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Synthesis of antimicrobial, antioxidant and insect antifeedant potent 3,4-dimethyl phenyl bicycle[2.2.1] heptane methanone derivatives

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ABSTRACT

A series containing eleven (3,4-dimethylphenyl-3-(substituted phenyl) bicyclo[2.2.1]hept-5-ene-2-yl) methanones have been synthesized by an aqueous phase fly-ash catalyzed [4+2] cycloaddition Diels-Alder reaction of cyclopentadiene and 3,4-dimethyl phenyl chalcones under cooling condition. The yields of the methanones are greaterthan 60%. The synthesized 3,4-dimethyl phenyl bicyclo methanones were characterized by their physical constants and spectral data. The antimicrobial and antioxidant activities of the synthesized methanones were studied using a variety of bacterial and fungal strains and DPPH radical scavenging methods. The insect antifeedant activities of these methanones were studied with 4th instar larvae *Achoea Janata L* using leaf disc bio-assay method.

KEYWORDS

3,4-dimethyl phenyl bicyclo[2.2.1]hept-5-ene-2-yl-methanones;
Diels-Alder reaction;
IR and NMR spectra;
Antimicrobial activities;
Antioxidant activity;
Insect antifeedant activity.

INTRODUCTION

Norbornyl, aryl and aliphaticethanones are versatile key[1,2] intermediates for construction of molecular buildings blocks[3,4] and they play an important role in bio active molecular chemistry[5,6] due to carbonyl tautomer's, presence of polar groups and the degree of hyrophilicity or hydrophobicity. Aliphatic, aryl and bicyclo methanones possess numerous pharmacological activities such as, AVP release and activation of vasopressin receptors[6], Antimicrobial[7-14], cannabinoid receptor agonists[15], neuronal nicotinic acetylcholine receptors (nAChRs)[16], anti-inflammatory[12, 17-19], anti-analgesic[19,20], anti-convulsant[19,20] anti-tumour[19,20], anti-cancer[19], antiviral[20], anti-diabetic[19,21], anti-tubercular[21], antihelmintic[12,21], antidepressant[22], ulcerogenic[18], antinociceptive[19],protein tyrosine kinase inhibitor[23], DNA cleavage[24], alzheimer's disease curing agent[25], antioxidant[14], acute-toxicity[18], anti-hypertensive[20] and insect antifeedant activities[14]. There are many 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 norbornylbicyclomethanones. 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. Catalysts including Lewis acids[29], Bronsted acids[29,30], asymmetric catalysts with helical polymers[31], Cu^{2+} 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 have reported the synthesis and pharmacological and insect antifeedant activities of some 2-naphthyl based bicyclonorbornylmethanones[14]. Within the above view, the synthesis and evaluation of biological activities of 5-bromo-2-thienyl based-heptane[2.2.1]methanones has not been reported. Hence, the author have synthesize some 2-(5-bromo-2-thienyl)-3-(substituted phenyl)heptene[2.2.1] methanones and evaluated their antimicrobial, antioxidant and insect antifeedant activities using the appropriate microbial strains with Bauer-Kirby[38], DPPH radical scavenging[39] and 4th instar larvae *Achoea Janata L* – castor leaf disc bio-assay[14] methods.

EXPERIMENTAL

General

All chemicals were procured from Sigma-Aldrich and E. Merck. Melting points of substituted 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 ^{13}C NMR spectra in $CDCl_3$ solvent using TMS as internal standard. Electron impact and chemical ionization mode FAB^+ mass spectra were recorded with a Shimadzu spectrometer. The elemental analysis of all methanones were performed in Perkin Elmer 240C Analyzer.

Synthesis of3,4-dimethyl phenyl chalcones

The substituted styryl3,4-dimethyl phenyl ketones were synthesized as described in reference[40].

General procedure for synthesis of 3,4-dimethyl phenyl bicyclo[2.2.1]heptene-2-yl-methanones

Appropriate equimolar quantities of 3,4-dimethyl phenyl chalcones (2 mmol) in 15 mL of ethanol, cyclopentadiene (2 mmol) and 4 g of fly-ash in 20 mL of water were stirred for 6 h at 0–4°C overnight (Scheme 2). 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 Na_2SO_4 and concentrated to give a solid product. The crude product was further purified by recrystallization with ethanol. The analytical, micro analysis, infrared, NMR and mass spectral data of the methanones are as follows.

