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Research Article

Synthesis and cytotoxicity of substituted aromatic curcuminoids against human oral epidermal carcinoma-KB cell line

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ABSTRACT

Introduction: The survival rate of oral cancer, like other types of cancers, has not been improved regardless of the early diagnosis and the introduction of advanced therapies. Treatment for oral cancer includes surgery, radiation therapy, and chemotherapy. However, the effectiveness has been limited due to recurrence and undesirable side effects. Metabolites from plant sources have been shown to be relatively less toxic and thus are considered as potential anti-cancer agents. Interestingly, curcumin isolated from the rhizome of *Curcuma longa* L. possesses broad-spectrum bioactivities. We focused on the synthesis of curcumin-based analogs bearing -OH/-OCH_3/-F groups on the phenyl rings in our continuous efforts to search for curcumin-based anti-cancer agents. The synthesized compounds were subsequently evaluated for the cytotoxic activities against KB cancer cell line (an epidermal carcinoma of the mouth).

Methods: The desired curcuminoids were synthesized via aldol reactions between benzaldehyde derivatives and pentane-2,4-dione using *n*-butylamine as a catalyst. Structures were distinguished by NMR and MS spectra. The cytotoxic activity against KB was determined through the half-maximal inhibitory concentration (IC_{50}, μM).

Results: Six curcumin analogs (**1**-**6**) were successfully synthesized in a yield of 48-76%. The 3-hydroxy/fluoro curcumin analogs (**3**, IC_{50} = 15.61 $\pm$ 0.13 μM; **6**, IC_{50} = 22.65 $\pm$ 1.76 μM) exhibited better anti-cancer activities when compared to curcumin (**1**, IC_{50} = 33.35 $\pm$ 2.66 μM), whereas the *para*-fluoro substitution patterns displayed lower inhibitory activities (**4**, **5**) against KB cancer cell line.

Conclusions: The synthetic yields are dependent on the position and nature of substituents in aromatic rings. The presence of electron-donating groups gives products (**1**-**3**) in lower yields when compared to those (**4-6**) prepared from fluorinated benzaldehydes as starting materials. The curcuminoids bearing -OH groups at *para*-positions in aromatic rings (**1**, **2**) can be responsible for better inhibition of cell growth, whereas the fluoro-substituted compounds (**4**, **5**) make a negative contribution to inhibitory activity. Furthermore, the contributions -OH/-F groups at *meta*-position in aromatic rings of (**3**, **6**) on the cytotoxicity against KB are remarkable and firstly reported in our findings.

Key words: Curcumin analogs, anti-cancer activity, aldol condensation, KB cancer cell line

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INTRODUCTION

KB cell line has been known to be a subline of the KERATIN-forming tumor cell line HeLa and was originally derived from an epidermal carcinoma of the mouth[1]. Oral cancer, known as lip, tongue and mouth cancers, is a serious and growing problem with more than 350,000 cases worldwide and about half of the patients died from it[2]. Despite the early diagnosis and the introduction of advanced therapies, the survival rate of oral cancer patients has not been improved[3]. The conventional treatments for oral cancer involving primary surgery followed by radiotherapy and/or chemotherapy are limited in effectiveness, recurrence, and undesirable side effects. In recent years, there has been a global trend toward natural products extracted from plant sources. Several phytochemicals have been selective, potent, and relatively less toxic and thus are considered potential anti-cancer agents in clinical cancer chemotherapy[4].

Curcumin (**1**), a constituent of turmeric powder derived from the rhizome of *C. longa*, is an attractive compound with broad-spectrum capacities including anti-oxidant[5], anti-inflammatory[6], and anti-tumour[7] activities. In particular, many studies reported that curcumin exhibited anti-cancer activity in a wide range of human cancers[8–15]. In addition, curcumin is pharmacologically safe as large quantities of curcumin, up to 10 g per day, can be consumed without inflicting toxicity[16]. However, despite the multiple potentials of curcumin, its clinical applications until now are limited due to its poor solubility in water, low chemical stability, and poor oral bioavail-

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ability[17]. To overcome these limitations, chemical modification of the curcumin structure is one of the promising approaches to explore curcumin-based analogs, which improve the therapeutic profile of the mother compound[8–12]. Structure-activity relationship (SAR) analysis on curcumin analogs revealed that the aromatic ring and its substituents are necessary for biological activities[10–13]. In view of this, benzaldehyde analogs bearing various functional groups in the phenyl ring were selected as starting materials to condense with pentane-2,4-dione under basic conditions to afford analogs of curcumin[10–13,18,19]. Within this framework, curcumin analogs containing hydroxy/methoxy/fluorine groups on phenyl rings were synthesized in our work, and their *in vitro* anticancer activities against oral cancer cells (KB) were assessed.

