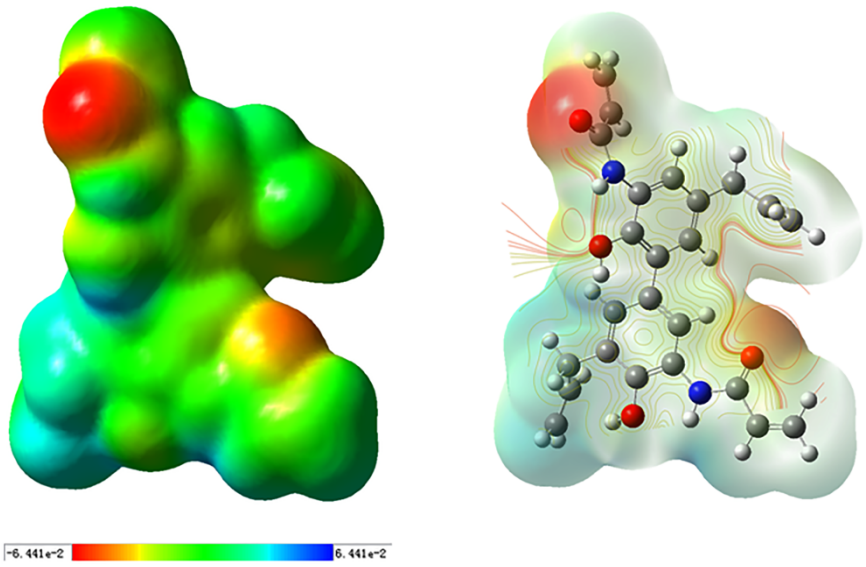


Fig. 4. ESP mapping of compound **A6**.

3. Conclusions

In conclusion, 17 honokiol derivatives were synthesized and evaluated for their anti-proliferative activity against HepG2, A549 and K562 cell lines. Compound **A6** and **A10** displayed the best anti-proliferative activities against K562 cell line with the IC_{50} values of 5.04 and 7.08 μM, which were obviously better than honokiol. Further research showed that the promising compounds **A6** and **A10** were relatively low toxic for normal cells and had potential clinical value. The preliminary SAR was discussed with reported honokiol derivatives. It's suggested that the hydrophobic side chains and free phenolic hydroxyl were essential for anti-proliferative activity, while the positions of phenolic hydroxyls had little influence. The substituents on phenyl will adjust the activity, and the restructuring of skeleton may cause surprising results. In addition, the log*P* value could be

considered as a significant parameter to predict the activity and design new compounds. Furthermore, the 3D-QSAR model and theoretical calculation results also provided useful suggestion which was given within each section. The results of this research will promote the development of honokiol derivatives in antitumor field and will also contribute to explore other biological activities.

4. Experimental

4.1. Chemistry

4.1.1. General methods and materials

All the reagents were commercially available and used directly without further purification. Melting points were determined on an X-4 binocular microscope melting point apparatus (Beijing Taike Instruments Co., Ltd., Beijing, China). ^{1}H and ^{13}C NMR spectra were recorded on a Bruker-400 (Bruker, Karlsruhe, Switzerland), using tetramethylsilane (TMS) as the internal standard and chemical shifts (δ) were expressed in ppm. Mass spectra were obtained by an Agilent 1100 series LC-MS (Agilent Technologies Inc., Santa Clara, America). Elemental analyses were performed on a Vario EL III (Elementar Analysensysteme GmbH, Langenselbold, Germany).

4.1.2. Synthesis of title compounds

Synthesis procedures and original spectra of all target compounds were provided in Supporting Information.

4.2. Biological Assays

4.2.1. Cell culture

The A549, K562, HepG2 and HUVEC cells were obtained from Institute of Cell Biology, Chinese Academy of Science (Shanghai China) and cultured in RPMI-1640 medium (Gibco; Thermo Fisher Scientifc, Inc., Waltham, MA, USA) supplemented with 10% fetal bovine serum (Gibco; Thermo Fisher Scientifc, Inc.) and 100 U/mL penicillin-streptomycin at 37 °C in incubator with 5% CO_2 /95% air atmosphere.

4.2.2. Anti-Proliferation Assay

The anti-proliferative activities of target compounds were evaluated by typical MTT assay or MTS assay according to our previous method [41,42]. The tumor cells were incubated with test compounds for 48 h. The IC_{50} (the concentration required for 50% inhibition) was calculated by the Logit method. The data are representative of 3 independent experiments.

4.3. Calculation methods

4.3.1. 3D-QSAR Model

The 3D structures of compounds were built and minimized by using SYBYL 7.3 and the CoMFA studies were carried out with the QSAR model of Sybyl. Each structure was fully geometry optimized using a conjugate gradient procedure based on the TRIPOS force field and Gasteiger and Hückel charges. Compounds without IC_{50} values didn't participate in the modeling. For establishing a more credible model, the data of compounds **A8**, **B3** and **C1** were removed, since compared to other compounds they have larger relative deviation, and along with other compounds they couldn't give a satisfying computational result.

The "leave-one-out" (LOO) cross-validation method was applied to determine the optimum number of partial least-squares (PLS) components. The leave-one-out q^2 value is 0.563 when the number of components is 4, indicating that the model is reliable. The non-cross-validated r^2 value is 0.974, with a standard error of estimate of 0.061 and an F value of 147.169. The steric and electrostatic contributions are 70.5% and 29.5%, respectively.

4.3.2. Theoretical calculation

Theoretical calculations carried out at the DFT-B3LYP/6-31G(d,p) [43,44] level and the full geometry optimization carried out using the 6-31G(d,p) basis set were implemented using the Gaussian 09 software [45]. Vibration analysis showed that the optimized structures were in accordance with the minimum points on the potential energy surfaces. All the convergent precisions were the system default values, and all the calculations were carried out on Xeon E5 server.

The oil-water partition coefficients (Log*P*) were calculated from online server: http://www.molinspiration.com/cgi-bin/properties.

Acknowlegement

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Graphical Abstract

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