(3,4-dimethyl phenyl)(3-phenylbicyclo[2.2.1]hept-5-en-2-yl)methanone (1)

Yield: 65%, m.p.103-104, IR(KBr, cm^{-1}): ν= 3098, 1662, 1524, 1367, 1258, 1025, 934, 728; ^1H NMR(400MHz, $CDCl_3$,25 °C, TMS): δ=3.700(dd, 1H, H_1, J = 4 and 6 Hz), 3.443(t, 1H, H_2, J = 19 Hz), 3.362 (t, 1H, H_3, J = 17 Hz), 2.691 (dd, 1H, H_4, J = 8 and 6 Hz), 6.572 (d, 1H, H_5, J = 15 Hz), 6.643 (d, 1H, H_6, J = 15 Hz), 1.803(dd, 1H, H_7, J = 6 and 4 Hz), 1.590 (dd, 1H, $H_{7'}$, J = 8 and 5.6Hz), 2.356(s, 6H, CH_3), 6.592-7.581(m, 8H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ=198.72(CO), 46.78(C_1), 52.73(C_2), 44.67(C_3), 46.64(C_4), 133.74(C_5),136.22(C_6), 46.32 (C_7), 21.32, 21.43(CH_3), 125.72-146.23(Ar-C); Anal. Calcd. for $C_{22}H_{22}O$(302): C, 87.38; H, 7.73. Found C, 87.41; H, 7.28.MS(m/z): 302[M^+], 287, 272, 225, 210, 133, 197, 169, 118, 105, 92, 91, 90, 77, 30, 28, 15.

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

Yield: 60%; m.p. 116-117; IR(KBr, cm^{-1}): ν= 3092, 2976, 1681, 1452, 1218, 1029, 838, 792, 628; ^1H NMR(400MHz, $CDCl_3$,25 °C, TMS): δ= 3.707(dd, 1H, H_1, J = 6 and 4 Hz), 3.449(t, 1H, H_2, J = 20Hz), 3.368 (t, 1H, H_3, J = 18 Hz), 2.686(dd, 1H, H_4, J = 5and 6 Hz), 6.568 (d, 1H, H_5, J = 15 Hz), 6.641(d, 1H, H_6, J = 15Hz), 1.860 (dd, 1H, H_7, J = 8 and 6 Hz), 1.593(dd, 1H, $H_{7'}$, J = 6 and 8 Hz), 2.347(s, 6H, CH_3), 6.542-7.925(m, 7H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ= 199.36(CO),46.69(C_1), 52.61(C_2), 44.73(C_3), 46.62(C_4), 133.46(C_5), 135.98(C_6), 46.33 (C_7), 22.02, 22.12(CH_3), 121.32-146.28(Ar-C);Anal. Calcd. for $C_{22}H_{21}BrO$(381): C, 69.30; H, 5.55. Found C, 69.32; H, 5.51; Ms(m/z): 381[M^+], 383[M^{2+}], 365, 350, 301, 275, 247, 225, 195, 133, 105, 91, 79, 76,

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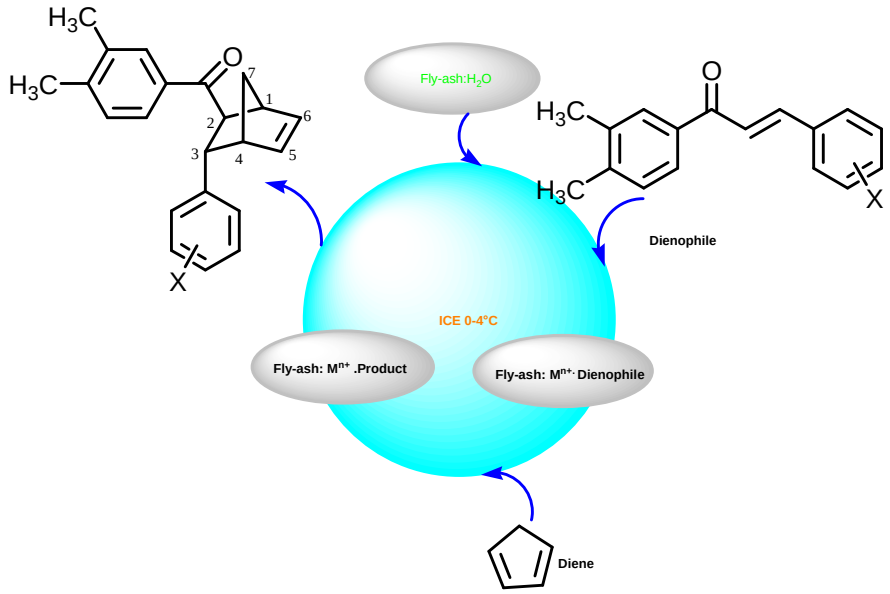

Scheme 1 : Synthesis of (3-substitutedphenyl)bicyclo[2.2.1]hept-5-en-2-yl)-3-(3,4-dimethylphenyl) methanone derivatives by fly-ash catalyzed aqueous phase Diels-Alder [4+2] cycloaddition of 3,4-dimethyl phenyl chalcones and cyclopentadiene.

