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Synthesis of *(E)*-7-arylidene-5-(hydroxy(aryl)methyl)bicyclo[3.2.0] heptan-6-one derivatives as anti-cancer agents

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Keywords:
α, β -Unsaturated ketones,
Anti-proliferative activity,
C6, HeLa, 5-Fu

Abstract — 7,7-Dichlorobicyclo [3.2.0]heptan-6-one was prepared by adding dichloroketene to cyclopentene. Reduction of 7,7-dichlorobicyclo[3.2.0]heptan-6-one with Zn in acetic acid afforded the bicyclo[3.2.0]heptan-6-one. *(E)*-7-Arylidene-5-(hydroxy(aryl)methyl)bicyclo [3.2.0]heptan-6-ones were synthesized by addition of related benzaldehydes to bicyclo[3.2.0]heptan-6-one. The anti-proliferative activities of synthesized compounds were elucidated against rat brain tumor (C6) and human cervical carcinoma cells (HeLa) cell lines. The most active compound was chloro derivative against C6 cell lines with $IC_{50} = 2.45$ µM value (5-FU, $IC_{50} = 14.82$ µM). Moreover, the most active compound was methyl derivative against HeLa cell lines with $IC_{50} = 26.30$ µM (5-FU, $IC_{50} = 29.30$ µM).

Subject Classification (2023): 92F05, 92E10

1. Introduction

Compounds containing cyclopentane and cyclopentene rings in their structures are widely found in nature [1]. With many bioactivities, these compounds' analogs and synthetic cyclopentane structures have important practical applications [2,3]. Many molecules containing natural or unnatural cyclopentyl units in their structures, such as alkaloids, steroids, prostaglandins, tricians, indanes, and guaians, have significant biological activity [4-10]. In addition, α,β-unsaturated carbonyls are presence in the structures of natural products and synthetic derivatives are frequently used in agricultural and industrial processes. The α,β-unsaturated carbonyl can be easily obtained synthetically from the corresponding ketone and aldehyde derivatives [11-17]. The α,β-unsaturated carbonyl compounds, especially chalcones and their analogs, have important biological activities (antifungal, bacteriostatic, antitubercular, fungistatic, antiparasitic, antileishmanial, cardiovascular, antitumor, anticancer, and anti-inflammatory) and allow the synthesis of many bioactive compounds such as pyrazole, imidazole, pardine, pyrimidine, etc. [18-20].

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Moreover, β-hydroxy ketones are very valuable starting compounds used in the synthesis of diols, amino alcohols, lactones and polyketides [21,22]. β-Hydroxy ketones are important intermediates for the synthesis of clinically used agents such as antibiotics (Erythromycin A), cholesterol-lowering (Lovastatin), antiviral (complex polyketide A-74,528), antitumor (Daunomycin) and antifungal (Patulin) [23-25]. This study reported the synthesis and investigation of anti-proliferative activities of the new α,β-unsaturated carbonyl compounds **4a-d** containing β-hydroxy unit, fused cyclopentane and cyclobutane rings.

2. Experimental Section

2.1. General

All chemical and reagents (analytical grade) were purchased from Sigma Chemicals (Germany), Roche (Germany)and COSTAR, Corning (USA). Melting points were measured on the Electrothermal 9100 apparatus. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance DPX-400 instrument. As internal standards served TMS for ^{1}H NMR and $CDCl_3$ for ^{13}C NMR spectroscopy *J* values are given in Hz. The multiplicities of the signals in the ^{1}H NMR spectra are abbreviated by s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad), and combinations of they. IR spectra were recorded on a Jasco FTIR-430 spectrophotometer with KCl optics. Elemental analyses were carried out from a LECO CHNS 932 Elemental Analyzer.

