SYNTHESIS AND EVALUATION OF BIOLOGICAL ACTIVITIES OF SOME (2-HYDROXY-1-NAPHTHYL)(3-(SUBSTITUTED PHENYL)BICYCLO[2.2.1] HEPTENE-2-YL)METHANONES

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Keywords: water-mediated Diels-Alder reaction; 2-hydroxy-1-naphthyl chalcones; cyclopentadiene; IR spectra; NMR spectra; antimicrobial activity; antioxidant activity.

Totally twelve ((2-hydroxy-1-naphthyl))(3-(substituted phenyl)bicyclo [2.2.1]hept-5-ene-2-yl)methanones have been synthesized by fly-ash catalyzed water-mediated Diels-Alder [4+2] cycloaddition reaction. The synthesized bicyclic ketones were characterized by their physical constants, analytical and spectroscopic data. The antimicrobial and antioxidant activities of these bicyclic methanones were evaluated using Bauer-Kirby disc diffusion and diphenyl picrylhydrazyl(DPPH) radical scavenging technique. Most of the bicyclic methanones showed good antibacterial and antifungal activities against their microbial strains. The hydroxy- and methoxy- substituted methanones shows significant antioxidant activity.

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INTRODUCTION

In stereo selective reactions, the Diels-Alder reaction is the most important for of six-membered bicyclic compound synthesis by [4+2] cycloaddition of diene and dienophiles.[1, 2] The retro-Diels-Alder reaction was possible when this reaction is carried out in thermal condition. The mechanistic aspects of reaction conditions, *endo-exo*-product selectivity, and influence of solvents of this Diels-Alder reaction have been reported.[3-7] Currently, greener Diels-Alder reaction is essential for the synthesis of bicyclic compounds with product selectivity. The ease of workup and technical procedure, non-hazardous, shorter reaction time, non-polluted to the environment and good yields are the advantages of this reaction.[1,2,8,9] Rideout and Breslow[10] have studied the cycloaddition reaction of ethylenic ketones and cyclopentadiene in an aqueous medium and they reported the reaction rate is greater than 700 times faster than in non-aqueous media. Many catalysts such as Lewis acids,[5] Bronsted acids,[6,11] asymmetric helical polymers,[12] Cu^{2+} ion-mediated nanotubes[13] and Micellar-DNAs[8,13-18] have been employed for the Diels-Alder [4+2] cycloaddition reaction of cyclopentadiene (diene) and (*E*)-chalcones (dienophiles). The unsaturated compounds, ethylenic ketones, substituted aryl bicyclic ketones possess important biological activities and antibodies.[19-22] Recently, Thirunarayanan has reported the synthesis and biological activities of naphthyl based bicyclo[2.2.1]heptane methanones using greener method.[23] The mono- or di- or tri- or poly –OH (alcohols) and $–OCH_3$ substituted organic compounds possess significant antioxidant activities.[24, 25] Literature survey reveals that the synthesis and the study of pharmacological effects of 2-hydroxy-1-naphthyl based bicyclic methanones are almost absent in the past. Hence, the author has taken efforts to synthesize some 2-hydroxy-1-naphthyl based heptane[2.2.1]methanones by greener method for the evaluation of antimicrobial activity by Bauer-Kirby[26] disc diffusion method and the antioxidant activities by diphenyl picrylhydrazyl (DPPH) radical scavenging[27] activity ability.

MATERIALS AND METHODS

Chemicals used in this investigation were procured from Sigma-Aldrich and E-Merck brands. The source of fly-ash is the Thermal Power Plant-II, Neyveli Lignite Corporation (NLC), Neyveli-607 807, Tamilnadu, India. The Mettler FP51 melting point apparatus was used for determining the melting points of all bicyclo [2.2.1]heptene-2-yl methanones. Thermo Scientific Nicolet iS5, USA made Fourier transform spectrophotometer was used for recording infrared spectra (KBr, 4000-400 cm^{-1}) of all bicyclic ketones. The Bruker AV 400 NMR spectrometer was used for recording nuclear magnetic resonance spectra, operating at 400 MHz for ^1H and 100 MHz for ^{13}C spectra in deuterated chloroform solvent using tetramethylsilane as an internal standard. The mass spectra of methanones were recorded in Shimadzu spectrometer using FAB^+ electron impact and chemical ionization mode.

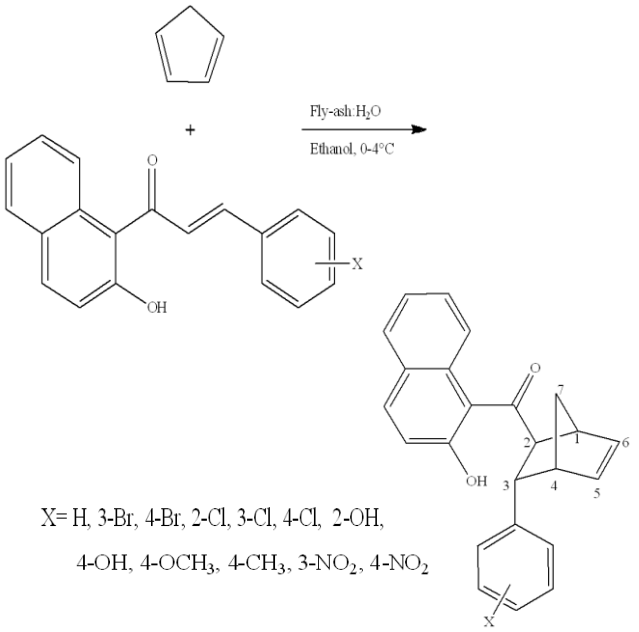
The bacterial and fungal strains were collected from Faculty of Marine Sciences, Annamalai University, Portonovo Campus, Portonovo-608 502, Tamilnadu, India.

