

Synthesis, characterization and evaluation of biological activities of some 2,3-diaryl bicyclo methanones

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Abstract. Sixteen (3,4-dichlorophenyl)-3-(substituted phenyl)bicyclo[2.2.1]hept-5-ene-2-yl) methanone derivatives have been synthesized by an aqueous phase fly-ash catalyzed [4+2] cycloaddition Diels-Alder reaction of cyclopentadiene and 3,4-dichloro phenyl chalcones. The yields of the methanones were greater than 60%. The synthesized methanones were characterized by their physical constants and spectral data. The antimicrobial and antioxidant activities of the synthesized methanones were evaluated using a variety of bacterial and fungal species and DPPH radical scavenging methods.

Keywords: bicyclo[2.2.1]hept-5-ene-2-yl-methanones; Diels-Alder reaction; antimicrobial activities; antioxidant activity.

1. Introduction

Methanones are versatile key intermediates [1] and important bioactive molecules [2, 3] due to carbonyl tautomer's, presence of polar groups and the degree of hydrophilicity or hydrophobicity. Methyl ketones and bicyclo methanones possess many pharmacological activities such as, AVP release and activation of vasopressin receptors [3], antimicrobial [4-15], cannabinoid receptor agonists [16], neuronal nicotinic acetylcholine receptors (nAChRs) [17], anti-inflammatory [12, 13, 18, 19], analgesic [10, 19], anticonvulsant [10, 19], antitumor [19], anticancer [10], antiviral [19], anti-diabetic [10, 20], antitubercular [20], antihelminthic [12, 20], antidepressant [21], ulcerogenic [18], antinociceptive [10], protein tyrosine kinase inhibitor [22], DNA cleavage [23], Alzheimer's disease curing agent [24], antioxidant [25], acute toxicity [18], antihypertensive [10] and insect antifeedant activities [25]. Numerous solvent-free and solvent assisted synthetic methods with or without catalysts were reported in the literature for the synthesis of stereo selective mono- and bicyclo- methanones [26-28]. Aqueous phase Diels-Alder reaction is one of the best reactions for the synthesis of bicyclo methanones. This reaction involves [4+2] cycloaddition of diene and dienophiles. Rideout and Breslow [29] have studied the aqueous phase reaction of cyclopentadiene and vinyl methyl ketones in water. Many catalysts including Lewis acids [29], Brönsted acids [29, 30], asymmetric catalysts with helical polymers [31], Cu²⁺ ion-mediated nanotubes [32], DNA and micellar-based catalysts [33-37], have been employed for this

[4+2] cycloaddition Diels-Alder reaction of cyclopentadiene (diene) and *E*-chalcones (dienophiles). Recently, Thirunarayanan has reported the synthesis and antimicrobial, antioxidant and insect antifeedant activities of some 2-naphthyl based bicyclo methanones [25]. The synthesis of 3,4-dichlorophenyl based-heptene[2.2.1]methanones by aqueous phase fly-ash catalyzed Diels-Alder reaction of cyclopentadiene and 3,4-dichlorophenyl chalcones has not been reported. Hence, the author have synthesize some 2-(3,4-dichlorophenyl)-3-(substituted phenyl)heptene[2.2.1]methanones and evaluated their antimicrobial and antioxidant activities using the appropriate microbial strains with Bauer-Kirby [38] and DPPH radical scavenging [39] methods.

2. Experimental

2.1. General

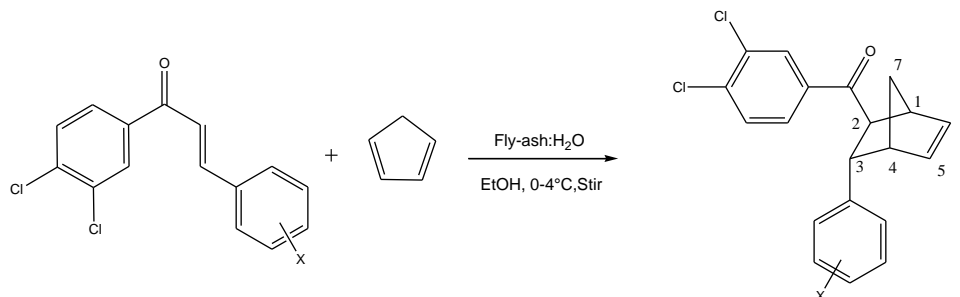
All chemicals were procured from Sigma-Aldrich and E. Merck. Fly-ash was collected from the Thermal Power Plant-II, Neyveli Lignite Corporation (NLC), Neyveli, Tamil Nadu, India. Melting points of substituted aryl bicyclo[2.2.1]heptene-2-yl-methanones were determined in open glass capillaries on a Mettler FP51 melting point apparatus and are uncorrected. Infrared spectra (KBr, 4000–400 cm⁻¹) were recorded on Thermo Scientific Nicolet iS5, US-made Fourier transform spectrophotometer. The NMR spectra of selective compounds were recorded on a Bruker AV 400 spectrometer operating at 400 MHz for ¹H NMR spectra and 100 MHz for ¹³C NMR spectra in CDCl₃ solvent using TMS as internal standard. Electron impact and chemical ionization

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mode FAB⁺ mass spectra were recorded with a Shimadzu spectrometer. The elemental analysis of all methanones were performed in a Perkin Elmer 240C analyzer.

2.2. Synthesis of 2-naphthyl chalcones

The substituted styryl 3,4-dichlorophenyl ketones were synthesized as described in reference [40].



X= H, 3-NH₂, 3-Br, 2-Cl, 3-Cl, 4-Cl, 4-N(CH₃)₂, 4-F, 2-OH, 4-OH, 3-OCH₃, 4-OCH₃, 4-CH₃, 2-NO₂, 3-NO₂, 4-NO₂

Scheme 1. Synthesis of (3-substituted phenyl)bicyclo[2.2.1]hept-5-en-2-yl-(3,4-dichlorophenyl) methanone derivatives by fly-ash catalyzed aqueous phase Diels-Alder [4+2] cycloaddition of 3,4-dichlorophenyl chalcones and cyclopentadiene.