2.2. Synthesis of 7,7-dichlorobicyclo[3.2.0]heptan-6-one (3)

The mixture of cyclopentene (1) (5 g, 73.5 mmol) and zinc powder (8 g, 123 mmol) in diethyl ether (150 mL) was cooled to 15°C. Trichloroacetyl chloride (2) (20.9 g, 123 mmol) in diethyl ether (100 mL) was introduced to the mixture for 30 min and stirred for 4 hours. The reaction mixture was washed with water, and the organic layer was dried over Na_2SO_4. Removing the solvent under reduced pressure gave the 7,7-dichlorobicyclo[3.2.0]heptan-6-one (3) (colorless liquid) yield of 75%. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 4.06 (t, J= 8.0 Hz, 1H), 3.41 (t, J= 8.0 Hz, 1H), 2.32-2.27 (m, 1H), 2.24-2.19 (m, 1H), 1.89-1.72 (m, 2H), 1.70-1.61 (m, 1H), 1.59-1.51 (m, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 199.5, 88.6, 62.2, 52.5, 30.4, 30.1, 25.7; IR (KCl, cm^{-1}): 2968, 2885, 1983, 1455, 1222, 1035, 948, 918, 811, 756, 663, 511; Analytically calculated for $C_7H_8Cl_2O$: C, 46.96; H, 4.50. Found: C, 46.91; H, 4.42.

2.3. Synthesis of bicyclo[3.2.0]heptan-6-one (4)

The zinc powder (5 g, 27.9 mmol) in acetic acid (20 mL) was heated to reflux temperature, and the 7,7-dichlorobicyclo[3.2.0]heptan-6-one (**3**) (3 g, 16.8 mmol) in acetic acid (15 mL) added to the mixture for 30 min.; and stirred 20 h. at the same temperature. The mixture was cooled to room temperature and stirred for 5-7 hours. The reaction mixture was filtered to remove the inorganic materials. The filtrate was extracted (chloroform (2×25 mL)), dried over Na_2SO_4, and removed the solvent in a vacuum. The residue was distilled in 10^{-4} mmHg at 53 °C, and pure bicyclo[3.2.0]hepan-6-one (**4**) (colorless liquid) was obtained in yield of 60%. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 3.52-3.50 (m, 1H), 3.19-3.13 (m, 1H), 2.87-2.85 (m, 1H), 2.49-2.43 (m, 1H), 2.02-1.99 (m, 1H), 1.82-1,51 (m, 5H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 214.9, 64.8, 51.5, 32.7, 29.8, 28.9, 24.7; IR (KCl, cm^{-1}): 2962, 2873, 1803, 1440, 1220, 1025, 948, 929, 806, 730, 673, 520; Analytically calculated for $C_7H_{10}O$: C, 76.33; H, 9.15. Found: C, 76.27; H, 9.02.

2.4. General Procedure for Synthesis of *(E)*-7-(arylidine)-5-((aryl)(hydroxy)methyl) bicyclo[3.2.0] heptan-6-one (6a-6d)

To solution of bicyclo[3.2.0]decan-6-one (**4**) (0.3 g, 2.73 mmol) and benzaldehyde derivative (**5a**) (0.69 g, 5.7 mmol) in ethanol was added NaOH (2.3 mL from 2.5 M solution) and stirred at room temperature for 5 hours. After the reaction, the mixture was diluted with CH_2Cl_2, neutralized with HCl solution (10%), and washed with water. The organic layer was dried over anhydrous Na_2SO_4 and the solvent evaporated. Solid compounds were recrystallized in ethanol. Other experiments were performed according to the above procedure.

2.4.1. *(E)*-7-(4-Bromobenzylidine)-5-((4-bromophenyl)(hydroxy)methyl)bicyclo [3.2.0]heptan-6-one (6a)

Slightly yellow solid, 1.03 g., $R_f = 0.38$, ^{1}H-NMR (400 MHz, $CDCl_3$): $\delta = 7.56$ (d, $J = 8.4$ Hz, 2H), 7.50 (d, $J = 8.4$ Hz, 2H), 7.43 (d, $J = 8.5$ Hz, 2H), 7.37 (d, $J = 8.4$ Hz, 2H), 6.99 (d, $J = 2.4$ Hz, 1H), 5.00 (s, 1H), 3.75 (dd, $J = 7.3$, 2.5 Hz, 1H), 2.63 (s, 1H), 2.19- 2.09 (m, 1H), 2.00-1.93 (m, 1H), 1.84 – 1.67 (m, 3H), 1.65 – 1.52 (m, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): $\delta = 205.08$, 146.55, 139.57, 132.88, 132.24, 132.00, 131.43, 128.86, 126.29, 124.72, 121.89, 79.34, 77.36, 75.01, 45.66, 31.59, 30.94, 26.10. IR (KCl, cm^{-1}): 3455; 2950; 2929; 2857; 1731; 1637; 1583; 1484; 1400; 1143; 1070; 1008; 800; 516. Analytically calculated for $C_{21}H_{18}Br_2O_2$: C, 54.57; H, 3.93; Found: C, 54.27; H, 3.91.