Synthesis of substituted styryl (*E*)-2-hydroxy-1-naphthyl ketones

The substituted styryl (*E*)-2-hydroxy-1-naphthyl ketones were synthesized by literature method.[28]

General procedure for synthesis of (2-hydroxy-1-naphthyl)(3-(substituted phenyl)bicyclo [2.2.1] hept-5-ene-2-yl)methanones

An equimolar quantities of substituted styryl (E)-2-hydroxy-1-naphthyl ketones (2 mmol) in 10 mL of ethanol, cyclopentadiene (2 mmol), and 0.5g of fly-ash in 5 mL of water were stirred for 6 h in 0-4 °C (Scheme 1). The reaction mixture was kept an overnight. Thin layer chromatogram was used for monitoring the completion of the reaction. Separated the organic layer extract by adding 10 mL of dichloromethane, washed with water, brine (10 mL), dried over on anhydrous Na_2SO_4 and concentration gave the solid product. Further, the crude bicyclic methanones were purified by recrystallization with ethanol.



Scheme 1. Synthesis of (2-hydroxy-1-naphthyl)(3-(substituted phenyl)bicyclo[2.2.1]hept-5-en-2-yl)methanones by water-mediated fly-ash catalyzed Diels-Alder reaction of 2-hydroxy-1-naphthyl chalcones and cyclopentadiene.

Antimicrobial activity

The antimicrobial sensitivity assay of prepared bicyclo[2.2.1]heptene-2-yl-methanones were evaluated by means of measuring the diameter of the zone of inhibition in millimeters against their bacterial and fungal strains. There are two gram-positive pathogenic strains (*Staphylococcus aureus, Enterococcus faecalis*) and four gram-negative strains (*Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa* and *Proteus vulgaris*) were used for evaluation of antimicrobial activities. The Bauer-Kirby[26] disc diffusion technique was employed at the concentration of 250 g mL^{-1} of compounds with ampicillin and streptomycin as standards. The disc diffusion technique was adopted for the evaluation of antifungal activity of all bicyclic ketones against *Candida albicans* strain, and the dilution method was adopted for *Penicillium sp*. and *Aspergillus niger* strains. The dilution concentrations of the prepared bicyclic ketones are 50 g mL^{-1}, and griseofulvin was employed as standard drug.

Measurement of antibacterial sensitivity

The disc diffusion technique was adopted for measurement of antibacterial sensitivity assay of all bicyclic keto compounds. Uniformly spread the prepared bicyclic methanones (0.5mL) over solidified Mueller-Hinton agar. Whatmann No. 1 filter paper discs (5 mm diameters) were made and placed on the medium with potential inhibitor solution. Prevent the collection of water droplets on the medium by kept the discs upside down and incubated at the temperature of 37ºC for 24 h. The discs were examined by measured the diameter in millimeters of the zone of inhibition. The triplicate results were recorded.

Measurement of antifungal sensitivity

The antifungal sensitivity assay of synthesized bicyclic methanones was evaluated using Bauer-Kirby[26] disc diffusion technique. The sterilized potato dextrose agar medium was added to the Petri plates containing 1mL of fungal strains. Uniform spreads of the agar on the plates were performed by means of a clock and anti-clockwise rotation of the discs. The test solution was prepared by dissolving 15 mg of the methanones in 1 mL of dimethylsulfoxide (DMSO) solvent, and it was applied to the discs. This medium was incubated to solidified for 24 or 72 h at 25 or 28 °C. Then these plates were examined for the evaluation of antifungal activity by measurement of the diameter of mm of the zone of inhibition. Triplicate measurement results were recorded.

Measurement of antioxidant activity

The diphenylpicrylhydrazyl (DPPH) radical scavenging activity technique[27] was employed for the measurement of the antioxidant activity of all prepared bicyclic methanones. Sodium acetate buffer solution (20 mL) was prepared by dissolving of sodium acetate (1.64 g) in 15 mL of water, and 150 µL of acetic acid and the final volume was adjusted to 20 mL with water. Diphenyl picrylhydrazyl (DPPH) solution (0.2 mmol, 50 mL) was prepared by dissolving 3.9 g of diphenyl picrylhydrazyl (DPPH) in 50 mL of ethanol. Alpha- tocopherol solution (10 mL) was prepared by dissolving 1mg of alpha-tocopherol in 10mL of ethanol. The buffer solution (1.0 mL) was mixed with 0.5 mL of diphenyl picrylhydrazyl (DPPH) solution in the test tubes and arranged serially. The test solution and α-tocopherol solution were added to the test tubes and kept aside for 30 minutes at room temperature. Measured the absorbance in UV spectrophotometer at 517 nm. The buffer and ethanol were used as the reference. The plot was made with the quantity of bicyclic ketones versus absorption, and the IC_{50} values were determined. The antioxidant activity was expressed by means of IC_{50} values (g mL^{-1}, the concentration required to inhibit DPPH radical formation by 50%). Alpha-Tocopherol was taken as a positive control. The radical scavenging activity (φ) (% of inhibition) was calculated as

$$\varphi = \frac{A_{\text{control}} - A_{\text{sample}}}{A_{\text{control}}}$$

where *A* is the absorbance.