Progress of the reaction was monitored by thin-layer chromatography. Dichloromethane (10 mL) was added and the extract was separated by filtration. The filtrate was washed with water, brine (10 mL), dried over anhydrous Na₂SO₄ and concentrated to give a solid product. The crude product was further purified by recrystallization with ethanol.

Infrared and NMR spectral data of methanones are as follows.

(3,4-Dichlorophenyl)(3-phenylbicyclo[2.2.1]hept-5-en-2-yl)methanone (Compound 1): IR (KBr, cm⁻¹): ν = 3028, 2913, 1665, 1463, 838, 723; ¹H NMR (400 MHz, CDCl₃, 25 °C, TMS): δ = 3.691 (dd, 1H, H₁, J = 6 and 4 Hz), 3.481 (t, 1H, H₂, J = 19 Hz), 3.367 (t, 1H, H₃, J = 16 Hz), 2.667 (dd, 1H, H₄, J = 4.6 and 4 Hz), 6.251 (d, 1H, H₅, J = 15 Hz), 6.424 (d, 1H, H₆, J = 15 Hz), 1.792 (dd, 1H, H₇, J = 4 and 6 Hz), 1.631 (dd, 1H, H₇, J = 8 and 6 Hz), 7.261-8.237 (m, 8H, Ar-H); ¹³C NMR (100 MHz, CDCl₃, 25 °C, TMS): δ = 198.25 (CO), 46.68 (C₁), 52.74 (C₂), 44.68 (C₃), 46.68 (C₄), 134.28 (C₅), 136.12 (C₆), 46.27 (C₇), 125.87-147.28 (Ar-C);

(3-(3-Aminophenyl)bicyclo[2.2.1]hept-5-en-2-yl)(3,4-dichlorophenyl)methanone (Compound 2): IR (KBr, cm⁻¹): ν = 3456, 2814, 1668, 1462, 1298, 864, 715; ¹H NMR (400 MHz, CDCl₃, 25 °C, TMS): δ = 3.692 (dd, 1H, H₁, J = 4 and 4.8 Hz), 3.471 (t, 1H, H₂, J = 18 Hz), 3.313 (t, 1H, H₃, J = 17 Hz), 2.728 (dd, 1H, H₄, J = 6 and 4 Hz), 6.115 (d, 1H, H₅, J = 16 Hz), 6.835 (d, 1H, H₆, J = 16 Hz), 1.802 (dd, 1H, H₇, J = 6.4 and 4 Hz), 1.624 (dd, 1H, H₇, J = 4.8 and 6 Hz), 6.643 (s, 2H, NH₂), 6.452-8.312 (m, 7H, Ar-H); ¹³C NMR (100 MHz, CDCl₃, 25 °C, TMS): δ = 197.66

2.3. General procedure for synthesis of 3,4-dichlorophenyl bicyclo[2.2.1]heptene-2-yl-methanones

Appropriate equimolar quantities of 3,4-dichlorophenyl chalcones (2 mmol) in 15 mL of ethanol, cyclopentadiene (2 mmol) and 1 g of fly-ash in 20 mL of water were stirred for 6 h at 0–4 °C overnight (Scheme 1).

(CO), 46.73 (C₁), 52.76 (C₂), 44.84 (C₃), 46.48 (C₄), 134.26 (C₅), 135.92 (C₆), 46.37 (C₇), 112.73-146.92 (Ar-C).

(3-(3-Bromophenyl)bicyclo[2.2.1]hept-5-en-2-yl)(3,4-dichlorophenyl)methanone (Compound 3): IR (KBr, cm⁻¹): ν = 3061, 2925, 1671, 1425, 1236, 1065, 892, 751, 623; ¹H NMR (400 MHz, CDCl₃, 25 °C, TMS): δ = 3.711 (dd, 1H, H₁, J = 6 and 4.8 Hz), 3.481 (t, 1H, H₂, J = 16 Hz), 3.363 (t, 1H, H₃, J = 14.5 Hz), 2.713 (dd, 1H, H₄, J = 6.8 and 4 Hz), 6.217 (d, 1H, H₅, J = 15.5 Hz), 6.301 (d, 1H, H₆, J = 15.5 Hz), 1.791 (dd, 1H, H₇, J = 4.8 and 4 Hz), 1.641 (dd, 1H, H₇, J = 8 and 6 Hz), 7.263-8.317 (m, 7H, Ar-H); ¹³C NMR (100 MHz, CDCl₃, 25 °C, TMS): δ = 194.25 (CO), 46.67 (C₁), 52.83 (C₂), 44.71 (C₃), 46.53 (C₄), 135.22 (C₅), 136.04 (C₆), 46.39 (C₇), 122.71-148.25 (Ar-C).

(3-(2-Chlorophenyl)bicyclo[2.2.1]hept-5-en-2-yl)(3,4-dichlorophenyl)methanone (Compound 4): IR (KBr, cm⁻¹): ν = 3026, 1647, 1563, 1358, 1245, 1064, 932, 810, 723; ¹H NMR (400 MHz, CDCl₃, 25 °C, TMS): δ = 3.721 (dd, 1H, H₁, J = 6 and 8 Hz), 3.507 (t, 1H, H₂, J = 19 Hz), 3.473 (t, 1H, H₃, J = 18 Hz), 2.695 (dd, 1H, H₄, J = 6.4 and 4 Hz), 6.217 (d, 1H, H₅, J = 18 Hz), 6.831 (d, 1H, H₆, J = 18 Hz), 1.781 (dd, 1H, H₇, J = 5.6 and 6.4 Hz), 1.645 (dd, 1H, H₇, J = 8 and 6.4 Hz), 7.217-8.349 (m, 7H, Ar-H); ¹³C NMR (100 MHz, CDCl₃, 25 °C, TMS): δ = 190.53 (CO), 46.72 (C₁), 52.71 (C₂), 44.69 (C₃), 46.51 (C₄), 135.72 (C₅), 136.14 (C₆), 46.28 (C₇), 126.41-143.72 (Ar-C).