2.4.2. *(E)*-7-(4-Chlorobenzylidine)-5-[(4-chlorophenyl)(hydroxy)methyl]bicyclo [3.2.0]heptan-6-one (6b)

Colorless solid, 0.99 g., Rf = 0.49, ^{1}H-NMR (400 MHz, $CDCl_3$): $\delta = 7.50$ (d, $J = 8.4$ Hz, 2H), 7.41 d, $J = 8.4$ Hz, 2H), 7.40 (d, $J = 8.4$ Hz, 2H), 7.34 (d, $J = 8.4$ Hz, 2H), 7.00 (d, $J = 2.4$ Hz, 1H), 5.01 (s, 1H), 3.76 (dd, $J = 7.2$, 2.5 Hz, 1H), 2.69 (s, 1H), 2.19-2.07 (m, 1H), 2.04-1.90 (m, 1H), 1.86-1.66 (m, 2H), 1.68-1.45 (m, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$): $\delta = 205.1$, 146.4, 139.1, 136.3, 133.6, 132.4, 131.8, 129.3, 128.5, 128.5, 126.2, 79.4, 74.9, 45.6, 31.6, 30.9, 26.1. IR (KCl, cm^{-1}): 3458; 2954; 2932; 2853; 1728; 1642; 1588; 1481; 1406; 1142; 1073; 1004; 800; 513. Analytically calculated for $C_{21}H_{18}Cl_2O_2$: C, 67.57; H, 4.86; Found: C, 65.40; H, 4.81.

2.4.3. *(E)*-5-[Hydroxy(4-methylphenyl)methyl]-7-(4-methylbenzylidene)bicyclo [3.2.0] heptan-6-one (6c)

White solid, 0.83 g., $R_f = 0.62$, ^{1}H- NMR (400 MHz, $CDCl_3$): $\delta = 7.49$ (d, $J = 8.0$ Hz, 2H), 7.39 (d, $J = 8.0$ Hz, 2H), 7.24 (d, $J = 8.0$ Hz, 2H), 7.19 (d, $J = 8.0$ Hz, 2H), 7.07 (d, $J = 2.4$ Hz, 1H), 5.05 (s, 1H), 3.78 (dd, $J = 6.8$, 2.4 Hz, 1H), 2.51 (s, 1H), 2.42 (s, 3H), 2.37 (s, 3H), 2.19-2.13 (m, 1H), 2.02-1.97 (m, 1H), 1.77-1.54 (m, 4H). ^{13}C-NMR (100 MHz, $CDCl_3$): $\delta = 205.8$, 140.7, 137.6, 137.4, 131.4, 130.8, 129.7, 128.9, 127.5, 127.0, 79.24, 75.4, 45.6, 31.2, 30.8, 26.0, 21.6, 21.2. IR (KCl, cm^{-1}): 3457; 2940; 2923; 2861; 1733; 1637; 1604; 1509; 1141; 1025; 811; 798; 526; 485. Analytically calculated for $C_{23}H_{24}O_2$: C, 83.10; H, 7.28; Found: C, 83.21; H, 7.12.