RESULTS AND DISCUSSION

Attempts have been made for the synthesis of (2-hydroxy-1-naphthyl)(3-(substituted phenyl)bicyclo[2.2.1]hept-5-ene-2-yl)methanone derivatives by water-mediated fly-ash catalyzed Diels-Alder reaction with cyclopentadiene as diene and substituted styryl (E)-2-hydroxy-1-naphthyl ketones as dienophiles. Numerous metals and their oxides such as Si, Al, Fe, Ca, C, Mg, K, Na, S, Ti, P, Mn, organic mud and insoluble residues present in the fly-ash.[29] The waste fly-ash was used as a catalyst for organic synthesis. The fly-ash particles are in the silt-sized range of 2-50 microns.30 Glass, mullite-quartz, and magnetic spinel are the three major mineralogical matrices identified in fly ash. The solubility of fly ash has been extensively investigated, and it is largely dependent on factors specific to the extraction methods.

The complete literature study reveals that the long-term leaching studies predicts the fly ash will lose substantial amounts of waste soluble salts, but simulation models predict that the loss of trace elements from fly ash deposits through leaching will be very slow. Traces of radioisotopes are found to be the constituents of fly ash which do not appear to be hazardous. Hence, the author has synthesized (2-hydroxy-1-naphthyl)(3-((un)substituted phenyl)bicyclo-[2.2.1]heptene-2-yl)methanones by water-mediated Diels-Alder reaction of substituted styryl (E)-2-hydroxy-1-naphthyl ketones and cyclopentadiene under cooling condition. During reaction, the chemical species present in the fly-ash was catalyzed the [4+2] cycloaddition reaction. In this water-mediated Diels-Alder reaction the observed yields are more than 60 %. The analytical data, physical constants and mass fragments of synthesized bicyclic methanones are presented in Table 1.

Table 1. The yield, physical constants and mass fragments of (2-hydroxy-1-naphthyl)-3-(substituted phenyl)-bicyclo[2.2.1]hept-5-en-2-yl)methanones

Entry	X	M.F.	M.W.	M.p. °C	Yield,%	Mass (m/z)
1	H	$C_{24}H_{20}O_2$	340	114-115	65	340[M^+], 323, 2623, 197, 171, 169, 143, 126, 120, 77, 17
2	3-Br	$C_{24}H_{19}BrO_2$	419	121-122	63	419[M^+], 421[M^{2+}], 402, 339, 275, 263, 154, 143, 90, 79, 76, 17
3	4-Br	$C_{24}H_{19}BrO_2$	419	116-117	63	419[M^+], 421[M^{2+}], 402, 339, 275, 263, 247, 154, 143, 126, 92, 90, 79, 76, 17
4	2-Cl	$C_{24}H_{19}ClO_2$	375	104-108	60	375[M^+], 377[M^{2+}], 357, 263, 246, 203, 171, 154, 143, 126, 120, 77, 35, 26, 17
5	3-Cl	$C_{24}H_{19}ClO_2$	375	112-113	62	375[M^+], 377[M^{2+}], 357, 263, 246, 231, 171, 143, 126, 120, 111, 77, 35, 17
6	4-Cl	$C_{24}H_{19}ClO_2$	375	132-133	63	375[M^+], 377[M^{2+}], 357, 339, 263, 246, 231, 203, 171, 154, 143, 126, 120, 111, 94, 77, 35, 26, 17
7	2-OH	$C_{24}H_{20}O_3$	356	98-99	62	356[M^+], 339, 263, 196, 171, 143, 120, 92, 77, 66, 34, 17,
8	4-OH	$C_{24}H_{20}O_3$	356	116-117	64	356[M^+], 339, 322, 263, 196, 171, 168, 143, 120, 93, 92, 77, 66, 54, 34, 17,
9	2-OCH_3	$C_{25}H_{22}O_3$	370	111-112	65	370[M^+], 355, 353, 339, 322, 263, 246, 227, 199, 196, 184, 171, 154, 143, 126, 107, 92, 31, 17, 15
10	4-CH_3	$C_{25}H_{22}O_2$	354	126-127	64	354[M^+], 339, 322, 263, 246, 211, 196, 171, 168, 154, 143, 126, 120, 91, 76, 17, 15
11	4-NO_2	$C_{25}H_{19}NO_3$	385	122-123	61	385[M^+], 368, 339, 263, 246, 171, 154, 126, 122, 92, 76, 46
12	4-NO_2	$C_{25}H_{19}NO_3$	385	122-123	61	385[M^+], 368, 339, 263, 246, 242, 214, 171, 154, 143, 126, 122, 92, 76, 46, 28, 17