(3-(3-Chlorophenyl)bicyclo[2.2.1]hept-5-en-2-yl)(3,4-dichlorophenyl)methanone (Compound 5): IR (KBr, cm⁻¹): ν = 3041, 1658, 1541, 1354, 1284, 1058,

959, 858, 784; ^1H NMR (400 MHz, CDCl_3 , 25 °C, TMS): δ = 3.741 (dd, 1H, H_1 , J = 8 and 4 Hz), 3.517 (t, 1H, H_2 , J = 16 Hz), 3.423 (t, 1H, H_3 , J = 17 Hz), 2.699 (dd, 1H, H_4 , J = 6 and 8 Hz), 6.301 (d, 1H, H_5 , J = 15 Hz), 6.714 (d, 1H, H_6 , J = 15 Hz), 1.794 (dd, 1H, H_7 , J = 6.4 and 4 Hz), 1.647 (dd, 1H, H_7 , J = 5.6 and 6.4 Hz), 7.817-8.371 (m, 7H, Ar-H); ^{13}C NMR (100 MHz, CDCl_3 , 25 °C, TMS): δ = 196.28 (CO), 46.68 (C_1), 52.74 (C_2), 44.89 (C_3), 46.54 (C_4), 135.64 (C_5), 136.27 (C_6), 46.23 (C_7), 125.19-149.37 (Ar-C).

(3-(4-Chlorophenyl)bicyclo[2.2.1]hept-5-en-2-yl)(3,4-dichlorophenyl)methanone (Compound **6**): IR (KBr, cm^{-1}): ν = 3038, 1678, 1554, 1362, 1228, 1081, 962, 848, 735; ^1H NMR (400MHz, CDCl_3 , 25 °C, TMS): δ = 3.729 (dd, 1H, H_1 , J = 6.4 and 4.8 Hz), 3.621 (t, 1H, H_2 , J = 19 Hz), 3.481 (t, 1H, H_3 , J = 19 Hz), 2.690 (dd, 1H, H_4 , J = 4 and 6.4 Hz), 6.314 (d, 1H, H_5 , J = 15.5 Hz), 6.617 (d, 1H, H_6 , J = 15.5 Hz), 1.751 (dd, 1H, H_7 , J = 8 and 6 Hz), 1.641 (dd, 1H, H_7 , J = 6 and 4 Hz), 7.245-8.217 (m, 7H, Ar-H); ^{13}C NMR (100 MHz, CDCl_3 , 25 °C, TMS): δ = 198.62 (CO), 46.62 (C_1), 52.69 (C_2), 44.72 (C_3), 46.53 (C_4), 135.72 (C_5), 136.18 (C_6), 46.33 (C_7), 126.81-144.44 (Ar-C).

(3-(4-Dimethylaminophenyl)bicyclo[2.2.1]hept-5-en-2-yl)(3,4-dichlorophenyl)methanone (Compound **7**): IR (KBr, cm^{-1}): ν = 3321, 2802, 1664, 1562, 1368, 1052, 813, 751; ^1H NMR (400 MHz, CDCl_3 , 25 °C, TMS): δ = 3.728 (dd, 1H, H_1 , J = 8 and 4 Hz), 3.611 (t, 1H, H_2 , J = 19 Hz), 3.396 (t, 1H, H_3 , J = 17 Hz), 2.482 (dd, 1H, H_4 , J = 6 and 4 Hz), 6.281 (d, 1H, H_5 , J = 18 Hz), 6.601 (d, 1H, H_6 , J = 18 Hz), 1.733 (dd, 1H, H_7 , J = 4 and 6 Hz), 1.655 (dd, 1H, H_7 , J = 8 and 6.4 Hz), 3.178 (s, 6H, 2CH_3); 7.127-8.231 (m, 7H, Ar-H); ^{13}C NMR (100 MHz, CDCl_3 , 25 °C, TMS): δ = 193.25 (CO), 46.34 (C_1), 51.97(C_2), 44.68(C_3), 46.47 (C_4), 135.66 (C_5), 136.26 (C_6), 46.27 (C_7), 40.83 (CH_3), 112.67-148.80 (Ar-C).

(3-(4-Fluorophenyl)bicyclo[2.2.1]hept-5-en-2-yl)(3,4-dichlorophenyl)methanone (Compound **8**): IR (KBr, cm^{-1}): ν = 3012, 2799, 1661, 1526, 1495, 1387, 1258, 1063, 952, 863, 729; ^1H NMR (400 MHz, CDCl_3 , 25 °C, TMS): δ = 3.770 (dd, 1H, H_1 , J = 6.4 and 8 Hz), 3.631 (t, 1H, H_2 , J = 17 Hz), 3.394 (t, 1H, H_3 , J = 16 Hz), 2.695 (dd, 1H, H_4 , J = 6 and 8 Hz), 6.341 (d, 1H, H_5 , J = 19 Hz), 6.675(d, 1H, H_6 , J = 19 Hz), 1.750(dd, 1H, H_7 , J = 4 and 4.8 Hz), 1.639 (dd, 1H, H_7 , J = 7.6 and 5.6 Hz), 7.167-8.317 (m, 7H, Ar-H); ^{13}C NMR (100 MHz, CDCl_3 , 25 °C, TMS): δ = 191.62 (CO), 47.71 (C_1), 52.81 (C_2), 44.81 (C_3), 46.78(C_4), 135.73 (C_5), 136.18 (C_6), 46.57 (C_7), 115.71-142.85 (Ar-C).