2.4.4. *(E)*-7-(3,5-Dchlorobenylidine)-5-[(3,5-dichlorophenyl)(hydroxy)methyl]bicyclo [3.2.0]heptan-6-one (6d)

Light yellow solid, 0.89 g., $R_f = 0.33$, ^{1}H-NMR (400 MHz, $CDCl_3$): $\delta = 7.44$-7.28 (m, 6H), 6.99 (d, $J = 2.4$ Hz, 1H), 5.00 (s, 1H), 3.75 (dd, $J = 7.2$, 2.4 Hz, 1H), 2.62 (s, 1H), 2.18-2.09 (m, 1H), 2.01-1.91 (m, 1H),

1.83-1.67 (m, 2H), 1.65- 1.48 (m, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 205.1, 146.5, 139.5, 132.8, 132.2, 131.9, 131.4, 128.8, 126.3, 124.7, 121.9, 79.3, 75.0, 45.6, 31.6, 30.9, 26.1. IR (KCl, cm^{-1}): 3460; 2955; 2934; 2863; 1734; 1641; 1586; 1481; 1402; 1153; 1073; 1012; 804; 518. Analytically calculated for $C_{21}H_{16}Cl_4O_2$: C, 57.05; H, 3.65; Found: C, 57.24; H, 3.61.

2.5. Bioassays

Bioassay studies, preparation standards and samples solution, cell culture and the BrdU Proliferation ELISA experiments were carried out according to published procedures [16, 26, 27].

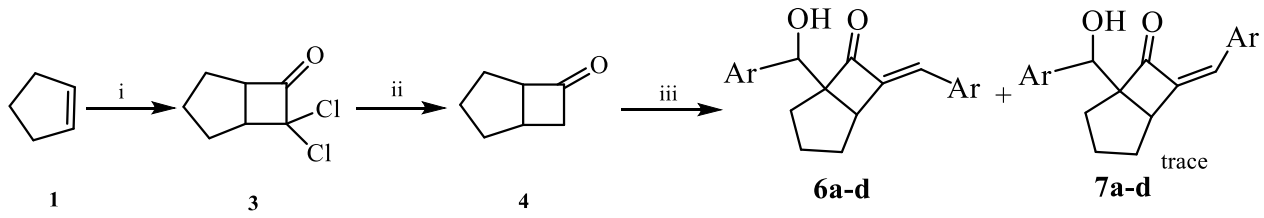
2.5.1. Determination of IC_{50} Values

The half-maximal inhibitory concentration (IC_{50}) is a measure of the effectiveness of a compound in inhibiting biological function. This study determines IC_{50} values using ED_{50} plus v1.0 and provides in Table 2.

3. Results and Discussions

3.1. Chemistry

The target compounds **6a-d**, *(E)*-7-arylidene-5-(hydroxy(aryl)methyl)bicyclo[3.2.0] heptan-6-ones, were prepared in three steps. In the first stage, 7,7-dichlorobicyclo[3.2.0]heptan-6-one (**3**) was obtained by addition of dichloroketene to cyclopentene (**1**). The reaction of cyclopentene (**1**) with trichloroacetyl chloride and zinc (Zn) in Et_2O at 15 °C for 5 hours gave the dichloroketene adduct **3** in yield of 75%. Then, the reduction of 7,7-dichlorobicyclo[3.2.0]heptan-6-one (**3**) with Zn in acetic acid afforded the bicyclo[3.2.0]heptan-6-one (**4**) in yield of 60%. Finally, *(E)*-7-arylidene-5-(hydroxy(aryl)methyl) bicyclo[3.2.0]heptan-6-one (**6a-d**) were synthesized by the base-catalyzed Claisen-Schmidt condensation of ketone **4** and appropriate benzaldehyde derivatives (**5a-d**) in ethanol. The base catalyzed addition reaction of benzaldehyde derivatives (2 equiv.) (**5**) to ketone **4** was performed at room temperature for 5 h. The NMR and TLC (Petroleum ether/Ethyl acetate (9/1)) studies of the mixture show that the isomeric 7-arylidinebicyclo [3.2.0] heptan-6-ones **6a-d** and **7a-d** (trace amounts) were occurred (Scheme 1 and Table 1).