30, 28, 15,

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

Yield: 61%; m.p.104-105; IR(KBr, cm^{-1}): ν= 3078, 2998, 1625, 1528, 1496, 1068, 928, 854, 731, 681; ^{1}H NMR(400MHz, $CDCl_3$,25 °C, TMS): δ= 3.709(dd, 1H, H_1, J = 8 and 6 Hz), 3.451(t, 1H, H_2, J = 19 Hz), 3.371(t, 1H, H_3, J = 20 Hz), 2.699(dd, 1H, H_4, J = 6 and 8 Hz), 6.553 (d, 1H, H_5, J = 16 Hz), 6.632(d, 1H, H_6, J = 16 Hz), 1.792(dd, 1H, H_7, J = 4 and 6 Hz), 1.587(dd, 1H, $H_{7'}$, J = 8 and 4 Hz), 3.387 (s, 6H, CH_3), 6.624-7.681(m, 7H, Ar-H);^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ= 200.12(CO), 46.823(C_1), 52.72(C_2), 45.02(C_3), 46.81(C_4), 133.99(C_5), 135.28(C_6), 46.22 (C_7), 22.81, 22.93(CH_3), 120.23-147.11(Ar-C); Anal. Calcd. for $C_{22}H_{21}BrO$(381): C, 69.30; H, 5.55. Found C, 69.34; H, 5.50; Ms(m/z): 381[M^+], 383[M^{2+}], 365, 350, 301, 275, 271, 247, 225, 195, 155, 133, 105, 103, 92, 91, 80, 76, 30, 28, 15,

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

Yield: 60%; m.p. 113-114; IR(KBr, cm^{-1}): ν= 3082, 1656, 1552, 1227, 1082, 957, 838, 791; ^{1}H NMR(400MHz, $CDCl_3$,25 °C, TMS): δ= 3.693(dd, 1H, H_1, J = 8 and 4Hz), 3.542(t, 1H, H_2, J = 20 Hz), 3.362(t, 1H, H_3, J = 20 Hz), 2.487(dd, 1H, H_4, J = 4 and 8 Hz), 6.357 (d, 1H, H_5, J = 16 Hz), 6.417(d, 1H, H_6, J = 16Hz), 1.809(dd, 1H, H_7, J = 6 and 8 Hz), 1.633(dd, 1H, $H_{7'}$, J = 4 and 8Hz), 2.973 (s, 6H, CH_3), 6.391-7.784(m, 7H, Ar-H);^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ= 199.27(CO), 46.73(C_1), 52.59(C_2), 45.30(C_3), 46.67(C_4), 134.22(C_5), 135.98(C_6), 46.32(C_7), 21.34, 21.64(CH_3), 125.81-144.37(Ar-C); Anal. Calcd. for $C_{22}H_{21}ClO$(336): C, 78.44; H, 6.28. Found C, 78.46; H, 6.19; MS(m/z): 336[M^+], 338[M^{2+}], 398[M^{4+}], 321, 306, 301, 225, 195, 91, 76, 35, 30, 28, 15.

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

Yield: 620%; m.p. 116-117; IR(KBr, cm^{-1}): ν= 3052, 1665, 1584, 1367, 1085, 964, 839, 716, 628; ^{1}H NMR(400MHz, $CDCl_3$,25 °C, TMS): δ= 3.692(dd, 1H, H_1, J = 4 and 6 Hz), 3.613(t, 1H, H_2, J = 20 Hz), 3.357(t, 1H, H_3, J = 20 Hz), 2.708(dd, 1H, H_4, J = 8 and 4 Hz), 6.417(d, 1H, H_5, J = 17 Hz), 6.510(d, 1H, H_6, J = 17 Hz), 1.748(dd, 1H, H_7, J = 8 and 4 Hz), 1.644(dd, 1H, $H_{7'}$, J = 6 and 4 Hz), 3.017 (s, 6H, CH_3), 7.245-7.663(m, 7H, Ar-H);^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ= 199.81(CO), 46.69(C_1), 52.67(C_2), 46.32(C_3),

46.70(C_4), 134.66(C_5), 135.21(C_6), 46.29(C_7), 21.34, 21.84(CH_3), 125.81-144.83(Ar-C); Anal. Calcd. for $C_{22}H_{21}ClO$(336): C, 78.44; H, 6.28. Found C, 78.44; H, 6.20; MS(m/z): 336[M^+], 338[M^{2+}], 398[M^{4+}], 321, 306, 301, 271, 231, 225, 203, 195, 133, 111, 105, 91, 76, 35, 30, 28, 15.