METHODS

Synthetic procedure for curcuminoids (1-6)

The published procedurewas used to carry out the synthetic procedure of curcuminoids (**1-6**) bearing various substituents on aromatic rings[12,13,18,19] (Figure 1). A mixture of boron oxide (10.0 mmol) and pentane-2,4-dione (10.0 mmol) in ethyl acetate (20.0 mL) was stirred at 70 °C for 1 h in a 100-mL two-neck round-bottom flask to yield the solution of acetylacetone-borate complex. Benzaldehyde (20.0 mmol) and tri-*n*-butyl borate (40.0 mmol) was next added, and the resulting mixture was stirred for 30 min. While stirring, *n*-butylamine (4.0 mmol) was added dropwise over 30 min. The resulting mixture was stirred and heated at 70 °C for 4-4.5 h (monitored by TLC using HEX/EA = 3/2 for **1-3**; 95/5 for **4**, **6**; 9/1 for **5** as eluent). The reaction mixture was treated with an aqueous HCl solution (0.1 N, 20 mL) with stirring for 1 h, then extracted with DCM (40 mL x 3). The combined organic layers were dried over Na_2SO_4 concentrated in vacuo. The residue was purified by flash column chromatography (SiO_2, eluent: HEX/EA = 20/1 to 7/3) to afford the pure products. The eluates from flask CC were fractionated by TLC using a mixture of HEX/EA as eluent.

Analytical methods

Nuclear magnetic resonance (NMR) spectra of curcuminoids (**1-6**) were recorded on a Bruker Avance (500 MHz (^{1}H), 125 MHz (^{13}C)). Mass spectrometry (MS) measurements were performed on an AGILENT 1200 series LC-MSD. Sample spots on TLC were detected by UV light at λ = 254 and 365 nm. Melting points (m.p) of pure products were determined by M5000 apparatus with a heating rate of 2.0 ^{o}C/min.

Cytotoxicity assay against KB cancer cell line

Curcuminoids (**1-6**) were tested *in vitro* for their cytotoxic activities against the KB cancer cell line. The assay was carried out at the Laboratory of Applied Biochemistry, Institute of Chemistry, Vietnam Academy of Science and Technology using a MTT method (the assay procedure can be found in the Supporting Information).

RESULTS

Target curcuminoids (**1-6**) were synthesized following the published procedure from literature in 48-76% yields[12,13,18,19] (Table 1). Chemical structures were elucidated by NMR and MS spectra (see the Supporting Information for ^{1}H, ^{13}C-NMR, HSQC, and MS spectra). All synthesized compounds were evaluated for cytotoxicity against human oral epidermal carcinoma-KB cell line using MTT method. The inhibitory activities were determined through their half-maximal inhibitory concentration (IC_{50}, μM) (Table 1).

(1*E*,4*Z*,6*E*) - 5-hydroxy-1,7 - bis(4-hydroxy-3-methoxyphenyl)hepta - 1,4,6-trien-3-one (1):

