Synthesis and Evaluation of Curcumin-Related Compounds Containing Inden-2-one for Their Effects on Human Cancer Cells

Daiying Zhou,^a Ning Ding,^c Suqing Zhao,^e Dongli Li,^e Jeremiah Van Doren,^c Yu Qian,^d Xingchuan Wei,^{*b} and Xi Zheng^{*c}

^aGuangdong Food and Drug Vocational College; Guangzhou 510520, China; ^bDepartment of Chemistry and Chemical Engineering, Guangzhou University; ^cAllan H Conney Laboratory for Research, Institute of Natural Medicinal Chemistry & Green Chemistry, Guangdong University of Technology; Guangzhou 510006, China; ^eErnest Mario School of Pharmacy, Rutgers, the State University of New Jersey; Piscataway, NJ 08854, U.S.A.; and ^dSchool of Chemistry and Chemical Engineering, South China University of Technology; Guangzhou 510640, China. Received June 26, 2014; accepted September 9, 2014

Indanones are very useful molecules as starting building blocks for the synthesis of biologically active compounds. A series of novel curcumin-related compounds containing inden-2-one were synthesized and screened for anticancer activities. The structures were confirmed by spectral data (IR, NMR, and Mass). Inhibitory effects of these compounds on the growth of prostate cancer PC-3 cells, pancreatic cancer BxPC-3 cells, colon cancer HT-29 cells, lung cancer H1299 cells and non-tumorigenic human prostate epithelial RWPE-1 cells were determined by the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay. The IC₅₀ for compound IND-4 was lower than 1 μ M in the four cancer cell lines. The present study indicates that IND-4 may have useful effects on human cancer cells.

Key words curcumin-related compound; cancer cell; inden-2-one

Curcumin isolated from turmeric: the “Golden spice,” possesses many biological properties. Numerous studies have shown that curcumin possesses multifunctional pharmacological properties including anti-oxidant activity,^{1–3)} anti-inflammatory activity^{4–6)} and anticancer activity.^{7–11)} Curcumin has been evaluated in clinical trials for the treatment of liver disease, rheumatoid arthritis, infectious diseases and cancer. Despite its safety, the clinical usefulness of curcumin is diminished by extensive first-pass metabolism, resulting in low oral bioavailability.^{12–14)} In the last decade curcumin has been greatly explored. Various synthetic analogues have been prepared and evaluated for various pharmacological activities.^{15–22)} Introduction of methoxy group on the aromatic rings of curcumin has been found to enhance its antitumor activity.²³⁾ Indan ring frameworks are ubiquitous in a large number of natural products, bioactive and pharmaceutically interesting molecules. Indanones therefore are very useful molecules as starting building blocks for the synthesis of biologically active compounds.²⁴⁾ A recent study demonstrated that curcumin-related compounds with an inden-2-one had enhanced activity and lower cytotoxicity.^{25,26)}

In the present study, seven curcumin-related compounds using inden-2-one as a linker and various substituents on the aryl rings (Chart 1) were synthesized and evaluated for their effects against four human cancer cell lines. These compounds were previously not reported except for IND-1. Results of the present study showed that some of the compounds had potent effects for inhibiting the growth of PC-3, BxPC-3, HT-29, H1299 and RWPE-1 cells.

RESULTS AND DISCUSSION

Chemistry A series of curcumin-related compounds containing inden-2-one were synthesized by coupling the appropriate substituted benzaldehyde with inden-2-one (Chart 1).

The synthesis and characterization of these compounds were not previously reported. Structures of curcumin and curcumin-related compounds containing an inden-2-one moiety are shown in Fig. 1.

Inhibitory Effects of Curcumin-Related Compounds Containing Inden-2-one toward Cultured Human Prostate, Pancreatic, Colon, Lung Cancer Cells and Non-tumorigenic Human Prostate Epithelial Cells The inhibitory effects of seven curcumin-related compounds containing inden-2-one on the growth of cultured prostate cancer PC-3 cells, pancreatic cancer BxPC-3 cells, colon cancer HT-29 cells, lung cancer cells H1299 and non-tumorigenic human prostate epithelial RWPE-1 cells were determined by using the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay. For this experiment, curcumin was evaluated as a positive control in each incubation. The inhibitory effect of curcumin toward same cell lines did not vary significantly between the different incubations. Data from all curcumin treatment in each cell line were averaged and presented in Table 1.