Table 2. The effect of solvents on the aqueous phase Diels-Alder reaction of styryl-2-hydroxy-1-naphthyl ketone and cyclopentadiene (entry1)

Solvent	Ethanol	Methanol	Dichloromethane	Dioxane	Tetrahydrofuran
Yield	65	63	62	60	62

The effect of the catalyst by means of reusability was studied in this cycloaddition reaction with 2 mmol of styryl (E)-2-hydroxy-1-naphthyl ketone and 2 mmol of cyclopentadiene (entry 1). The first run yield was 65%. The 2nd and 3rd runs gave 60 and 53%. The fourth and fifth runs yield 40% product. The substituted styryl (E)-2-hydroxy-1-naphthyl ketones possess electron-donating substituents (OCH3) gave a higher yield than electron-withdrawing (halogens and nitro) substituents. The catalytic effect of catalyst loading on this cycloaddition reaction was studied by varying the catalyst quantity from 0.1 to 1 g. As the quantity of catalyst increased from 0.1 to 0.4 g, the percentage of yield increased from 60-65%. Further, increase the catalyst quantity beyond 0.4 g, there is no increase in the percentage of yield. The effect of catalyst loading was illustrated in Fig.1.

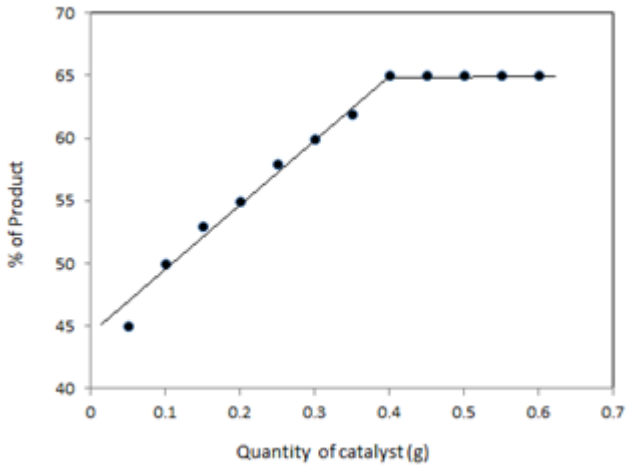


Figure 1. The effect of catalyst loading

The optimum quantity of catalyst loading was in the cycloaddition reaction was found to be 0.4 g. The influence of solvents on this cycloaddition reaction (entry 1) was studied with the same quantity of reactants with solvents such as methanol, dichloromethane, dioxane and tetrahydrofuran and is presented in Table 2. The higher yield was obtained in ethanol with the fly-ash in aqueous medium.The proton and carbon-13 nuclear magnetic resonance spectrum of parent bicyclic methanone are shown in Figs. 2 and 3. The infrared and nuclear magnetic resonance spectral data of bicyclic methanones are summarized as follows.

(2-Hydroxynaphthalen-1-yl)(3-phenylbicyclo[2.2.1]-hept-5-en-2-yl)methanone (1)

IR(KBr) 3468.28, 2989.27, 1675.37, 1548.28, 1431.61, 1024.51, 884.11 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 2.652 (dd, 1H, H_1) *J* = 5.22 and 12.42 Hz, 3.622 (t, 1H, H_2), 3.196(t, 1H, H_3), 2.128(dd, 1H, H_4) *J* = 5.12 and 4.11Hz, 5.478(d, 1H, H_5), 5.939(d, 1H, H_6), 2.078(dd, 1H, H_7) *J* = 9.4 and 16.2Hz, 1.584(dd, 1H, $H_{7'}$) *J* = 6.6 and 12.2 Hz, 7.096-8.435(m, 11H, Ar-H); ^{13}C NMR(100 MHz, $CDCl_3$): δ = 190.53(CO), 40.33(C_1), 54.47(C_2), 46.03(C_3), 50.29(C_4), 135.47($C_{5,6}$), 45.86(C_7), 125.98-141.34(Ar-C).

(3-(3-Bromophenyl)bicyclo[2.2.1]hept-5-en-2-yl)(2-hydroxynaphthalen-1-yl)methanone (2)

IR(KBr) 3438.18, 2968.56, 2822.63, 1678.28, 1558.82, 1462.37, 1131.79, 1088.79, 822.85 cm^{-1}; ^1H NMR(400 MHz, $CDCl_3$): δ 3.076(dd, 1H, H_1), *J* = 7.24 and 9.44 Hz, 3.781(t, 1H, H_2), 3.660(t, 1H, H_3), 2.640(dd, 1H, H_4) *J* = 7.40 and 10.46Hz, 6.621(d, 1H, H_5), 6.618(d, 1H, H_6), 2.041(dd, 1H, H_7)*J* = 5.64 and 7.84 Hz, 1.788(dd, 1H, $H_{7'}$) *J* = 8.66 and 5.94Hz, 7.668-8.881(m, 10H, Ar-H); ^{13}C NMR(100 MHz, $CDCl_3$): δ 190.81(CO), 42.64(C_1), 54.72(C_2), 45.68(C_3), 51.77(C_4), 135.73($C_{5,6}$), 46.23(C_7), 123.52-156.89(Ar-C).