(3-(2-Fluorophenyl)bicyclo[2.2.1]hept-5-en-2-yl)(3,4-dimethylphenyl)methanone (6)

Yield: 60%; m.p. 121-122; IR(KBr, cm^{-1}): ν= 3092, 1638, 1529, 1085, 964, 761, 698; ^{1}H NMR(400MHz, $CDCl_3$,25 °C, TMS): δ= 3.666(dd, 1H, H_1, J = 8 and 6 Hz), 3.551(t, 1H, H_2, J = 22 Hz), 3.371(t, 1H, H_3, J = 20 Hz), 2.677(dd, 1H, H_4, J = 8 and 4 Hz), 6.317 (d, 1H, H_5, J = 17 Hz), 6.591(d, 1H, H_6, J = 17 Hz), 1.751(dd, 1H, H_7, J = 8 and 4 Hz), 1.651(dd, 1H, $H_{7'}$, J = 4 and 6 Hz), 3.017 (s, 6H, CH_3), 6.682-7.651(m, 7H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ= 196.82(CO), 46.83(C_1), 52.74(C_2), 46.51(C_3), 46.72(C_4), 134.89(C_5), 135.33(C_6), 46.32(C_7), 22.08, 21.37(CH_3), 115.23-141.67(Ar-C); Anal. Calcd. for $C_{22}H_{21}FO$(320): C, 82.47; H, 6.61. Found C, 82.51; H, 6.56; MS(m/z): 320[M^+], 322[M^{2+}], 398[M^{4+}], 305, 225, 215, 187, 133, 105, 91, 76, 30, 28, 19, 15.

(3-(4-Fluorophenyl)bicyclo[2.2.1]hept-5-en-2-yl)(3,4-dimethylphenyl)methanone (7)

Yield: 620%; m.p. 116-117; IR(KBr, cm^{-1}): ν= 3052, 1665, 1584, 1367, 1085, 964, 839, 716, 628; ^{1}H NMR(400MHz, $CDCl_3$,25 °C, TMS): δ= 3.692(dd, 1H, H_1, J = 4 and 6 Hz), 3.613(t, 1H, H_2, J = 20 Hz), 3.357(t, 1H, H_3, J = 20 Hz), 2.708(dd, 1H, H_4, J = 8 and 4 Hz), 6.417(d, 1H, H_5, J = 17 Hz), 6.510(d, 1H, H_6, J = 17 Hz), 1.748(dd, 1H, H_7, J = 8 and 4 Hz), 1.644(dd, 1H, $H_{7'}$, J = 6 and 4 Hz), 3.017 (s, 6H, CH_3), 7.245-7.663(m, 7H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ= 199.81(CO), 46.69(C_1), 52.67(C_2), 46.32(C_3), 46.70(C_4), 134.66(C_5), 135.21(C_6), 46.29(C_7), 21.34, 21.84(CH_3), 125.81-144.83(Ar-C); Anal. Calcd. for $C_{22}H_{21}FO$(320): C, 82.47; H, 6.61. Found C, 82.48; H, 6.54; MS(m/z): 320[M^+], 322[M^{2+}], 301, 290, 271, 225, 215, 195, 187, 133, 105, 103, 91, 76, 35, 30, 28, 15.

(3-(4-Hydroxyphenyl)bicyclo[2.2.1]hept-5-en-2-yl)(3,4-dimethylphenyl)methanone (8)

Yield: 63%; m.p. 118-119; IR (KBr, cm^{-1}): ν= 3452, 3098, 2902, 1668, 1523, 1428, 1076, 934, 826, 746, 619; ^{1}H NMR(400MHz, $CDCl_3$,25 °C, TMS): δ= 3.666(dd, 1H, H_1, J = 8 and 6 Hz), 3.641(t, 1H, H_2, J = 17 Hz), 3.421(t, 1H, H_3, J =18 Hz), 2.657(dd, 1H, H_4, J = 6 and 4 Hz), 6.481(d, 1H, H_5, J = 15 Hz), 6.564 (d, 1H, H_6, J = 15 Hz), 1.808(dd, 1H, H_7, J = 8 and 4 Hz), 1.635(dd, 1H, $H_{7'}$, J = 4 and 6 Hz), 3.217(s, 6H, CH_3), 5.713(s, 1H, OH), 6.672-7.7581(m. 7H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ= 196.19(CO), 46.47(C_1), 53.34(C_2), 46.38(C_3), 46.54(C_4), 135.83(C_5), 136.64(C_6), 46.34(C_7), 22.41, 23.18(CH_3), 115.67-141.72(Ar-C); Anal. Calcd.for $C_{22}H_{22}O_2$(318): C, 82.99; H, 6.96. Found C, 82.97; H, 6.91; MS(m/z): 318[M^+], 303, 301, 288, 225, 213, 195, 185, 133, 105, 91, 76, 71, 28, 17.