All compounds had stronger inhibitory effects than curcumin as determined by the MTT assay except IND-3 in lung cancer H1299 cells. Among the seven curcumin-related compounds tested, IND-4 exhibited exceptionally potent inhibitory effects on the growth of cultured PC-3, BxPC-3, HT-29 and H1299 cells. The IC₅₀ for this compound was $\leq 1 \mu$ M in all four cell lines, indicating that IND-4 was approximately 20-fold more active than curcumin. As shown in Table 1, the IC₅₀ values of all seven curcumin-related compounds ranged from 0.64 to 18.94 μ M in the four cancer cell lines studied.

When comparing the results of MTT assay in prostate cancer PC-3 and non-tumorigenic prostate epithelial RWPE-1 cells, all compounds except curcumin had lower cytotoxicity (higher IC₅₀) in RWPE-1 cells than in PC-3 cells. As shown in Table 1, the IC₅₀ values of IND-4 in RWPE-1 cells was approximately 14-fold higher than that in PC-3 cells indicating this compound is more toxic to cancer cells than to non-cancer cells.

The authors declare no conflict of interest.

* To whom correspondence should be addressed. e-mail: xing6363@126.com; xizheng@pharmacy.rutgers.edu

Chart 1. Synthesis of Curcumin-Related Compounds

Fig. 1. Structures of Curcumin and Curcumin-Related Compounds

Earlier studies on the analysis of the relationship between the structures of curcumin-related compounds and their ability to inhibit the growth of cultured cancer cells showed that the linker, the aromatic rings and steric hinderance are all very important for activity.²⁷⁾ Comparing different substituted groups on curcumin-related compounds with the same linker, we found that introduction of methoxy groups on the aromatic rings enhanced anticancer activity.²²⁾ IND-4 showed some increases in activities over the corresponding IND-1 and IND-2. For the same linker and same aromatic rings, such as IND-3 and IND-4, steric hinderance is very important for activity, IND-4 had increased activity as compared to IND-3. As

shown in Table 1, the IC_{50} values of IND-4 was approximately 12- to 19-fold more active than IND-3 in the four cancer cells, which suggests that less steric hinderance compounds may enhance their antitumor activities by having interactions with the DNA of cancer cells.

CONCLUSION

In conclusions, we found that curcumin-related compounds with an indan-2-one as the core structure had a more potent inhibitory effect on cancer cells than curcumin. Compounds IND-4 exhibited particularly potent inhibitory effects on the

Table 1. Inhibitory Effects of Curcumin and Curcumin-Related Compounds on the Growth of PC-3, Panc-1, HT-29 and H1299 Cells

Compound	IC ₅₀ (μM)				
	PC-3	BxPC-3	HT-29	H1299	RWPE-1
Curcumin	19.98±2.4	18.25±2.2	18.74±2.2	18.93±2.1	15.62±1.5
IND-1	8.30±0.9	3.12±0.4	4.17±0.5	3.39±0.4	39.26±5.1
IND-2	3.05±0.4	5.27±0.6	6.98±0.8	5.18±0.6	18.13±5.4
IND-3	10.06±1.3	14.30±1.6	12.31±1.4	18.94±2.5	18.44±1.1
IND-4	0.64±0.1	0.99±0.1	0.98±0.1	0.95±0.1	9.12±0.4
IND-5	9.6±1.1	4.62±0.5	14.47±1.4	8.83±0.9	29.23±3.9
IND-6	2.46±0.3	1.72±0.2	3.65±0.4	2.95±0.3	4.2±0.5
IND-7	8.12±0.9	7.18±0.8	7.96±0.7	6.00±0.7	27.66±2.3

Human prostate cancer PC-3, pancreas cancer BxPC-3, colon cancer HT-29, Lung cancer cells H1299 and non-tumorigenic human prostate epithelial RWPE-1 cells were seeded at a density of 2×10^4 cells/mL of medium in 96-well plates (0.2 mL/well) and incubated for 24 h. The cells were then treated with various concentrations (0.2–50 μM) of the different compounds for 72 h. Effects of the different compounds on the growth of PC-3, BxPC-3, HT-29, H1299 and RWPE-1 cells were determined by the MTT assay.

growth of cultured prostate cancer PC-3 cells, pancreatic cancer BxPC-3 cells, lung cancer H1299 and colon cancer HT-29 cells. The IC₅₀ for IND-4 in all four cell lines was less than 1 μM. From preliminary studies of structure–activity relationships, it was found that indane as a core structure and methoxy groups in the aromatic rings may be promising lead structures for new agents with potent anticancer activity.