(3-(4-Bromophenyl)bicyclo[2.2.1]hept-5-en-2-yl)(2-hydroxynaphthalen-1-yl)methanone (3)

IR(KBr) 3431.16, 2982.26, 2894.83, 1667.18, 1541.72, 1476.97, 1141.78, 1043.89, 838.78 cm^{-1}; ^1H NMR(400MHz, $CDCl_3$): δ = 2.860(dd, 1H, H_1) *J* = 9.4 and 10.2Hz, 3.768(t, 1H, H_2), 3.573(t, 1H, H_3), 2.816(dd, 1H, H_4) *J*= 7.42and 3.6Hz, 5.3(d, 1H, H_5), 5.958(d, 1H, H_6), 2.158(dd, 1H, H_7) *J* = 12.4 and 6.8 Hz, 1.618(dd, 1H, $H_{7'}$) *J* = 9.5 and 12.4 Hz, 7.638-8.862(m, 10H, Ar-H); ^{13}C NMR(100MHz, $CDCl_3$): δ 189.38(CO), 37.42(C_1), 54.93(C_2), 34.88(C_3), 45.46(C_4), 135.73($C_{5,6}$), 44.54(C_7), 126.78-142.96(Ar-C).

(3-(2-Chlorophenyl)bicyclo[2.2.1]hept-5-en-2-yl)(2-hydroxynaphthalen-1-yl)methanone (4)

IR(KBr) 3432.34, 2996.49, 2889.89, 1683.49, 1595.19, 1463.02, 1224.87, 1068.76, 835.25 cm^{-1}; ^1H NMR(400MHz, $CDCl_3$): δ 3.043(dd, 1H, H_1) *J* = 8.4 and 7.5Hz, 3.432(t, 1H, H_2), 3.238(t, 1H, H_3), 2.220(dd, 1H, H_4) *J* = 6.4 and 8.0Hz, 6.218(d, 1H, H_5), 6.325(d, 1H, H_6), 2.034(dd, 1H, H_7) *J* = 6.72 and 8.92Hz, 1.589(dd, 1H, $H_{7'}$) *J* = 9.81 and 7.5Hz, 7.658-8.741(m, 10H, Ar-H); ^{13}C NMR(100MHz, $CDCl_3$): δ 191.44(CO), 48.28(C_1), 54.68(C_2), 45.73(C_3), 51.41(C_4), 136.48($C_{5,6}$),46.41(C_7), 124.36-152.47(Ar-C).

(3-(3-Chlorophenyl)bicyclo[2.2.1]hept-5-en-2-yl)(2-hydroxynaphthalen-1-yl)methanone (5)

IR(KBr) 3452.13, 2951.09, 2848.09, 1688.59, 1521.89, 1490.02, 1171.28, 1062.27, 861.28 cm^{-1}; ^1H NMR(400MHz, $CDCl_3$): δ 2.738(dd, 1H, H_1) *J* = 4.8 and 10.4Hz, 3.486(t, 1H, H_2), 2.492(t, 1H, H_3), 2.682(dd, 1H, H_4) *J* = 14.8 and 9.2Hz, 5.493(d, 1H, H_5), 6.965(d, 1H, H_6), 2.414(dd, 1H, H_7) *J* = 7.4 and 12.6 Hz, 1.438(dd, 1H, $H_{7'}$) *J*= 9.4 and 8.2 Hz, 7.583-8.776(m, 10H, Ar-H); ^{13}C NMR(100MHz, $CDCl_3$): δ 190.05(CO), 41.20(C_1), 54.81(C_2), 45.19(C_3), 50.37(C_4), 136.26($C_{5,6}$), 46.22(C_7), 125.69-148.80(Ar-C).

(3-(4-Chlorophenyl)bicyclo[2.2.1]hept-5-en-2-yl)(2-hydroxynaphthalen-1-yl)methanone (6)

IR(KBr) 3449.58, 2978.56, 2884.33, 1683.78, 1568.27, 1484.07, 1141.59, 1091.99, 890.85 cm^{-1}; ^1H NMR(400MHz, $CDCl_3$): δ 3.111(dd, 1H, H_1) *J* = 7.4 and 6.2Hz, 3.784(t, 1H, H_2), 3.612(t, 1H, H_3), 2.453(dd, 1H, H_4) *J* = 9.4 and 10.4Hz,

6.017(d, 1H, H_5), 6.102(d, 1H, H_6), 2.036(dd, 1H, H_7) *J* = 11.5 and 8.62Hz, 1.284(dd, 1H, $H_{7'}$) *J* = 8.4 and 6.8Hz, 7.678-8.874(m, 10H, Ar-H); ^{13}C NMR(100MHz, $CDCl_3$): δ 191.48(CO), 41.32(C_1), 54.52(C_2), 46.14(C_3), 51.83(C_4), 136.32($C_{5,6}$), 46.73(C_7), 126.57-153.69(Ar-C).