(3-(2-Hydroxyphenyl)bicyclo[2.2.1]hept-5-en-2-yl)(3,4-dichlorophenyl)methanone (Compound **9**): IR (KBr, cm^{-1}): ν = 3462, 2841, 1667, 1535, 1428, 1068, 958, 754; ^1H NMR (400 MHz, CDCl_3 ,

25 °C, TMS): δ = 3.776 (dd, 1H, H_1 , J = 8 and 6.4 Hz), 3.629 (t, 1H, H_2 , J = 16 Hz), 3.381 (t, 1H, H_3 , J = 19 Hz), 2.704 (dd, 1H, H_4 , J = 4 and 8 Hz), 6.352 (d, 1H, H_5 , J = 16 Hz), 6.627 (d, 1H, H_6 , J = 16 Hz), 1.766 (dd, 1H, H_7 , J = 4.8 and 6Hz), 1.658 (dd, 1H, H_7 , J = 8 and 4 Hz), 5.621 (s, 1H, OH), 7.124-8.524 (m, 7H, Ar-H); ^{13}C NMR (100 MHz, CDCl_3 , 25 °C, TMS): δ = 198.23 (CO), 47.24 (C_1), 52.37(C_2), 44.62 (C_3), 46.83 (C_4), 135.84 (C_5), 136.36 (C_6), 46.54 (C_7), 115.62-137.38 (Ar-C).

(3-(4-Hydroxyphenyl)bicyclo[2.2.1]hept-5-en-2-yl)(3,4-dichlorophenyl)methanone (Compound **10**): IR (KBr, cm^{-1}): ν = 3458, 2871, 1674, 1562, 1482, 1028, 935, 781; ^1H NMR (400 MHz, CDCl_3 , 25 °C, TMS): δ = 3.769 (dd, 1H, H_1 , J = 4 and 6 Hz), 3.637 (t, 1H, H_2 , J = 19 Hz), 3.271 (t, 1H, H_3 , J = 17 Hz), 2.968 (dd, 1H, H_4 , J = 8 and 4 Hz), 6.314 (d, 1H, H_5 , J = 15 Hz), 6.651 (d, 1H, H_6 , J = 15 Hz), 1.756 (dd, 1H, H_7 , J = 6 and 4 Hz), 1.640 (dd, 1H, H_7 , J = 8 and 6 Hz), 5.371 (s, 1H, OH), 6.671-8.391 (m, 7H, Ar-H); ^{13}C NMR (100 MHz, CDCl_3 , 25 °C, TMS): δ = 199.72 (CO), 47.34 (C_1), 52.74(C_2), 44.56 (C_3), 46.67 (C_4), 135.67 (C_5), 136.29 (C_6), 46.32 (C_7), 115.61-138.73 (Ar-C).

(3-(3-Methoxyphenyl)bicyclo[2.2.1]hept-5-en-2-yl)(3,4-dichlorophenyl)methanone (Compound **11**): IR (KBr, cm^{-1}): ν = 3065, 2810, 1628, 1539, 1424, 1246, 1095, 962, 827, 739; ^1H NMR (400 MHz, CDCl_3 , 25 °C, TMS): δ = 3.721 (dd, 1H, H_1 , J = 6 and 4 Hz), 3.621 (t, 1H, H_2 , J = 18 Hz), 3.267 (t, 1H, H_3 , J = 17 Hz), 2.674 (dd, 1H, H_4 , J = 4 and 6 Hz), 6.431 (d, 1H, H_5 , J = 18 Hz), 6.649 (d, 1H, H_6 , J = 18 Hz), 1.775 (dd, 1H, H_7 , J = 8 and 6 Hz), 1.646(dd, 1H, H_7 , J = 4 and 6 Hz), 3.817 (s, 3H, OCH_3), 6.817-8.571 (m, 7H, Ar-H); ^{13}C NMR (100 MHz, CDCl_3 , 25 °C, TMS): δ = 193.05 (CO), 47.54 (C_1), 53.76 (C_2), 44.92 (C_3), 46.83 (C_4), 135.74 (C_5), 136.34 (C_6), 46.59 (C_7), 59.73 (OCH_3), 114.47-145.78 (Ar-C).

(3-(4-Methoxyphenyl)bicyclo[2.2.1]hept-5-en-2-yl)(3,4-dichlorophenyl)methanone (Compound **12**): IR (KBr, cm^{-1}): ν = 3071, 2812, 1623, 1542, 1436, 1229, 1081, 968, 851, 746; ^1H NMR (400 MHz, CDCl_3 , 25 °C, TMS): δ = 3.743 (dd, 1H, H_1 , J = 8 and 4 Hz), 3.613 (t, 1H, H_2 , J = 16 Hz), 3.224 (t, 1H, H_3 , J = 17 Hz), 2.663 (dd, 1H, H_4 , J = 4 and 6 Hz), 6.441 (d, 1H, H_5 , J = 15 Hz), 6.637 (d, 1H, H_6 , J = 15 Hz), 1.747 (dd, 1H, H_7 , J = 6 and 4.8 Hz), 1.631(dd, 1H, H_7 , J = 4 and 6 Hz), 3.837 (s, 3H, OCH_3), 6.913-8.538 (m, 7H, Ar-H); ^{13}C NMR (100 MHz, CDCl_3 , 25 °C, TMS): δ = 193.25 (CO), 47.59 (C_1), 53.87 (C_2), 44.83 (C_3), 46.72 (C_4), 135.66 (C_5), 136.22 (C_6), 46.34 (C_7), 62.78 (OCH_3), 113.92-139.75 (Ar-C).

(3-(4-Methylphenyl)bicyclo[2.2.1]hept-5-en-2-yl)(3,4-dichlorophenyl)methanone (Compound **13**): IR (KBr, cm^{-1}): ν = 2994, 2801, 1654, 1598, 1423,

1459, 1062, 965, 824, 751; ^1H NMR (400 MHz, CDCl_3 , 25 °C, TMS): δ = 3.747 (dd, 1H, H_1 , J = 6 and 8 Hz), 3.607 (t, 1H, H_2 , J = 19 Hz), 3.217 (t, 1H, H_3 , J = 16 Hz), 2.689 (dd, 1H, H_4 , J = 8 and 4 Hz), 6.437 (d, 1H, H_5 , J = 16 Hz), 6.651 (d, 1H, H_6 , J = 16 Hz), 1.748 (dd, 1H, H_7 , J = 4 and 8 Hz), 1.639 (dd, 1H, H_7 , J = 6 and 8 Hz), 2.37 (s, 3H, CH_3), 7.158-8.536 (m, 7H, Ar-H); ^{13}C NMR (100 MHz, CDCl_3 , 25 °C, TMS): δ = 195.24 (CO), 47.61 (C_1), 53.97 (C_2), 44.92 (C_3), 46.69 (C_4), 135.72 (C_5), 136.34 (C_6), 46.28 (C_7), 24.72 (CH_3), 126.38-143.81 (Ar-C).