(3-(4-Methoxyphenyl)bicyclo[2.2.1]hept-5-en-2-yl)(3,4-dimethyl phenyl)methanone (9)

Yield: 67%; m.p. 115-116; IR (KBr, cm^{-1}): ν= 3071, 2836, 1665, 1452, 1267, 1029, 935, 821, 756, 695; ^{1}H NMR(400MHz, $CDCl_3$,25 °C, TMS): δ= 3.668(dd, 1H, H_1, J = 8 and 8 Hz), 3.417(t, 1H, H_2, J = 20 Hz), 3.342 (t, 1H, H_3, J = 21 Hz),2.634(dd, 1H, H_4, J = 4 and 8 Hz), 6.541 (d, 1H, H_5, J =17 Hz), 6.621 (d, 1H, H_6, J = 17 Hz), 1.733 (dd, 1H, H_7, J = 8 and 4 Hz), 1.581(dd, 1H, $H_{7'}$, J = 4 and 8 Hz), 3.817 (s, 3H, OCH_3), 2.372(s, 6H, CH_3), 6.195-7.581(m. 7H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ= 197.66(CO), 46.67(C_1), 52.22(C_2), 44.38(C_3), 46.51(C_4), 133.62(C_5), 136.08(C_6), 46.21(C_7), 55.72(OCH_3), 20.98, 21.07(CH_3), 113.18-141.47(Ar-C); Anal. Calcd. for $C_{23}H_{24}O_2$(322): C, 83.10; H, 7.28. Found C, 83.14; H, 7.22; MS(m/z): 322[M^+], 317, 301, 227, 225, 199, 195, 107, 105, 92, 91, 76, 31, 28, 16, 15.

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

Yield: 65%; m.p. 123-124; IR (KBr, cm^{-1}): ν= 3031, 2901, 1632, 1524, 1439, 1308, 1291, 1061, 924, 716, 628; ^{1}H NMR(400MHz, $CDCl_3$,25 °C, TMS): δ= 3.676(dd, 1H, H_1, J = 6 and 8 Hz), 3.428(t,

1H, H_2, *J* = 19Hz), 3.362 (t, 1H, H_3, *J* = 20 Hz),2.230(dd, 1H, H_4, *J* = 4 and 6 Hz), 6.521(d, 1H, H_5, *J* =17 Hz), 6.608(d, 1H, H_6, *J* = 17 Hz), 1.738(dd, 1H, H_7, *J* = 6 and 4 Hz), 1.595(dd, 1H, $H_{7'}$, *J* =4 and 8 Hz), 2.471 (s, 3H, CH_3), 2.452 (s, 3H, CH_3), 6.472-7.817(m. 7H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS):δ= 198.91(CO), 46.61(C_1), 52.32(C_2), 44.41(C_3), 46.54(C_4), 133.82(C_5), 136.19(C_6), 46.44(C_7), 21.31, 21.62, 23.66(CH_3), 125.82-142.72(Ar-C); Anal. Calcd. for $C_{23}H_{24}O$(316): C, 87.30; H, 7.64. Found C, 87.33; H, 7.60; MS(m/z): 316[M^+], 301, 286, 225, 211, 195, 183, 133, 120, 105, 92, 91, 82, 79, 76, 28, 15.

(3-(4-Nitrophenyl)bicyclo[2.2.1]hept-5-en-2-yl)(3,4-dimethyl phenyl)methanone (11)

Yield: 60%; m.p. 111-112; IR (KBr, cm^{-1}): ν= 3192, 2899, 1682, 1575, 1498, 1095, 938, 874, 691:^{1}H NMR(400MHz, $CDCl_3$,25 °C, TMS):δ= 3.803(dd, 1H, H_1, *J*= 8 and 4 Hz), 3.493(t, 1H, H_2, *J* = 16 Hz), 3.392 (t, 1H, H_3, *J* = 19 Hz), 2.791 (dd, 1H, H_4, *J* = 4 and 6 Hz), 6.613(d, 1H, H_5, *J* = 16 Hz), 6.792 (d, 1H, H_6, *J* = 16 Hz), 1.818(dd, 1H, H_7, *J* = 4 and 8 Hz), 1.647(dd, 1H, $H_{7'}$, *J* = 6 and 4 Hz), 3.171 (s, 3H, CH_3), 6.656-8.218(m, 7H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS):δ= 199.92(CO), 46.83(C_1), 53.84(C_2), 44.96(C_3), 46.92(C_4), 135.74(C_5,), 136.97(C_6), 46.82 (C_7), 24.72(CH_3), 123.58-146.28(Ar-C); Anal. Calcd. for $C_{22}H_{21}NO_3$(347): C, 76.06; H, 6.09; N, 4.03. Found C, 76.08; H, 6.02; N, 3.98.MS(m/z): 347[M^+], 301, 332, 242, 225, 214, 210, 195, 133, 122, 120, 118, 105, 91 76, 46, 28, 15.