(3-(2-Hydroxyphenyl)bicyclo[2.2.1]hept-5-en-2-yl)(2-hydroxy-naphthalen-1-ylmethanone (7)

IR(KBr) 3452.93, 2981.57, 2888.59, 1668.34, 1491.51, 1041.89, 893.78 cm^{-1}; ^{1}H NMR(400MHz, $CDCl_3$): δ 3.153(dd, 1H, H_1) *J* = 7.84 and 6.70Hz, 3.563(t, 1H, H_2), 3.792(t, 1H, H_3), 2.618(dd, 1H, H_4) *J* = 11.35 and 7.64Hz, 6.421(d, 1H, H_5), 6.422(d, 1H, H_6), 2.126(dd, 1H, H_7) *J* = 5.18 and 7.42Hz, 1.082(dd, 1H, $H_{7'}$) *J* = 10.24 and 8.63Hz, 7.181-8.579(m, 10H, Ar-H); ^{13}C NMR(100MHz, $CDCl_3$): δ 190.68(CO), 42.81(C_1), 54.72(C_2), 46.62(C_3), 51.79(C_4), 136.23($C_{5,6}$), 47.04(C_7), 125.12-139.92(Ar-C).

(3-(4-Hydroxyphenyl)bicyclo[2.2.1]hept-5-en-2-yl)(2-hydroxy-naphthalen-1-ylmethanone (8)

(IR(KBr) 3478.63, 2991.35, 2888.23, 1689.64, 1468.21, 1048.69, 868.30 cm^{-1}; ^{1}H NMR(400MHz, $CDCl_3$): δ 2.813(dd, 1H, H_1) *J* =16.0 and 6.04Hz, 3.573(t, 1H, H_2), 3.758(t, 1H, H_3), 2.716(dd, 1H, H_4) *J* =11.40 and 8.40Hz, 5.388(d, 1H, H_5), 5.962(d, 1H, H_6), 2.538(dd, 1H, H_7) *J* = 12.2 and 8.2Hz, 1.590(dd, 1H, $H_{7'}$) *J* =10.4 and 11.2Hz, 7.344-8.630(m, 10H, Ar-H); ^{13}C NMR(100MHz, $CDCl_3$): δ 189.88(CO), 43.76(C_1), 52.54(C_2), 44.53(C_3), 50.38(C_4), 135.68($C_{5,6}$), 47.57(C_7), 125.35-153.29(Ar-C).

(3-(4-Methoxyphenyl)bicyclo[2.2.1]hept-5-en-2-yl)(2-hydroxy-naphthalen-1-yl)methanone (9)

IR(KBr) 3538.51, 3022.34, 2993.42, 1663.54, 1561.24, 1458.16, 1255.21, 1088.91, 831.68 cm^{-1}; ^{1}H NMR(400MHz, $CDCl_3$): δ 3.248(dd, 1H, H_1) *J*= 6.4 and 8.4Hz, 3.822(t, 1H, H_2), 3.188(t, 1H, H_3), 2.754(dd, 1H, H_4) *J* = 9.8 and 6.0Hz, 5.582(d, 1H, H_5), 5.638(d, 1H, H_6), 2.215(dd, 1H, H_7) *J* = 12.4 and 7.4Hz, 1.438(dd, 1H, $H_{7'}$) *J* = 10.4 and 11.2Hz, 3.691(s, 3H, OCH_3), 7.688-8.371(m, 10H, Ar-H); ^{13}C NMR(100MHz, $CDCl_3$): δ 190.15(CO), 42.74(C_1), 46.19(C_2), 54.39(C_3), 51.34(C_4), 136.36($C_{5,6}$), 45.88(C_7), 62.80(OCH_3), 125.81-158.94(Ar-C).

(3-(4-Methylphenyl)bicyclo[2.2.1]hept-5-en-2-yl)(2-hydroxynaphthalen-1-yl)methanone (10)

IR(KBr) 3469.13, 3091.00, 2993.87, 1665.34, 1532.65, 1476.34, 1228.31, 1075.34, 873.96 cm^{-1}; ^{1}H NMR(400MHz, $CDCl_3$): δ 2.934(dd, 1H, H_1) *J* = 10.4 and 6.8Hz, 3.694(t, 1H, H_2), 3.190(t, 1H, H_3), 2.688(dd, 1H, H_4) *J* = 9.82 and 7.62Hz, 6.438(d, 1H, H_5), 6.487(d, 1H, H_6), 2.046(dd, 1H, H_7) *J* = 8.64 and 6.60Hz, 1.128(dd, 1H, $H_{7'}$) *J* = 10.34 and 7.62Hz, 3.102(s, 3H, CH_3), 7.322-8.304(m, 10H, Ar-H); ^{13}C NMR(100MHz, $CDCl_3$): δ 189.05(CO), 42.02(C_1), 54.20(C_2), 46.64(C_3), 51.83(C_4), 136.32($C_{5,6}$), 45.56(C_7), 25.87(CH_3), 124.87-154.26(Ar-C).