(3-(2-Nitrophenyl)bicyclo[2.2.1]hept-5-en-2-yl)(3,4-dichlorophenyl)methanone (Compound **14**): IR (KBr, cm^{-1}): ν = 3123, 2954, 1674, 1532, 1428, 1047, 946, 825, 792; ^1H NMR (400 MHz, CDCl_3 , 25 °C, TMS): δ = 3.767 (dd, 1H, H_1 , J = 6 and 8 Hz), 3.617 (t, 1H, H_2 , J = 17 Hz), 3.513 (t, 1H, H_3 , J = 17 Hz), 2.758 (dd, 1H, H_4 , J = 4 and 6 Hz), 6.417 (d, 1H, H_5 , J = 19 Hz), 6.617 (d, 1H, H_6 , J = 19 Hz), 1.826 (dd, 1H, H_7 , J = 8 and 4 Hz), 1.676 (dd, 1H, H_7 , J = 6 and 4 Hz), 7.531-8.517 (m, 7H, Ar-H); ^{13}C NMR (100 MHz, CDCl_3 , 25 °C, TMS): δ = 198.64 (CO), 46.732 (C_1), 52.71 (C_2), 45.87 (C_3), 46.72 (C_4), 135.78 (C_5), 136.67 (C_6), 46.54 (C_7), 124.51-152.47 (Ar-C).

(3-(3-Nitrophenyl)bicyclo[2.2.1]hept-5-en-2-yl)(3,4-dichlorophenyl)methanone (Compound **15**): IR (KBr, cm^{-1}): ν = 3098, 2875, 1668, 1554, 1484, 1056, 981, 882, 753; ^1H NMR (400 MHz, CDCl_3 , 25 °C, TMS): δ = 3.764 (dd, 1H, H_1 , J = 4 and 8 Hz), 3.623 (t, 1H, H_2 , J = 16 Hz), 3.519 (t, 1H, H_3 , J = 16 Hz), 2.784 (dd, 1H, H_4 , J = 6 and 4 Hz), 6.501 (d, 1H, H_5 , J = 15 Hz), 6.651 (d, 1H, H_6 , J = 15 Hz), 1.799 (dd, 1H, H_7 , J = 4 and 6 Hz), 1.689 (dd, 1H, H_7 , J = 8 and 4 Hz), 7.634-8.513 (m, 7H, Ar-H); ^{13}C NMR (100 MHz, CDCl_3 , 25 °C, TMS): δ = 199.87 (CO), 46.76 (C_1), 52.69 (C_2), 45.79 (C_3), 46.70 (C_4), 135.76 (C_5), 136.41 (C_6), 46.34 (C_7), 121.05-146.94 (Ar-C).

(3-(4-Nitrophenyl)bicyclo[2.2.1]hept-5-en-2-yl)(3,4-dichlorophenyl)methanone (Compound **16**): IR (KBr, cm^{-1}): ν = 3095, 2884, 1671, 1562, 1494, 1073, 959, 852, 781; ^1H NMR (400 MHz, CDCl_3 , 25 °C, TMS): δ = 3.772 (dd, 1H, H_1 , J = 8 and 4 Hz), 3.697 (t, 1H, H_2 , J = 17 Hz), 3.521 (t, 1H, H_3 , J = 17 Hz), 2.796 (dd, 1H, H_4 , J = 8 and 4 Hz), 6.511 (d, 1H, H_5 , J = 16 Hz), 6.654 (d, 1H, H_6 , J = 16 Hz), 1.835 (dd, 1H, H_7 , J = 8 and 4 Hz), 1.693 (dd, 1H, H_7 , J = 6 and 8 Hz), 7.562-8.551 (m, 7H, Ar-H); ^{13}C NMR (100 MHz, CDCl_3 , 25 °C, TMS): δ = 199.94 (CO), 46.77 (C_1), 52.71 (C_2), 45.84 (C_3), 46.79 (C_4), 135.71 (C_5), 136.51 (C_6), 46.38 (C_7), 123.514-152.11 (Ar-C).

2.4. Antimicrobial activity

The prepared bicyclo[2.2.1]heptene-2-yl-methanones were subjected to evaluate the antimicrobial activities by measuring the zone of inhibition against their bacterial and fungal strains.

Two gram-positive pathogenic strains (*Staphylococcus aureus*, *Enterococcus faecalis*) and four gram-negative strains (*Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa* and *Proteus vulgaris*) were applied for evaluation of antimicrobial activities. The Bauer-Kirby [38] disc diffusion technique was adopted at the concentration of 250 $\mu\text{g/mL}$ of compounds with ampicillin and streptomycin as standards. The disc diffusion technique was used for the evaluation of antifungal activity of ketones against *Candida albicans* strain and the dilution method was adopted for *Penicillium sp.* and *Aspergillus niger* strains. The dilution concentration of the compounds are 50 $\mu\text{g/mL}$ and Griseofulvin was employed as standard drug.

2.4.1. Measurement of antibacterial sensitivity

The Bauer-Kirby [38] disc diffusion technique was adopted for measurement of antibacterial sensitivity assay of all compounds. About 0.5 mL of bacterial test compounds were spread uniformly over solidified Mueller-Hinton agar. About 5 mm diameter of discs made from Whatmann No. 1 filter paper were placed on the medium with potential inhibitor solution. The plates were incubated for 24 h at 37 °C upside down for prevention of collection of water droplets over the medium. Then the plates were examined and the diameter values (mm) of zone of inhibition were measured. The triplicate results were recorded.