Yield 53% (1.95 g), red-orange solid, $C_{21}H_{20}O_6$ [368.13 g/mol]; R_f = 0.31 (HEX/EA = 3/2); m.p. 182.3 °C ^{1}H-NMR (500 MHz, $CDCl_3$): δ (ppm) = 3.96 (*s*, OCH_3, 3H), 3.95 (*s*, OCH_3, 3H), 6.42 (*s*, H_4, 1H), 6.83 (*d*, H_1, ^3J (H,H) = 16.0 Hz, 1H); 6.93 (*d*, $H_{5'}$, ^3J (H,H) = 8.0 Hz, 1H), 6.94 (*d*, $H_{5''}$, ^3J (H,H) = 8.0 Hz, 1H), 6.99 (*d*, H_7, ^3J (H,H) = 16.5 Hz, 1H), 7.02-7.08 ($H_{2',2'',6',6''}$, 4H), 7.11 (*d*, H_2, ^3J (H,H) = 16.5 Hz, 1H), 7.29 (*d*, H_6, ^{3} *J* (H,H) = 16.5 Hz, 1H). ^{13}C-NMR (125 MHz, $CDCl_3$): δ (ppm) = 55.9 (OCH_3), 55.9 (OCH_3), 97.6 (C_4), 108.2 ($C_{2'}$), 108.8 ($C_{2''}$), 110.9 ($C_{5'}$), 113.8 ($C_{5''}$), 114.6 ($C_{6'}$), 114.8 ($C_{6''}$), 121.5 (C_2), 121.6 (C_6), 128.2 ($C_{1'}$), 128.5 ($C_{1''}$), 134.8 (C_1), 135.6 (C_7), 146.7-146.9 ($C_{4',4'',3',3''}$, 4C), 162.1 (C_5), 168.5 (C_4). ESI-MS *m/z* calc for $[M+H]^+$: 369.14; found: 368.90.

(1 *E*,4 *Z* ,6 *E*)-5-hydroxy-1,7-bis(4-hydroxyphenyl) hepta- 1,4,6 -trien-3-one (2):

Yield 48% (1.48 g), orange solid, $C_{19}H_{16}O_4$ [308.10 g/mol]; R_f = 0.45 (HEX/EA = 3/2); m.p. 213.5 °C; ^{1}H-NMR (500 MHz, DMSO-d_6): δ (ppm) = 6.04 (*s*, H_4, 1H), 6.68 (*d*, $H_{2,6}$, ^3J(H,H) = 16.0 Hz, 2H), 6.82 (*d*, $H_{3',3'',5',5''}$, ^{3} *J*(H,H) = 8.5 Hz, 4H), 7.52-7.57 ($H_{1,7,2',2'',6',6''}$, 6H), 7.95 (*s*, C=C-OH, 1H), 10.02 (*s*, C_6H_4-OH, 2H). ^{13}C-NMR (125 MHz, DMSO-d_6): δ (ppm) = 100.8 (C_4), 115.8 ($C_{3',3'',5',5''}$), 120.7 ($C_{2,6}$), 125.8 ($C_{1',1''}$), 130.2 ($C_{2',2'',6',6''}$), 140.3 ($C_{1,7}$), 159.7-162.3 ($C_{4',4''}$), 183.1 ($C_{3,5}$). ESI-MS *m/z* calc for $[M+H]^+$: 309.11; found: 308.90.