MATERIALS AND METHODS

General Procedures Melting points were determined on a Yanagimoto micro melting apparatus and were uncorrected. The ¹H-NMR spectra were measured on a Varian Gemini-2000 spectrometer using dimethyl sulfoxide (DMSO) as solvent unless otherwise specified. Chemical shifts for ¹H-NMR (400 MHz) and ¹³C-NMR (101 MHz) were expressed in ppm units with tetramethylsilane (TMS) as an internal standard. Multiplicities were recorded as s (singlet), brs (broad singlet), d (doublet), t (triplet), q (quartet), and m (multiplet). Mass spectra were obtained on an LC-MS-2010A spectrometer with electrospray ionization (ESI). Elemental analyses were performed on an elemental analyser (Vario El). Thin-layer chromatography (TLC) was performed on Merck silica gel plates (DC-60 F254). Curcumin was isolated from the extract of *Curcuma longa* LINN according to a previous report.²⁶⁾ All reagents (highest grade) were used as received unless otherwise stated.

Synthesis of Curcumin-Related Compounds A total of 7 curcumin-related compounds containing inden-2-one were synthesized as previously described with modification.^{27,28)} A mixture of the appropriate aldehyde (0.012 mol) and the inden-2-one (0.004 mol) was dissolved in glacial acetic acid saturated with anhydrous hydrogen chloride and heated in a water bath at 40°C for 3 h, the mixture was treated with cold water and filtered. The solid obtained was then washed and dried. The crude product was recrystallized from appropriate solvents (methanol or ethanol). Curcumin was isolated from the extract of *Curcuma longa* LINN according to a previous report.²⁸⁾

(1*E*,3*E*)-1,3-Bis(4-methoxybenzylidene)-1,3-dihydroinden-2-one (**IND-1**) This compound was characterized earlier as PMIND in ref. 25.

(1*E*,3*E*)-1,3-Bis(3,4-dimethoxybenzylidene)-1,3-dihydroinden-2-one (**IND-2**) Yellow powder. Yield 85%. mp 252.6–254.1°C. IR (KBr): 3021, 2839, 1706, 1560, 1507, 1420,

1308 cm⁻¹. ¹H-NMR (400 MHz, CDCl₃) δ (ppm): 7.58 (s, 2H, –CH=), 7.50 (s, 2H, ArH), 7.53–7.18 (m, 4H, ArH), 6.90–6.73 (m, 4H, ArH), 3.98 (s, 12H, –OCH₃). ¹³C-NMR (101 MHz, CDCl₃) δ: 193.28, 152.34, 149.62, 140.06, 135.02, 132.93, 130.42, 129.46, 128.41, 120.51, 115.66, 111.77, 57.33, 57.14. Electron ionization (EI)-MS (*m/z*): 428(M⁺).

(1*E*,3*E*)-1,3-Bis(2,3,4-trimethoxybenzylidene)-1,3-dihydroinden-2-one (**IND-3**) Yellow powder. Yield 72%. mp 166.0–167.5°C. IR (KBr): 3100, 2940, 1706, 1594, 1496, 1409, 1302, 1173, 1033, 826 cm⁻¹. ¹H-NMR (400 MHz, CDCl₃) δ (ppm): 7.75 (s, 2H, –CH=), 7.60–7.35 (m, 4H, ArH), 6.91–6.75 (m, 4H, ArH), 3.96 (s, 18H, –OCH₃). ¹³C-NMR (101 MHz, CDCl₃) δ: 195.45, 156.45, 154.57, 143.78, 138.63, 133.78, 130.54, 129.76, 125.50, 124.60, 123.51, 108.31, 62.96, 62.39, 57.47. EI-MS (*m/z*): 488 (M⁺).