2.4.2. Measurement of antifungal sensitivity

The Bauer-Kirby [38] disc diffusion technique was used for the evaluation of antifungal activity of synthesized methanones. The sterilized Potato Dextrose Agar medium was added to the Petri plates containing 1 mL of fungal strains. Uniform spread of the agar on the plates were performed by means of clock and anti-clockwise rotation of the discs. The test solution was prepared by dissolving 15 mg of the methanones in 1 mL of DMSO solvent and it was applied on the discs. This medium was incubated to solidify for 24 or 72 h at 25 or 28 °C. Then these plates were examined for the evaluation of antifungal activity by means of measuring the diameter (mm) of zone of inhibition. Triplicate measurement results were recorded.

2.5. Antioxidant activity

The DPPH radical scavenging activity technique [39] was used for the measurement of antioxidant activity of all prepared methanones. About 20 mL of sodium acetate buffer solution was prepared by dissolving 1.64 g of sodium acetate in 15 mL of water and 150 μL of acetic acid, and the final volume was adjusted to 20 mL of water. About 50 mL of 0.2 mmol DPPH solution was prepared by dissolving 3.9 g of DPPH in 50 mL of ethanol. About 10 mL of α -tocopherol solution was prepared by dissolving 1 mg of α -tocopherol in 10 mL of ethanol. About 1.0 mL

of buffer solution was mixed with 0.5 mL of 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. The absorbance was measured on an UV-Vis spectrophotometer (Shimadzu-1650) at 517 nm. Mixture of sodium acetate buffer and ethanol was used as the reference. The plot was made with the quantity of the compound versus absorption and the IC_{50} values were determined. The antioxidant activity was expressed in terms of IC_{50} ($\mu\text{g/mL}$, concentration required to inhibit DPPH radical formation by 50%). α -Tocopherol was taken as a positive control.

The radical scavenging activity was calculated as:

$$\text{DPPH radical scavenging activity} = \frac{\text{Control absorbance} - \text{Sample absorbance}}{\text{Control absorbance}} \times 100$$

3. Results and Discussion

The synthesis of 3,4-dichlorophenyl bicyclo[2.2.1]heptene-2-yl-methanone derivatives by aqueous phase fly-ash catalyzed Diels-Alder reaction with cyclopentadiene as the diene and *E*-3,4-dichlorophenyl chalcones as dienophiles was undertaken under solvent-free cooling conditions. During the reaction, the chemical species present in the fly-ash catalyzed the [4+2] cycloaddition reaction [25]. In this reaction the yield obtained was greater than 60%. The determined physical constants and mass fragments are presented in Table 1.

Table 1. The analytical physical constants and mass fragments of (3-(3-substituted phenyl)bicyclo[2.2.1]hept-5-en-2-yl)(3,4-dichlorophenyl)methanone derivatives

Entry	X	M.F.	Yield (%)	M.W.	M.p. (°C)	Micro analysis			Mass (m/z)
						C (Calcd.)	H (Calcd.)	N (Calcd.)	
1	H	C ₂₀ H ₁₆ Cl ₂ O	65	343	112-113	69.93 (69.98)	4.68 (4.70)	---	343[M ⁺], 345[M ²⁺], 347[M ⁴⁺], 308, 265, 230, 173, 170, 145, 138, 120, 110, 92, 77, 75, 35, 28
2	3-NH ₂	C ₂₀ H ₁₇ Cl ₂ NO	60	358	98-99	67.09 (67.05)	4.71 (4.78)	3.88 (3.91)	358[M ⁺], 360[M ²⁺], 362[M ⁴⁺], 341, 322, 265, 230, 212, 184, 173, 145, 138, 120, 110, 92, 77, 75, 38, 35, 28, 16
3	3-Br	C ₂₀ H ₁₅ BrCl ₂ O	60	422	107-108	56.93 (56.90)	3.49 (3.56)	---	422[M ⁺], 424[M ²⁺], 426[M ⁴⁺], 385, 341, 275, 265, 173, 155, 145, 120, 110, 92, 79, 35, 28
4	2-Cl	C ₂₀ H ₁₅ Cl ₃ O	61	377	105-106	63.63 (63.60)	3.94 (4.00)	---	377[M ⁺], 379[M ²⁺], 381[M ⁴⁺], 341, 306, 265, 173, 145, 120, 111, 75, 35
5	3-Cl	C ₂₀ H ₁₅ Cl ₃ O	61	377	114-115	63.58 (63.60)	3.97 (4.00)	---	377[M ⁺], 379[M ²⁺], 381[M ⁴⁺], 341, 306, 265, 203, 173, 145, 120, 111, 103, 75, 35
6	4-Cl	C ₂₀ H ₁₅ Cl ₃ O	62	377	102-103	63.62 (63.60)	3.95 (4.00)	---	377[M ⁺], 379[M ²⁺], 381[M ⁴⁺], 341, 306, 265, 203, 173, 145, 138, 120, 111, 103, 92, 75, 35
7	4-N(CH ₃) ₂	C ₂₂ H ₂₁ Cl ₂ NO	61	386	116-117	68.42 (68.40)	5.42 (5.48)	3.59 (3.63)	386[M ⁺], 388[M ²⁺], 390[M ⁴⁺], 370, 355, 341, 265, 182, 173, 145, 138, 120, 110, 92, 90, 76, 35, 29, 15
8	4-F	C ₂₀ H ₁₅ Cl ₂ FO	62	361	121-122	66.54 (66.50)	4.22 (4.19)	---	361[M ⁺], 363[M ²⁺], 365[M ⁴⁺], 341, 265, 187, 173, 145, 120, 110, 92, 76, 28, 19
9	2-OH	C ₂₀ H ₁₆ Cl ₂ O ₂	62	359	116-117	66.82 (66.87)	4.43 (4.49)	---	359[M ⁺], 361[M ²⁺], 363[M ⁴⁺], 341, 323, 271, 265, 230, 185, 173, 145, 120, 111, 103, 92, 76, 35, 28, 17
10	4-OH	C ₂₀ H ₁₆ Cl ₂ O ₂	62	359	123-124	66.88 (66.87)	4.40 (4.49)	---	359[M ⁺], 361[M ²⁺], 363[M ⁴⁺], 341, 323, 288, 271, 265, 230, 216, 213, 195, 185, 173, 145, 138, 120, 110, 103, 92, 76, 35, 28, 17
11	3-OCH ₃	C ₂₁ H ₁₈ Cl ₂ O ₂	67	373	113-114	67.59 (67.57)	4.82 (4.86)	---	373[M ⁺], 375[M ²⁺], 377[M ⁴⁺], 357, 341, 265, 227, 173, 145, 120, 110, 107, 91, 76, 35, 28, 15
12	4-OCH ₃	C ₂₁ H ₁₈ Cl ₂ O ₂	67	373	118-120	67.55 (67.57)	4.79 (4.86)	---	373[M ⁺], 375[M ²⁺], 377[M ⁴⁺], 357, 341, 265, 227, 199, 192, 173, 145, 120, 110, 107, 91, 76, 35, 28, 15
13	4-CH ₃	C ₂₁ H ₁₈ Cl ₂ O	65	357	122-123	70.62 (70.60)	5.02 (5.08)	---	357[M ⁺], 359[M ²⁺], 361[M ⁴⁺], 341, 321, 286, 265, 211, 196,