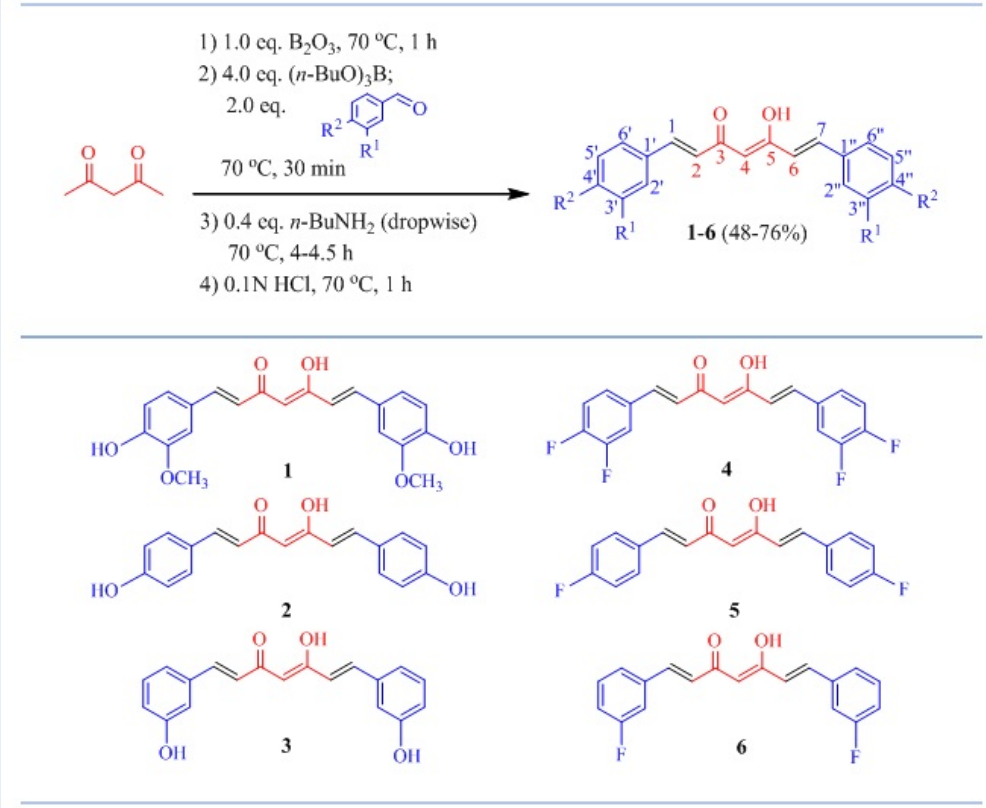

Figure 1: The synthetic procedure and structures of curcuminoids (**1-6**).

Table 1: Reaction time, isolated yields, and IC_{50} (μM) values against KB cancer cell line of curcuminoids (1-6).

Compound	Time (h)	Yield (%)	$IC_{50} \pm SD^{[a]}$ (μM)
1	4.5	53	33.35 ± 2.66
2	4	48	43.94 ± 3.18
3	4	55	15.61 ± 0.13
4	4	72	66.36 ± 5.80
5	4	66	366.19 ± 28.48
6	4	76	22.65 ± 1.76

[a] MTT viability assay after 72 h, n = 3, mean ± SD.

(1 *E*,4 *Z* ,6 *E*)-5-hydroxy-1,7-bis(3-hydroxyphenyl) hepta- 1,4,6 -trien-3-one (3):

Yield 55% (1.69 g), yellow solid, $C_{19}H_{16}O_4$ [308.10 g/mol]; R_f = 0.43 (HEX/EA = 3/2); m.p. 185.5 °C; ^{1}H-NMR (500 MHz, DMSO-d_6): δ (ppm) = 6.22 (*s*, H_4, 1H), 6.81 (*s*, $H_{2,6}$, 2H), 6.84 (*m*, $H_{4',4''}$, 2H), 7.07 (*d*, $H_{2',2''}$, ^3J(H,H) = 1.5 Hz, 2H), 7.15 (*d*, $H_{6',6''}$, ^3J(H,H) = 7.5 Hz, 2H), 7.24 (*dd*, $H_{5',5''}$, ^3J(H,H) = 7.5 Hz, ^3J(H,H) = 7.5 Hz, 2H), 7.56 (*d*, $H_{1,7}$, ^3J(H,H) = 16.0 Hz, 2H), 9.63 (*s*, C_6H_4-OH, 2H). ^{13}C-NMR (125 MHz, DMSO-d_6): δ (ppm) = 100.6 (C_4), 114.5 ($C_{2',2''}$), 117.5 ($C_{4',4''}$), 119.3 ($C_{6',6''}$), 124.1 ($C_{2,6}$), 129.9 ($C_{5',5''}$), 135.9 ($C_{1',1''}$), 140.5 ($C_{1,7}$), 157.7 ($C_{3',3''}$), 183.1 ($C_{3,5}$). ESI-MS *m/z* calc for $[M+H]^+$: 309.11; found: 308.80.