Antimicrobial activity

The antimicrobial activities of the prepared(3,4-dimethyl phenyl)bicyclo[2.2.1]heptene-2-yl-methanones were evaluated by measuring the zone of inhibition of the compounds against the indicated 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 chosen. The disc diffusion technique followed the Bauer-Kirby(Bauer et al. 1966) method, at a concentration of 250 μg/mL with ampicillin and streptomycin used as the standard drugs. For the study of antifungal activities of all methanones with *Candida albicans* the disc diffusion technique was followed, while the two other strains (*Penicillium* sp. and *Aspergillus niger),* the dilution methodwas used. The drug dilution was 50 μg/mL. Griseofulvin was used as the standard drug.

Measurement of antibacterial sensitivity

The Bauer-Kirby[38] disc diffusion mm of zone of inhibitions methods was adopted for measurement of antibacterial sensitivity assay. In each Petri plate about 0.5 mL of the bacterial test sample was spread uniformly over solidified Mueller-Hinton agar using a sterile glass spreader. Then 5 mm discs made from Whatman No.1 filter paper were saturated with the potential inhibitor solution and placed on the medium using sterile forceps. The plates were incubated for 24 h at 37 °C upside down to prevent the collection of water droplets over the medium. After 24 h, the plates were examined and the diameter values of the zone of inhibition were measured. Triplicate results were recorded.

Measurement of antifungal sensitivity

The Bauer-Kirby[38] disc diffusion mm of zone of inhibitions methods was adopted for measurement of antifungal sensitivity assay. The PDA medium was prepared and sterilized as above and added to the Petri plate containing 1 mL of the fungal species. The plates were rotated clockwise and counter clockwise for uniform spreading. The discs were impregnated with the test solution, prepared by dissolving 15 mg of the methanone in 1 mL of DMSO solvent. The medium was allowed to solidify and incubate for 24 h. The plates were examined and the diameter of the zone of inhibition was measured. Triplicate results were recorded.

Antioxidant activity

The antioxidant activities of the synthesized methanones were evaluated by the DPPH radical scavenging technique(Vanangamudi et al. 2013). Acetate (0.1 mol/L) was prepared by dissolving 1.64 g of sodium acetate in 15 mL of water and 150 μL of acetic acid. The final volume was adjusted to 20 mL by adding water. DPPH solution (0.2 mmol) was prepared by dissolving 3.9 g of DPPH in 50 mL of ethanol, and α-

tocopherol solution was prepared by adding 1 mg to 10 mL of ethanol. A series of test tubes was arranged with 1.0 mL of buffer solution mixed with 0.5 mL of DPPH solution. A series of concentrations of synthesized methanones with -tocopherol (1 μg in 1 mL of ethanol) was added to each tube and mixed. After 30 min at room temperature the absorbance of each solution was measured by UV spectrophotometry at 517 nm. A mixture of buffer solution and ethanol was used as the reference for the spectrophotometer. A graph was plotted with the weight of the compound *versus* absorption and IC_{50} values were determined. The antioxidant activity was expressed in terms of IC_{50} (μg/mL, concentration required to inhibit DPPH radical formation by 50%). α-Tocopherol was used as a positive control. The radical scavenging activity was calculated as

DPPH radical scavenging activity (% of inhibition) =

$$\frac{\text{Control absorbance - Sample absorbance}}{\text{Control absorbance}} \times 100$$

Insect antifeedant activity

Carbonyl compounds containing unsaturation and halogen or polar substitutions, they possess insect antifeedant activity. Therefore, the author wishes to examine the insect antifeedant activity of these bicyclo[2.2.1]heptene-2-yl methanone derivatives (compounds11-19) and found to be active as insect antifeedants. This test was performed with a 4th instar larva *Achoea janataL* against castor *semilooper,*were reared as described on the leaves of castor, *Ricinuscommunis* in the laboratory at the temperature range of 26°C ±1°C and a relative humidity of 75-85%. The leaf – disc bioassay method was used against the 4th instar larvae to measure the antifeedant activity. The 4th instar larvae were selected for testing because the larvae at this stage feed very voraciously.

About 1.85 cm diameter of castor leaf discs were punched and intact with the petioles. The synthesized aryl bicyclo [2.2.1]heptane-2-yl methanones (entries 11-19) were dissolved in acetone at a concentration of 200 ppm dipped for 5 minutes. The leaf discs were air-dried and placed in one litre beaker containing little water in order to facilitate translocation of water. Therefore, the leaf discs remain fresh throughout the duration of the rest, 4th instar larvae of the test insect, which had been preserved on the leaf discs of all bicyclo[2.2.1]hepane-2-yl methanones and allowed to feed on them for 24 h. The area of the leaf disc consumed were measured by Dethler'smethod[41].