(3-(3-Nitrophenyl)bicyclo[2.2.1]hept-5-en-2-yl)(2-hydroxy-naphthalen-1-yl)methanone (11)

IR(KBr) 3459.86, 3097.15, 2889.31, 1691.36, 1578.32, 1465.37, 1342.36, 1105.35, 1023.34, 823.51cm^{-1}; ^{1}H NMR(400MHz, $CDCl_3$): δ 3.234(dd, 1H, H_1) *J* = 10.28 and 8.63Hz, 3.668(t, 1H, H_2), 3.551(t, 1H, H_3), 2.679(dd, 1H, H_4) *J* = 9.82 and 10.60Hz, 6.462(d, 1H, H_5), 6.439(d, 1H, H_6), 2.001(dd, 1H, H_7 *J* = 6.82 and 6.68Hz, 1.742(dd, 1H, $H_{7'}$) *J* = 8.84 and 6.62 Hz, 7.766-8.683(m, 10H, Ar-H); ^{13}C NMR(100MHz, $CDCl_3$): δ 191.23(CO), 44.82(C_1), 51.98(C_2), 45.84(C_3), 50.16(C_4), 136.82($C_{5,6}$), 47.37(C_7), 124.95-154.95(Ar-C).

(3-(4-Nitrophenyl)bicyclo[2.2.1]hept-5-en-2-yl)(2-hydroxy-naphthalen-1-yl)methanone (12)

IR(KBr) 3455.98, 3092.34, 1686.76, 1548.22, 1498.13, 1176.16, 998.83, 885.43 cm^{-1}; ^{1}H NMR(400 MHz, $CDCl_3$): δ 3.124(dd, 1H, H_1) *J* = 17.2 and 6.1Hz, 3.743(t, 1H, H_2), 3.527(t, 1H, H_3), 2.758(dd, 1H, H_4) *J*= 12.4 and 4.8Hz, 6.349(d, 1H, H_5), 6.438(d, 1H, H_6), 2.212(dd, 1H, H_7) *J*= 12.4 and 4.4Hz, 1.442(dd, 1H, $H_{7'}$) *J*= 10.4 and 7.4Hz, 7.268-8.558(m, 10H, Ar-H); ^{13}C NMR(100MHz, $CDCl_3$): δ 189.38(CO), 43.74(C_1), 52.46(C_2), 44.55(C_3), 50.38(C_4), 135.76($C_{5,6}$), 46.57(C_7), 125.36-153.29(Ar-C).

Antibacterial activity assay

The disc diffusion technique was followed [24, 27, 30] at a concentration of 250 μg mL-1 ampicillin and streptomycin used as the standard drugs. The measured antibacterial activities regarding zone of inhibition in millimetres of all bicyclic ketones are presented in Table 3.

Compounds **3-6** were shown maximum zone of inhibition against *Escherichia coli*, with greater than 20 mm of the zone of inhibition compared to the methanones **2, 9**, and **12** are moderately active in 13-19 mm of the zone of inhibition. Ketones **8** and **11** are active within 8-12 mm the of zone of inhibition. The bicyclic ketones **4**, **6** and **7** were found to be effective against *S. aureus* greater than 20-24 mm of the zone of inhibition. Compounds **3**, **9** and **10** were moderately active greater than 13-19 mm of the zone of inhibition. The bicyclic methanone **2** and **5** were active within 8-12 mm of the zone of inhibition.

The bicyclic keto derivatives **4** and **6** were more active against *Pseudomonas* showing greater than 20 mm zone of inhibition and the other derivatives **1, 3, 7, 8**, 11 and 12 were showed the zone of inhibitions between 13-19 mm. Compounds **5, 9** and **10** have shown moderately active with the zone of inhibition of 8-12 mm. The bicyclic ketones **2, 5, 6** and **12** are effective against *K. pneumoniae* with 20-24 mm zone of inhibition while the other ketones showed a moderate activity. The methanones **1, 4, 6** and **19** were active when it is screened against *P. vulgaris*, and the other compounds were found to be less effective. The ketones **1, 3** and **5** showed activities against E. faecalis when they are screened with 20-24 mm zone of inhibition.

Table 3. Antibacterial activities of (2-hydroxy-1-naphthyl)(3-(substituted phenyl)bicyclo[2.2.1]hept-5-en-2-yl)methanones.

No	X	*E. coli*	*S. aureus*	*P. aeruginosa*	*K. pneumoniae*	*P.vulgaris*	*E. faecalis*
1	H	---	---	+	---	++	++
2	3-Br	+		---	++	+	---
3	4-Br	++	+	+	---	---	++
4	2-Cl	++	++	++	---	++	+
5	3-Cl	++			++	+	++
6	4-Cl	++	++	++	++	++	---
7	2-OH	---	++	+	---	+	+
8	4-OH	---	---	+	---	---	+
9	4-OCH_3	+	+	---	---	++	---
10	4-CH_3	---	+	---	---	+	---
11	3- NO_2	---	---	+	+	---	+
12	4-NO_2	+	---	+	++	+	---

Disc size:6.35 mm; duration:24-45 h; standard:ampicillin (30-33 mm) and streptomycin (20-25 mm); Control:methanol; ---: No activities; --:active (8-12 mm); +: Moderately active(13-19 mm); ++: active (20-24 mm).