(1*E*,4*Z*,6*E*)- 1,7 -bis(3,4-difluorophenyl)- 5 -hydroxyhepta- 1,4,6 -trien-3-one (4):

Yield 72% (2.50 g), yellow solid, $C_{19}H_{12}F_4O_2$ [348.08 g/mol]; R_f = 0.48 (HEX/EA = 95/5); m.p. 212.3 °C; ^{1}H-NMR (500 MHz, $CDCl_3$): δ (ppm) = 5.81 (, H_4, 1H), 6.52 (*d*, $H_{2,6}$, ^3J (H,H) = 16.0 Hz, 2H); 7.19 (*m*, $H_{5',5''}$, 2H), 7.27 (*m*, $H_{2',2''}$, 2H), 7.37 (*m*, $H_{6',6''}$, 2H),

7.57 (*d*, $H_{1,7}$, ^3J (H,H) = 16.0 Hz, 2H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ (ppm) = 102.1 (C_4), 116.1-117.9 ($C_{5',5'',6',6''}$), 124.9 ($C_{2,6}$), 124.9 ($C_{2',2''}$), 132.2 ($C_{1',1''}$), 138.5 ($C_{1,7}$), 150.6 (*d*, $C_{4'}$, ^1J (C,F) = 247.5 Hz), 150.7 (*d*, $C_{4''}$, ^1J (C,F) = 248.7 Hz), 151.3 (*d*, $C_{3'}$, ^1J (C,F) = 251.2 Hz), 151.4 (*d*, $C_{3''}$, ^1J (C,F) = 251.2 Hz), 182.8 ($C_{3,5}$); ESI-MS *m/z* calc for $[M+H]^+$: 349.09; found: 348.80.

(1*E*,4*Z*,6*E*)- 1,7 -bis(4-fluorophenyl)- 5 -hydroxyhepta- 1,4,6 -trien-3-one (5):

Yield 66% (2.06 g), yellow solid, $C_{19}H_{14}F_2O_2$ [312.10 g/mol]; R_f = 0.34 (HEX/EA = 9/1); m.p. 185.7 °C; ^{1}H-NMR (500 MHz, $CDCl_3$): δ (ppm) = 5.81 (*s*, H_4, 1H), 6.54 (*d*, $H_{2,6}$, ^3J(H,H) = 16.0 Hz, 2H), 7.08 (*dd*, $H_{3',3'',5'.5''}$, ^3J(H,H) = 8.5 Hz,^3J(H,H) = 2.0 Hz, 4H), 7.25 (*s*, C=C-OH, 1H), 7.54 (*m*, $H_{2',2'',6',6''}$, 4H), 7.62 (*d*, $H_{1,7}$,^{3} J(H,H) = 16.0 Hz, 2H).^{13}C-NMR (125 MHz, $CDCl_3$): δ (ppm) = 101.7 (C_4), 116.0-116.2 ($C_{3',3'',5'.5''}$), 123.7-123.8 ($C_{2,6}$), 129.9-129.9 ($C_{2',2'',6',6''}$), 131.2-131.3 ($C_{1',1''}$), 139.4 ($C_{1,7}$), 162.8-164.8 ($C_{4'.4''}$), 183.1 ($C_{3,5}$). ESI-MS *m/z* calc for $[M+H]^+$: 313.11; found: 312.9.

(1*E*,4*Z*,6*E*)- 1,7 -bis(3-fluorophenyl)- 5 -hydroxyhepta- 1,4,6 -trien-3-one (6):

Yield 76% (2.37 g) yellow-orange solid, $C_{19}H_{14}F_2O_2$ [312.10 g/mol]; R_f = 0.49 (HEX/EA = 95/5); m.p. 138.5 °C; ^{1}H-NMR (500 MHz, $CDCl_3$): δ (ppm) = 5.85 (*s*, H_4, 1H), 6.61 (*d*, $H_{2,6}$, ^3J(H,H) = 15.5 Hz, 2H), 7.07 (*m*, $H_{5',5''}$, 2H), 7.25 (*d*, $H_{6',6''}$, ^3J(H,H) = 8.0 Hz, 2H), 7.31 (*d*, $H_{2',2''}$, ^3J(H,H) = 8.0 Hz, 2H), 7.36 (*m*, $H_{4',4''}$, 2H), 7.62 (*d*, $H_{1,7}$, ^{3} J(H,H) = 16.0 Hz, 2H). ^{13}C-NMR (125 MHz, $CDCl_3$): δ (ppm) = 102.2 (C_4), 114.1-114.3 ($C_{4',4''}$), 116.9-117.1 ($C_{2',2''}$), 124.2-124.3 ($C_{2,6}$), 125.2 ($C_{6',6''}$), 130.4-130.5 ($C_{5',5''}$), 137.2-137.3 ($C_{1',1''}$), 139.4-139.5 ($C_{1,7}$), 162.1-164.1 ($C_{3',3''}$), 183.0 ($C_{3,5}$). ESI-MS *m/z* calc for $[M+H]^+$: 313.11; found: 312.9.