(1*E*,3*E*)-1,3-Bis(3,4,5-trimethoxybenzylidene)-1,3-dihydroinden-2-one (**IND-4**) Orange crystal. Yield 78%. mp 177.9–180.6°C. IR (KBr): 3066, 2839, 1706, 1577, 1501, 1457, 1420, 1280, 1241, 1168, 831 cm⁻¹. ¹H-NMR (400 MHz, CDCl₃) δ (ppm): 7.91 (s, 2H, –CH=), 7.63–7.38 (m, 4H, ArH), 6.93–6.78 (m, 4H, ArH), 3.90 (s, 18H, –OCH₃). ¹³C-NMR (101 MHz, CDCl₃) δ: 195.65, 154.69, 140.53, 138.60, 134.62, 133.73, 131.84, 130.09, 125.11, 107.70, 62.39, 57.60. EI-MS (*m/z*): 488(M⁺).

(1*E*,3*E*)-1,3-Bis(4-hydroxybenzylidene)-1,3-dihydroinden-2-one (**IND-5**) Deep green powder. Yield 75%. mp 272.4–273.1°C. IR (KBr): 3652, 3063, 1693, 1511, 841 cm⁻¹. ¹H-NMR (400 MHz, DMSO) δ (ppm): 9.49 (s, 2H, –OH), 7.86 (s, 2H, –CH=), 7.57–7.31 (m, 4H, ArH), 7.25–7.11 (m, 4H, ArH), 6.93–6.78 (m, 4H, ArH). ¹³C-NMR (101 MHz, DMSO) δ: 195.00, 161.02, 138.33, 135.30, 133.25, 131.82, 130.58, 126.82, 124.32, 117.44. EI-MS (*m/z*): 340 (M⁺).

(1*E*,3*E*)-1,3-Bis(4-hydroxy-3,5-dimethoxybenzylidene)-1,3-dihydroinden-2-one (**IND-6**) Yellowish green powder. Yield 83%. mp 220.1–221.7°C. IR (KBr): 3527, 3108, 2934, 1674, 1570, 1461, 1357, 1271, 1129, 1109, 1062, 810 cm⁻¹. ¹H-NMR (400 MHz, CDCl₃) δ (ppm): 9.02 (s, 2H, –OH), 7.82 (s, 2H, –CH=), 7.62–7.35 (m, 4H, ArH), 6.93–6.78 (m, 4H, ArH), 3.96 (s, 12H, –OCH₃). ¹³C-NMR (101 MHz, CDCl₃) δ: 194.06, 148.44, 147.93, 135.13, 129.80, 127.59, 124.78, 120.79, 110.98, 107.72, 57.79. EI-MS (*m/z*): 460 (M⁺).

(1*E*,3*E*)-1,3-Bis(furan-2-ylmethylene)-1,3-dihydroinden-2-one (**IND-7**) Tan powder. Yield 81%. mp 173.5–174.6°C. IR (KBr): 3108, 1702, 1612, 1566, 1481, 1419, 1283, 1155, 1020, 927 cm⁻¹. ¹H-NMR (400 MHz, DMSO) δ (ppm): 8.14 (s,

2H, -CH=), 7.98–7.54 (m, 4H, ArH), 6.80–6.51 (m, 6H, FuH). ¹³C-NMR (101 MHz, DMSO) δ : 193.34, 148.97, 148.36, 143.48, 140.93, 136.03, 129.51, 126.51, 112.30, 112.08. EI-MS (m/z): 288 (M^+).

Cell Culture and Reagents PC-3, BxPC-3, HT-29, H1299 and RWPE-1 cells were obtained from the American Type Culture Collection (ATCC, Rockville, MD, U.S.A.). RPMI-1640 tissue culture medium, penicillin–streptomycin, L-glutamine and fetal bovine serum (FBS) were from Gibco (Grand Island, NY, U.S.A.). The cells were maintained in RPMI-1640 culture medium, which were supplemented with 10% FBS, penicillin (100 units/mL)–streptomycin (100 μ g/mL) and L-glutamine (300 μ g/mL). Cultured cells were grown at 37°C in a humidified atmosphere of 5% CO₂ and were passaged twice a week. Curcumin-related compounds were dissolved in DMSO and the final concentration of DMSO in all experiments was 0.1%.

MTT PC-3, BxPC-3, HT-29, H1299 and RWPE-1 cells were seeded at a density of 2×10^4 cells/mL of medium in 96-well plate (0.2 mL/well) and incubated for 24 h. The cells were then treated with various concentrations (0.2–20 μ M) of curcumin-related compounds containing inden-2-one for 72 h. After treatment, MTT was added to each well of the plate and incubated for 1 h. After careful removal of the medium, 0.1 mL DMSO was added to each well, and absorbance at 550 nm was recorded on a microplate reader.

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