Entry	X	M.F.	Yield (%)	M.W.	M.p. (°C)	Micro analysis			Mass (m/z)
14	2-NO ₂	C ₂₁ H ₁₅ Cl ₂ NO ₃	60	388	115-116	61.89 (61.87)	3.82 (3.89)	3.58 (3.61)	183, 173, 168, 145, 110, 103, 91, 83, 76, 35, 28, 15 388[M ⁺], 390[M ²⁺], 392[M ⁴⁺], 352, 341, 317, 230, 199, 192, 173, 145, 122, 120, 110, 107, 91, 76, 35, 28, 15
15	3-NO ₂	C ₂₁ H ₁₅ Cl ₂ NO ₃	60	388	103-104	61.92 (61.87)	3.85 (3.89)	3.59 (3.61)	388[M ⁺], 390[M ²⁺], 392[M ⁴⁺], 352, 341, 317, 317, 306, 230, 214, 199, 192, 173, 145, 122, 120, 110, 107, 91, 76, 35, 28, 15
16	4-NO ₂	C ₂₁ H ₁₅ Cl ₂ NO ₃	60	388	126-127	61.90 (61.87)	3.80 (3.89)	3.60 (3.61)	388[M ⁺], 390[M ²⁺], 392[M ⁴⁺], 352, 341, 317, 317, 306, 271, 242, 230, 214, 199, 195, 192, 173, 145, 138, 122, 120, 110, 107, 91, 76, 35, 28, 15

Table 2. Antibacterial^a, antifungal^b and antioxidant^c activities (3-(3-substituted phenyl)bicyclo[2.2.1]hept-5-en-2-yl)(3,4-dichlorophenyl)methanones.

Compound	Antibacterial activity						Antifungal activity			Antioxidant activity (DPPH radical scavenging)
							Disc diffusion technique (250 µg/mL)	Drug dilution method (250 µg/mL)		
	<i>E. coli</i>	<i>S. aureus</i>	<i>P. aeruginosa</i>	<i>K. pneumoniae</i>	<i>P. vulgaris</i>	<i>E. faecalis</i>	<i>C. albicans</i>	<i>Penicillium sp.</i>	<i>A. niger</i>	
1	+	+	+	+	±	+	±	+	+	18.08±1.08
2	+	±	+	+	+	±	++	+	++	23.81±1.94
3	++	++	++	++	++	+	+	+	+	19.58±1.09
4	++	++	++	++	+	++	±	±	+	22.95±1.54
5	++	++	++	++	++	++	±	±	+	21.45±1.64
6	++	++	++	++	++	++	±	±	±	17.95±1.24
7	+	–	±	+	+	±	++	++	++	27.01±1.65
8	++	++	++	++	++	++	±	+	+	25.34±1.72
9	+	++	+	±	±	±	+	++	+	36.04±1.82
10	±	+	+	++	±	+	+	±	++	37.99±1.01
11	++	+	±	+	++	±	+	+	++	35.12±1.11
12	++	++	++	++	++	++	+	++	±	35.56±0.86
13	++	+	±	±	+	+	+	±	±	29.45±1.50
14	±	±	±	±	+	±	++	++	++	22.34±1.45
15	+	±	±	+	±	±	++	++	++	20.37±1.28
16	±	±	±	±	±	+	++	++	++	20.05±1.09

^aDisc size: 6.35 mm; duration: 24-45 h; standard: ampicillin (30–33 mm) and streptomycin (20–25 mm); control: methanol; –: no activity; ±: active (8–12 mm); +: moderately active (13–19 mm); ++: active (20–24 mm).

^bStandard: griseofulvin and gentamycin; duration: 72 h; control: methanol; medium: Potato dextrose agar; ++: no fungal colony; +: one fungal colony; ±: two-three fungal colonies; –: Multiple fungal colonies.

^cStandard: α -Tocopherol (39.14±1.57)

The catalyst was reusable up to 5th run [25]. The chalcone containing electron-donating substituents (OCH₃) gave higher yield than electron-withdrawing (halogen and nitro) substituents. The effect of solvents on the percentage of product of this reaction for compound **1** was studied with the same quantity

of reactants with methanol, dichloromethane, dioxane and tetrahydrofuran. The highest yield was obtained in ethanol with fly-ash in water medium (65%). The infrared and NMR data of compounds are summarized in experimental section.