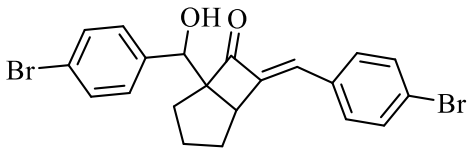
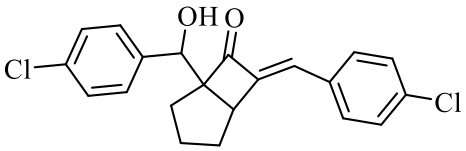
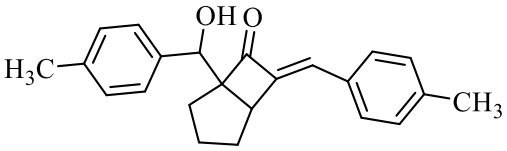
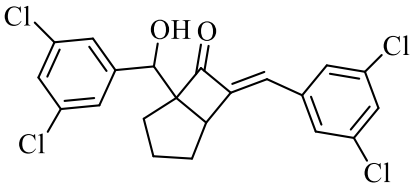


Ar = a) 4-BrPh, b) 4-ClPh, c) 4-CH_3Ph, d) 3,5-diClPh

Scheme 1. Reagents and conditions: i) Zn, Cl3COCl (2), Et2O, 15°C, 5 h.; ii) Zn, AcOH, ref, 20 h. to rt. 7 h.; iii) ArCHO (**5a-d**), NaOH, EtOH, rt. 5 h.

The structures of compounds **6a-d** were determined based on spectral data. In each case, the ^{1}H NMR spectra of arylidenes (**6a-d**) showed the characteristic signals for H atom of -OH and CH of -CH-OH groups at δ 5.00-5.05 and 3.75-3.78 ppm, respectively. The other determinative signals belong to olefinic protons that resonate at δ 7.07-6.99 ppm. In addition, the signals observed at δ 79.40-79.24 and 75.40-75.00 ppm in the ^{13}C-NMR spectrum support the structures.

Table 1. Synthesized *(E)*-7-benzylidene-5-(hydroxy(phenyl)methyl)bicyclo[3.2.0]heptan-6-one (**6a-d**)

Entry	Compounds	Yield (%)	Mp.(^{0}C)
1	**6a** 	82	189-192
2	**6b** 	78	196-199
3	**6c** 	92	136-138
4	**6d** 	74	235-238

3.2. Anti-proliferative Activity

The anti-proliferative activities of compounds **6a-d** were investigated against C6 and HeLa cell lines using BrdU cell proliferation ELISA assay [26, 27]. The experiments were carried out three times (n=9). The anti-proliferative activities of **6a-d** and the control were screened on 5, 10, 20, 30, 40, 50, 75, and 100 µM concentrations, and 5-FU was chosen as positive control due to its availability, and widespread using. The results are given as the IC_{50} value. The inhibitory potency of compounds against C6 and HeLa cell lines were shown in Figure 1A and 1B, respectively, and the IC_{50} values were given in Table 2. According to the ELISA assay, the compounds display more potent inhibitory effects on C6 cells (Figure 1A and Table 2). Data are presented as mean ± SD (n=6). A statistically significant difference ($p<0.01$) was observed between treatments in Figure 1 and Table 2 (ANOVA, Duncan).