RESULTS AND DISCUSSION

The synthesis of 3,4-dimethyl phenyl bicyclo[2.2.1]heptene-2-yl-methanone derivatives by aqueous phase fly-ash catalyzed [2+4]cyclo addition Diels-Alder reaction with cyclopentadiene as the diene and *E*-3,4-dimethylphenyl chalcones as dienophiles was undertaken under solvent-free cooling conditions. During the reaction the chemical species present in the fly-ash are catalyzed the [4+2] cycloaddition reaction[14]. In this reaction the obtained yield was greater than 60%. The catalyst was reusable up to 5th run. The chalcone containing electron-donating substituents (OCH_3) 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 analytical, infrared, NMR and mass fragment data of compounds are summarizedin experimental section.

Antibacterial sensitivity assay

The Bauer-Kirby[38] disc-diffusion technique was used for the study of antibacterial activity of ketones. In this method, at a concentration of 250 μg/mL, with ampicillin and streptomycin used as the standard drugs. All methanones were shows antibacterial activities against their bacterial strains. The measured antibacterial activities of all methanones are presented in TABLE 1. Compounds 2-5and 9 showed the maximum zone of inhibition against *Escherichia coli*, at 20–24 mm, compared to other methanones such as 6-8. These latter compoundsare moderately active, with 13–19 mm zones of inhibition. Ketone10was active with an 8–12 mm of zone of inhibition. Compounds 1 and 11 were inactive. The ketones 2-5and 8were found to be effective against *S. aureus* strain with 20–24 mm of zones of inhibition. Compounds 9and 10 are moderately active with 13–19 mm of zones of inhibition. The methanones

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TABLE 1 : Antibacterial[a], antifungal[b] and antioxidant[c] activities (3-(3-substituted phenyl)bicyclo[2.2.1]hept-5-en-2-yl)(3,4-dimethyl phenyl)methanones.

Compd.	Antibacterial activity						Antifungal activity: Disc diffusion technique (250µg/mL)	Antifungal activity: Drug dilution method (250µg/mL)		Antioxidant activity (DPPH radical scavenging)
	E. coli	*S. aures*	*P. aeruginosa*	*K. pneumoniae*	*P. vulgaris*	*E. faecalis*	*C. albicans*	*Penicillium sp.*	*A. niger*	
1	---	---	±	±	+	+	±	±	+	19.34±1.14
2	++	++	++	++	++	++	+	+	+	16.81±1.94
3	++	++	++	++	++	++	+	+	±	19.58±1.19
4	++	++	++	++	++	++	+	+	+	22.95±1.04
5	++	++	++	++	++	++	+	+	±	17.86±1.01
6	+	±	++	++	++	++	+	±	+	16.25±1.18
7	+	±	++	++	++	++	+	±	±	13.41±1.65
8	+	++	+	++	++	++	++	++	±	36.02±1.11
9	++	+	±	++	+	++	++	++	++	34.12±1.48
10	±	+	±	+	++	+	++	++	++	37.19±1.23
11	---	---	+	±	±	±	++	++	++	14.32±1.13

[a]Disc 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); [b]Standard: 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; [c]Standard: α-Tocopherol (39.14±1.57).

6 and 7 were active with 8-12 mm zone of inhibition. The methanone derivatives 2-7and 10 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 8 and11 were moderately active against the *Pseudomonas aeruginosa* strain at 13-19 mm of zone of inhibition. Methanones 1and 10were active at 8-12 mm of zone of inhibition. Ketones2-8and 9were more effective against the *Klebsiella pneumoniae* strain with 20–24 mm zones of inhibition, while ketone 10 showed moderate activity with a 13–19 mm zone of inhibition. Compounds 1 and11 were active with an 8–12 mm zone of inhibition. The methanones 2-8and 10 were active when they were screened with *Phaseolus vulgaris* with 20–24 mm zones of inhibitionand compounds1and 9 were moderately active with 13–19 mm zones of inhibition. The ketones 2-9showed greater activity against *Enterococcus faecalis*, with 20–24 mm zones of inhibition. Compounds 1 and 10were moderately active with 13–19 mm zones of inhibition. The methanones derivative11 was active with 8–12 mm zones of inhibition.