DISCUSSION

The details of the synthetic procedure of curcuminoids were discussed in literatures[12,13,17]. Generally, the synthetic yields are dependent on the nature and position of substituents on the aromatic rings of benzaldehyde analogs (Table 1). When the carbonyl group is more positively charged, the attack of an enolate as nucleophile on it becomes more accessible. The presence of the hydroxy group (-OH), an electron-donating group at *para*-position on the aromatic ring, resulted in lower isolated yields (**1**: 53%; **2**: 48%), while higher yields (**3**: 55%, **4**: 72%; **5**: 66%; **6**: 76%) were obtained when benzaldehyde derivatives containing inductively electron-withdrawing groups (*meta*-OH/-OCH_3/-F groups) were used as starting materials. Adding one more fluoro group to **6** (76%) on the *para*-position resulted in a small decrease in the yield (**4**: 72%), confirming the negative effect of the resonance electron-donating group at *para*-position on the reaction yield.

Chemical structures of the synthesized compounds were elucidated by NMR and MS spectra. The presence of a singlet signal with one proton in a range from 5.80 to 6.40 ppm in ^{1}H-NMR spectra indicates that the enol forms of products (**1**-**6**) are predominant. Furthermore, the $^3J_{H-H}$ values of ~16.0 Hz of two doublet signals between 6.50 and 7.80 ppm were indicators of *trans*-configurations in the seven-carbon chain of curcuminoid structures.

Six target compounds were tested for cytotoxicity against human oral epidermal carcinoma-KB cell line using MTT method. The curcumin derivatives showed inhibitory activities toward KB (Table 1). A better insight into the mode of action of curcumin in the oral cancer cell is pivotal for the development of new curcumin-based antitumor agents. When the KB cells were treated with curcumin, the observations of Jeon *et al.* on the nuclear morphology in cells revealed that the apoptotic cell death was attributed to the nuclear condensation and fragmentation as well as internucleosomal DNA fragmentation[14]. Considering the chemically structural characteristics, curcuminoids are classified as an *a* , -unsaturated ketone, in which the C_β is activated by the carbonyl group and it becomes electrophilic, also called a Michael acceptor center. The ability of curcumin to selectively induce apoptosis in cancer cells can be explained through the detoxification mechanism, which has received much attention among possible mechanisms to elucidate the complex nature of interactions of curcumin with biological molecules[20–23]. In that respect, the Michael acceptor center of curcumin structure is much prone to nucleophilic addition with the available –SH groups and glutathione (GSH), which can invalidate toxic agents in cells. This may lead to the cytotoxicity of curcuminoids against cancer cell lines. The removal of methoxy groups from the structure of lead compound (**1**, IC_{50} = 33.35±2.66 μM) resulted in a decrease in anti-cancer activity against KB (**2**, IC_{50} = 43.94±3.18 μM). The result suggested that the *meta*-methoxy substituent was beneficial to the cytotoxicity. It should be noted that the potency of compound **3** (IC_{50} = 15.61±0.13 μM) bearing -2-fold improved OH group at *meta*-position in the aromatic ring over curcumin (**1**). The stronger anticarcinogenic property of curcumin analogs containing substituted -OH group at *meta* or *ortho* positions compared to curcumin was reported in the literature,

but the mechanism has remained unclear[12,15,23,24]. Here, our finding indicated a similar trend when curcuminoids were assayed toward KB cancer cell line.