Antifungal activity assay

The observed antifungal activities of all prepared methanones are presented in Table 4. Evaluation of antifungal activities of all methanones against *C. albicans* showed that the three compounds **9**, **11** and **12** are effective with 20 mm as the zone of inhibition in 250 µg mL-1 concentration. The methanones **3, 4, 6** and **7** are active with 13-19 mm zone of inhibition containing one fungal colony, and the compounds **1** and **10** were least active with 8-12 mm zone of inhibition containing two or three fungal colonies. Methanones **2, 5** and **8** were inactive in antifungal activity and they contain heavy fungal colonies.

Table 4. Antifungal activities of (2-hydroxy-1-naphthyl)-3-(substituted phenyl)bicyclo[2.2.1]hept-5-en-2-ylmethanones

No.	X	Disc diffusion technique (250 µg mL^{-1}) *C. albicans*	Drug dilution method (50µg mL^{-1})	
			P. species	*A. niger*
1	H	---	+	+
2	3-Br	---	++	+
3	4-Br	+	---	---
4	2-Cl	+	---	++
5	3-Cl	---	---	---
6	4-Cl	+	---	+
7	2-OH	+	+	++
8	4-OH	---	+	---
9	2-OCH_3	++	++	+
10	4-CH_3		++	+
11	3-NO_2	++	++	++
12	4-NO_2	++	++	++

Standard: Griseofulvin and Gentamycin; Duration: 72 h; Control: Methanol; Medium: Potato dextrose agar; ++: No fungal colony; +: One fungal colony; Two-three fungal colonies; ---: Heavy fungal colony.

Compounds **2, 9** and **10-12** are highly active against *Penicillium species* in 20mm of the zone of inhibitions. Ketones **1, 7** and **8** are active, and they show one fungal colony in13-19 mm of the zone of inhibition. Compounds **5** and **6** produced 2-3 fungal colonies and inactive in 8-12 mm of the zone of inhibition against *Penicillium species*. Heavy fungal colonies were produced by the compounds **3** and **4** leads to inactive against *Penicillium species* fungal strain species. The mm of zone inhibition of ketones against *A. niger* was higher for the compounds **4, 7, 11** and **12** at 20 mm of the zone of inhibition. Compounds **1, 2, 6, 9** and **10** were active in 13-19 mm of the zone of inhibition with one fungal colony. The ketone **13** was least active with 2-3 fungal colonies against *A. niger* fungal strain in 8-12 mm of the zone of inhibition. Bicyclic methanone compounds **5** and **8** are inactive against *A. niger* fungal strain and produced heavy fungal colonies. The presence of bromo-, chloro-, methoxy-, methyl- and nitro- substituents are responsible for the enhancement of antimicrobial activities of methanones.

Anti-oxidant activity

From the statistical results of radical scavenging activity experiments, the observed antioxidant activities of methanones [29,30] were presented in Table 5. From Table 5, all bicyclic methanones are active and shows antioxidant activity referred to standard.

Table 5. Antioxidant activities of (2-hydroxy-1-naphthyl)-3-(substituted phenyl)bicyclo[2.2.1]hept-5-en-2-ylmethanones

Entry	X	Antioxidant activity (DPPH radical scavenging)
1	H	34.78 ± 1.18
2	3-Br	32.89 ± 1.26
3	4-Br	31.59 ± 1.18
4	2-Cl	31.85 ± 1.92
5	3-Cl	32.58 ± 1.19
6	4-Cl	32.95 ± 1.54
7	2-OH	37.01 ± 1.65
8	4-OH	37.16 ± 1.69
9	2-OCH_3	36.90 ± 1.78
10	4-CH_3	34.19 ± 1.25
11	3-NO_2	31.18 ± 1.64
12	4-NO_2	31.94 ± 1.82
	α-Tocoferol	37.34 ± 1.57

The observed percentages of inhibition of diphenyl picrylhydrazyl (DPPH) radical scavenging activities are 31.18–37.16 and the standard have 37.34. Among all methanones, the hydroxy and methoxy-substituted methanones (**7** and **8**) were shown most significant antioxidant activity.

CONCLUSIONS

Some (2-hydroxynaphthalen-1-yl)(3-(substituted phenyl)-bicyclo[2.2.1]hept-5-en-2-yl)methanones have been synthesized by water mediated fly-ash catalyzed Diels-Alder [4+2] cycloaddition of cyclopentadiene and substituted styryl (*E*)-2-hydroxy-1-naphthyl ketones. The yields of these methanones were more than 60 %. This greener method offered pollution free environment, less solvent hazard synthesis, simple operative and handling procedure and obtained the good yields. The purities of the synthesized methanones were examined by their physical constants and spectroscopic data. These data were supported for conformation of formation of bicyclic methanones. The antimicrobial activities of these ketones were evaluated by the Bauer-Kirby method. The halogens, methoxy- and nitro- substituted bicyclic methanones show good antibacterial and antifungal activities against their respective microbial strains. The hydroxy- and methoxy- substituted bicyclic ketones shows significant antioxidant activity.

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