Antifungal sensitivity assay

The measured antifungal activities by means mm of zone of inhibitions of all prepared methanones are presented in TABLE 1. The study of antifungal activities of all methanones against *Candida albicans*showed that compounds8-11are most effective, with 20 mm zones of inhibition at 250 µg/mL per disc, while methanones 2-7 are moderately active

TABLE 2 : The insect antifeedant activities of the 3,4-dimethyl phenyl bicyclo[2.2.1]hepatene-2-yl-methanones

Compound	X	4-6 pm	6-8 pm	8-10 pm	10-12 pm	12-6 pm	6-8 pm	8 am-12 Nn	12 Nn-2 pm	2-4 pm	Total leaf disc consumed in 24 hrs
1	H	1	1	1	1	1	1	1	1	1	8
2	2-Br	0.5	0.25	0.25	0.5	0.5	0.5	1	1	0.5	5
3	4-Br	0.25	0.25	0.25	0.25	0.5	0.5	0.5	1	0.5	4
4	2-Cl	0.5	0.5	0.5	0.5	0	0	0	1	1	4
5	4-Cl	0.5	0.25	0.25	0.25	0	1	0.25	0.5	0.5	3.5
6	2-F	0.5	1	0.5	0.25	0.25	1	0.5	1	0.5	5.5
7	4-F	0.5	0.5	1	1	0	0	1	1	0	5
8	4-OH	1	0.5	1	1	1	0.5	1	0.5	0.5	7
9	4-CH_3	1	1	0.5	1	0.5	0.5	0.5	0.5	0.5	6
10	4CH3	1	1	2	0.5	0	1	1	0.5	0.5	7
11	4-NO_2	1	0.5	1	0.5	0.5	1	1	1	1	8

Number of leaf discs consumed by the insect (Values are mean + SE of five).

TABLE 3 : Antifeedant activity of compound 5 (3-(4-chlorophenyl)bicyclo[2.2.1]hept-5-en-2-yl)(3,4-dimethyl phenyl)methanoneshowed an appreciable antifeedant activity at 3 different concentrations

ppm	4-6 pm	6-8 pm	8-10 pm	10-12 pm	12 am-6 am	6-8 am	8 am-12 Nn	12 Nn-2 pm	2-4 pm	Total leaf disc consumed in 24 h
50	0.5	0.25	0.25	0	0	0	0	0	0	1
100	0.5	0.5	0.25	0	0	0	0	0	0	1.25
150	0.25	0	0.25	0	0	0	0	0	0	0.5

Number of leaf discs consumed by the insect (Values are mean + SE of five)

with 13–19 mmzones of inhibition and compound 1was active with an 8–12 mm zone of inhibition. Compounds 8-11are more effective against *Penicillium* species relative to compounds2-5. The methanones 1and7 were active against the *Penicillium* sp. fungal strain. The zone of inhibition of ketones 6, 7 and 9were shown active with one or two fungal colonies. The bicyclo ketones 9-11 were most effective against *Aspergillus niger* relative to compounds 1, 2, 4 and 6. The ketones 3, 5, 7and8 showed little effectiveness with a fungal strain. The presence of a halo, diethyl, dimethyl, fluoro, methoxy and nitro substituents appear to be responsible for the antimicrobial activities of methanones.

Antioxidant activity

The DPPH radical scavenging activity method was adopted for studying the antioxidant activities of (3,4-dimethylphenyl)-3-(substituted phenyl)bicyclo [2.2.1]hept-5-ene-2-yl) methanone derivatives[39]. The observed antioxidant activities of methanones are presented in TABLE 2. From the TABLE 2, the hydroxy- and methoxy-substituted

methanones (compounds 8and 9) showed significant antioxidant activity. The other ketones including the parent compound showed lesser antioxidant activity.

Insect antifeedant activity

The halo-substituted enones possess insect antifeedant activities[14,39,41]. In the present investigation, the observed antifeedant activity of bicyclo[2.2.1] heptene-2-yl methanones was presented in TABLE 2, and the TABLE 1 reveals that compound 5(3-(4-chlorophenyl)bicyclo[2.2.1]hept-5-en-2-yl)(3,4-dimethyl phenyl)methanone was found to reflect satisfactory antifeedant. This test is performed with the insects which ate only two-leaf disc soaked under the solution of this compound. Compound 2, 3, 4, 6 and 7 showed enough antifeedant activity but lesser than 5. Further compound 5 was subjected to measure the antifeedant activity at different 50, 100, 150 ppm concentrations and the observation reveals that as the concentrations decreased, the activity also decreased. It is observed from the results in TABLE 3 and that the 5(3-(4-chlorophenyl)bicyclo[2.2.1]hept-5-en-2-yl)(3,4-dimethyl phenyl)methanoneshowed an appreciable antifeedant activity at 150 ppm concentration.

CONCLUSIONS

Some novel (3,4-dimethyl phenyl)-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)*-5-bromo-2-thienyl chalcones. The yields of the methanones were greater than 60%. The antimicrobial activities of the methanones have been evaluated using Bauer-Kirby methods. All halogenated, methoxy, methyl and hydroxy substituted methanones shows antimicrobial activities. The antioxidant activities of the methanoneswere measured by a DPPH radical scavenging method; the compounds containing hydroxy and methoxy substituents showed antioxidant activity. The 4-chloronyl substituted methanone shows significant insect antifeedant activities.

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