3.1. Antibacterial sensitivity assay

The disc-diffusion technique was followed using the Bauer-Kirby [38] method, at a concentration of 250 µg/mL, with ampicillin and streptomycin used as the standard drugs. All methanones show antibacterial activities against their bacterial strains. The measured antibacterial activities of all methanones are presented in Table 2. Compounds **3-6**, **8**, **11-13**, showed the maximum zone of inhibition against *Escherichia coli*, at 20–24 mm, compared to other methanones such as **2**, **7**, **9**, **12** and **15**. These latter compounds are moderately active, with 13–19 mm zones of inhibition. Ketones **10**, **14** and **16** were active with an 8–12 mm of zone of inhibition. The ketones **1**, **3-6**, **9** and **12** were found to be effective against *S. aureus* strain with 20–24 mm of zones of inhibition. Compounds **7**, **10**, **11** and **13** are moderately active with 13–19 mm of zones of inhibition. The methanones **2** and **14-16** were active with an 8–12 mm zone of inhibition. The methanone derivatives **3-6**, **8** and **12** were shown to be more active against *Pseudomonas*, with greater than a 20 mm zone of inhibition, while the other derivatives showed zones of inhibition between 12–19 mm. Compounds **1**, **2**, **9** and **10** were moderately active against the *Pseudomonas aeruginosa* strain at 13-19 mm of zone of inhibition. Methanones **7**, **11** and **13-16** were active at 8-12 mm of zone of inhibition. Ketones **3-6**, **8**, **12** and **10** were more effective against the *Klebsiella pneumoniae* strain with 20–24 mm zones of inhibition, while ketone **1**, **2**, **7**, **11** and **15** showed moderate activity with a 13–19 mm zone of inhibition. Compounds **9**, **13**, **14** and **16** were active with an 8–12 mm zone of inhibition. The methanones **3**, **5**, **6**, **8**, **11** and **12** were active when they were screened with *Phaseolus vulgaris* with 20–24 mm zones of inhibition and compounds **2**, **4**, **7**, **13** and **14** were moderately active with 13–19 mm zones of inhibition. The ketones **4-6**, **8**, **10** and **12** showed greater activity against *Enterococcus faecalis*, with 20–24 mm zones of inhibition. Compounds **1-3**, **13** and **16** were moderately active with 13–19 mm zones of inhibition. The methanones derivatives **2**, **7**, **9**, **11**, **14** and **15** were active with 8–12 mm zones of inhibition.

3.2. Antifungal sensitivity assay

The observed antifungal activities of all prepared methanones are presented in Table 2. The study of antifungal activities of all methanones against *Candida albicans* showed that compounds **2**, **3**, **7** and **14-16** are most effective, with 20 mm zones of inhibition at 250 µg/mL per disc, while methanones **4**, **9** and **11-13** are moderately active with 13–19 mm zones of inhibition and compounds **1**, **5**, **6** and **8** were active with an 8–12 mm zone of inhibition. Compounds **7**, **9**, **12**, and **14-16** are more effective against *Penicillium* species relative to compounds **1**, **2**, **3** and **11**. The methanones **4-6**, **8**, **10** and **13** were

active against the *Penicillium* sp. fungal strain. The zone of inhibition of ketones **2**, **7**, **10**, **11** and **14-16** were most effective against *Aspergillus niger* relative to compounds **1**, **3-5**, **8** and **9**. The ketones **6**, **12** and **13** showed little effectiveness with a fungal strain. The presence of a halo, diethyl, dimethyl, fluoro, methoxy and nitro substituents appears to be responsible for the antimicrobial activities of methanones.

3.3. Antioxidant activity

The antioxidant activities of (3,4-dichlorophenyl)-3-(substituted phenyl)bicyclo[2.2.1]hept-5-ene-2-yl) methanone derivatives were measured using the DPPH radical scavenging method [39]. The observed antioxidant activities of methanones are presented in Table 2. From the Table 2, the hydroxy- and methoxy-substituted methanones (compounds **10** and **9**) showed significant antioxidant activity. The other ketones including the parent compound showed lesser antioxidant activity.

4. Conclusions

A series of (3,4-dichlorophenyl)-3-(substituted phenyl)bicyclo[2.2.1]hept-5-ene-2-yl) methanone derivatives have been synthesized by aqueous-phase fly-ash catalyzed Diels-Alder [4+2] cycloaddition of cyclopentadiene and aryl (*E*)-3,4-dichlorophenylchalcones. The yields of the methanones were greater than 60%. The antimicrobial activities of the methanones have been evaluated using Bauer-Kirby methods. All compounds are active in antibacterial and antifungal activity against their microbial strains. The methanones **1**, **3-6** and **8-12** were most active against *E. coli*, *S. aureus*, *P. aeruginosa*, *K. pneumoniae*, *P. vulgaris* and *E. faecalis* bacterial strains with 20–24 mm of zones of inhibition. Methanone derivatives **2**, **7**, **9** and **15** were moderately active against *E. coli*, *S. aureus*, *P. aeruginosa*, *K. pneumoniae*, *P. vulgaris* and *E. faecalis* bacterial strains with 13-19 mm of zones of inhibition. The ketones **10** and **14-16** were more active against *E. coli*, *S. aureus*, *P. aeruginosa*, *K. pneumoniae*, *P. vulgaris* and *E. faecalis* bacterial strains with 8-12 mm of zones of inhibition. Compounds **2**, **7** and **14-16** were most active against *C. albicans* and *Penicillium* sp. and *A. niger* fungal strains within 20 mm of zone of inhibitions. Methanones **1**, **3**, **9** and **11-13** were active *C. albicans* and *Penicillium* sp. fungal strains within 13 mm of zone of inhibitions. The ketones **1**, **4-6**, **8**, **10** and **12** developed a zone of inhibitions within 8 mm. The all halo substituted compounds show antimicrobial activities. The antioxidant activities of the methanones were measured by a DPPH radical scavenging method; the compounds containing hydroxy and methoxy substituents showed antioxidant activity.

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