Curcuminoids bearing -OH groups displayed anti-cancer activities against KB higher than the fluorinated analogs (**2** > **5**, **3** > **6**). The designed 4-fluorinated curcumin analogue (**5**, IC_{50} = 366.19±28.48 μM) dramatically reduced activity in comparison with (**2**, IC_{50} = 43.94±3.18 μM). The replacement of -OH and -OCH_3 of (**1**, IC_{50} = 3.35±2.66 μM) by two fluorine atoms (**4**, IC_{50} = 66.36±5.80 μM) leads to a 2-fold reduction in anti-cancer capacity. The lower activities of (**4**, **5**) obviously resulted from the existence of fluorine atoms in the aromatic rings. The apoptotic activity of curcumin correlated closely with the formation of reactive oxygen species (ROS). Compounds (**1**) and (**2**) can lose an H-atom from the phenolic group to form phenoxyl radicals, which are stabilized by the conjugated system in their structure. The reactive free radicals are directly involved in cell apoptosis by attacking the cellular DNA strands[15,25–27]. In this context, the lower inhibitory activities of (**4**) and (**5**) can be attributed to the alteration of electronic properties of the fluorinated aromatic rings, due to which the formation of free radicals is unfavorable when compared to structures containing phenolic motifs.

In addition, the hydrophobic nature of the curcumin molecule often limits its bioavailability due to its poor absorption and penetration through the cell membrane. Fluorine substituent affects the physical properties of molecules, and aromatic fluorination always increases their lipophilicity[28]. The decreased cytotoxicity of the fluoro-substituted curcumin analogs (**4, 5**) can be due to their increased lipophilicities.

Interestingly, regardless of the presence of fluorine, the 3-fluorinated compound (**6**, IC_{50} = 22.65±1.76 μM) showed higher anticancer activity than (**1**) and (**2**). It might be concluded that the effect of the *meta*-position of -OH or -F substitution in the aromatic ring is crucial for anti-cancer activity against the KB cell line.

CONCLUSION

Six curcumin-based analogs were synthesized and evaluated for anti-cancer activities against the KB cancer cell line. The position and nature of substituents affect the isolated yields and cytotoxic activities. The synthetic yields of products containing electron-donating groups (**1**-**3**) are lower when compared to those of analogs (**4**-**6**) prepared from fluorinated benzaldehydes as starting materials. Fluorine atoms at *para* or both *para*/*meta* positions in compounds (**4, 5**) exhibited lower activities against the KB cell line than those of compounds (**1**-**3**). Structure-activity relationship analysis suggested that i) the ability of inhibitory activity of synthesized curcumin analogs might rely on detoxification mechanism. ii) The phenolic motif is responsible for better inhibition of cell growth, whereas the fluoro substituents in the aromatic ring make a negative contribution to inhibitory activity. iii) the effects of -OH/-F groups at *meta*-position in the aromatic ring of (**3**, **6**) on the cytotoxicity against KB are remarkable and firstly reported in our findings. In general, we have provided more promising results from curcumin-based agents against the KB cancer cell line.

LIST OF ABBREVIATIONS

DCM: Dichloromethane
EA: Ethyl acetate
HEX: *n*-Hexane
KB: Human oral epidermal carcinoma cell line
IC_{50}: Half-maximal inhibitory concentration
MTT: (3-(4,5-dimethylthiazol-2-yl)- 2,5 - diphenyl-tetrazolium bromide
SAR: Structure-activity relationship
NMR: Nuclear magnetic resonance
HSQC: Heteronuclear single quantum correlation
TLC: Thin layer chromatography
CC: Column chromatography
MS: Mass spectrometry
ROS: reactive oxygen species

AUTHOR CONTRIBUTIONS

Conceptualization: Hoang Minh Hao, Vo Thi Nga, and Pham Nguyen Kim Tuyen; synthesis of curcuminoids: Phan Phuoc Hoai Nhan and Hoang Minh Hao; structural assignment via NMR, MS, and analysis of cytotoxicity basing on structure: Hoang Minh Hao, Vo Thi Nga, and Pham Nguyen Kim Tuyen; writing-original draft preparation: Phan Phuoc Hoai Nhan and Hoang Minh Hao; writing-review and editing: Hoang Minh Hao. All authors have read and agreed to the published version of the manuscript.

COMPETING INTERESTS

The authors declare that they have no competing interests.

SUPPORTING INFORMATION

Chemicals used for the synthetic procedure, cytotoxicity assay, and NMR and MS spectra of curcuminoids (**1**-**6**) can be found in the Supporting Information.

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