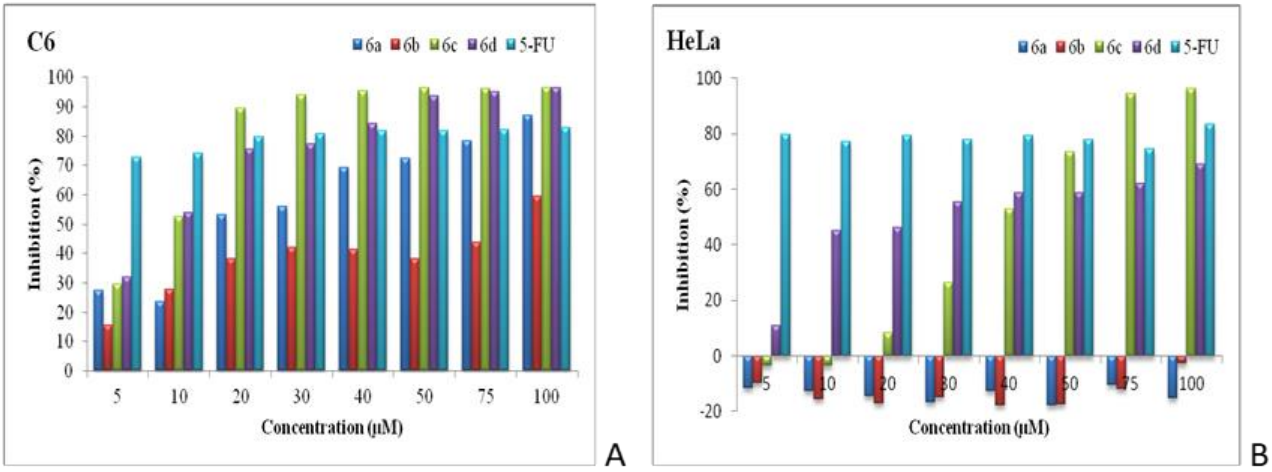


Figure 1. Anticancer activity of **6a-d** and 5-FU against C6 (A) and HeLa (B) cell lines, respectively.

All compounds **6a-d** displayed an inhibitory effect at all concentrations against C6 cells, and inhibitory potency depended on dose increase (Figure 1). Furthermore, compound **6c** demonstrated higher activity than 5-FU at 20-100 µM concentrations. Among compounds **6a-d**, the most effective anticancer agents were found as compounds **6b** and **6d** (IC_{50} = 2.45 µM and 6.00 µM), followed by compound **6c** (IC_{50} = 11.45 µM), **6a** (IC_{50} = 26.39 µM) against C6 cell lines when compared with 5-FU (IC_{50} = 14.82 µM) (Table 2).

On the other hand, compounds **6a** and **6b** were inactive at all concentrations, while **6c** and **6d** showed activity at 10-100 µM concentrations against HeLa cells, and inhibitory potency was dependent on dose increase (Figure 1B). Moreover, while compound **6c** showed higher activity than 5-FU at 75 and 100 µM, **6d** exhibited remarkable anticancer activity, especially at high concentrations. Among the compounds **6a-d**, the most active compound against HeLa cell lines was found as compound **6c** (IC_{50} = 26.20 µM) compared with 5-FU (IC_{50} = 29.30 µM) (Table 2).

Table 2. IC_{50} values of 6a-d against C6 and Hela

Compounds	C6	Hela
6a	26.39	38.11
6b	2.45	78.78
6c	11.45	26.20
6d	6.00	32.44
5-FU	14.82	29.30

4. Conclusion

The target compounds **6a-d**, *(E)*-7-arylidene-5-(hydroxy(aryl)methyl)bicyclo[3.2.0] heptan-6-one were synthesized in three steps. In the first stage, 7,7-dichlorobicyclo [3.2.0]heptan-6-one (**3**) was obtained by addition of dichloroketene to cyclopentene (**1**) in a yield of 75%. Then, the reduction of 7,7-dichlorobicyclo [3.2.0]heptan-6-one (**3**) with Zn in acetic acid afforded the bicyclo[3.2.0]heptan-6-one (**4**) in yield of 60%. Finally, *(E)*-7-arylidene-5-(hydroxy(aryl)methyl)bicyclo[3.2.0]heptan-6-one (**6a-d**) were synthesized by the base-catalyzed Claisen-Schmidt condensation of ketone **4** and appropriate benzaldehyde derivatives (**5**) in ethanol. The structures of compounds were explained by spectroscopic methods such as NMR, IR, and Elemental analysis. The anti-proliferative activities of compounds **6a-6d** were determined against C6 and HeLa cell lines using BrdU cell proliferation ELISA assay. 5-FU was used as standard. The most active compound was **6b** against C6 cell lines with IC_{50} = 2.45 µM value (5-FU, IC_{50} = 14.82 µM). Furthermore, the most active compound was **6c** against HeLa cell lines with IC_{50} = 26.30 µM (5-FU, IC_{50} = 29.30 µM).

Author Contributions

All the authors equally contributed to this work. They all read and approved the final version of the paper.

Conflict of Interest

All the authors declare no conflict of interest.

Supplementary Material

https://dergipark.org.tr/en/download/journal-file/29128

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