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GREEN APPROACH USING WATER MEDIATED DIELS-ALDER REACTION FOR THE SYNTHESIS OF SOME 2-(4-BROMO-1-NAPHTHYL)-3-(ARYL)BICYCLO [2.2.1]HEPT-5-ENE METHANONES AND EVALUATION OF THEIR ANTIMICROBIAL AND ANTIOXIDANT ACTIVITIES

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Some (4-bromo-1-naphthyl)-(3-(substituted phenyl) bicyclo[2.2.1]hept-5-en-2-yl) methyl ketones were synthesized by fly-ash catalyzed environmentally benign Diels-Alder [4+2] cycloaddition reaction of 4-bromo-1-naphthyl chalcones and cyclopentadiene in water medium. In this reaction, the obtained yield was more than 60%. The synthesized methanones were characterized by their physical constants, microanalysis, infrared, nuclear magnetic resonance and mass spectroscopic data. The antibacterial and antifungal activities of these ketones were evaluated by the disc diffusion-zone of inhibition and two-fold serial-dilution-minimum inhibitory concentration of their corresponding bacterial and fungal strains using the Bauer-Kirby method. The antioxidant activities of these methanones were measured using the diphenyl picryl hydrazyl (DPPH) radical scavenging activity method.

Key words: Diels-Alder reaction; 4-bromo-1-naphtyl bicyclo[2.2.1]methanones; antimicrobial activities; antioxidant activity

ЗЕЛЕН ПРИСТАП НА ДИЕЛС-АЛДЕРОВА РЕАКЦИЈА ВО ВОДНА СРЕДИНА ЗА СИНТЕЗА НА НЕКОИ 2-(4-БРОМО-1-НАФТИЛ)-3-АРИЛ БИЦИКЛО[2.2.1]ХЕПТ-5-ЕН МЕТАНОНИ И ПРОЦЕНА НА НИВНАТА АНТИМИКРОБНА И АНТИОКСИДАЦИСКА АКТИВНОСТ

Некои (4-бромо-1-нафтил)-(3-супституирани фенил) бицикло[2.2.1]хепт-5-ен-2-ил) метил кетони беа синтетизирани во присуство на лебдечки пепел како катализатор во еколошки прифатлива Диелс-Алдерова [4+2] циклоадициска реакција на арил халкони и циклопентадиен во водна средина. Приносот на реакцијата изнесуваше над 60%. Синтетизираните метанони беа карактеризирани преку нивните физички константи, микроанализа, како и преку инфрацрвени, нуклеарномагнетно-резонантни и масеноспектроскопски податоци. Антибактериските и антифунгицидните активности на добиените кетони беа проценети со активноста на диск дифузивна зонска инхибиција и двократна минимално инхибиторска концентрација при сериско разредување на соодветните видови бактерии и фунги со употреба на методот на Bauer-Kirby. Антиоксидацискатa активност на овие метанони беше определена со методот на прибирање на радикали со употреба на дифенил пикрил хидразил (DPPH).

Клучни зборови: Диел-Алдерова реакција; 4-бромо-1-нафтил бицикло[2.2.1]метанони; антимикробна активност; антиоксидациска активност

1. INTRODUCTION

The environmentally benign water-mediated hetero Diels-Alder [4+2] cyclo-addition reaction is most important for deriving numerous stereospecific, stereoselective, region and enantioselective bicyclo organic substrates [1, 2]. Chemists and scientists have paid much more attention to this

environmentally benign water-mediated reaction for synthesizing methanones [3], cyclic imines [4], cyclohexanone derivatives [5, 6], diones [7], peptide-oligonucleotide conjugates [8], aza compounds [9], bicyclic esters [10], anthracene derivatives [11], cyclic diacids [12], Michael adducts [13], cantharidine-like molecules [14] and melamine peptides [8]. The water mediated environmentally benign hetero Diels-Alder [4+2] cycloaddition reaction was 700 times faster than in non-aqueous phase [3]. Numerous catalysts were employed to perform this Diels-Alder reaction, such as specific and chiral Lewis acids [3, 15], chiral bases [16], chiral amines [5, 6], non-natural α-amino acids [17], bimodal catalysts [18], hydrogen bonding interactions [1], chiral silver phosphates [4], Ti(IV) compounds [19], alkaline salts [20], lithium perchlorate [10], pyridyl-modified RNA [11], fly-ash [21–25], carbocations [13], Cu(II) compounds [2], organo-tungstates with ionic-liquids [26], ribozymes [27], low melting carbohydrates [28], and metal-free non-covalent compounds [29]. Fard *et al*. have studied the solvent effect and performed DFT analysis of acid catalyzed Diels-Alder cycloaddition reaction of 2,5-dimethyl furan and maleic anhydride [30]. Kerbs and Laschat reported the isomerization of multiple bonds in tetrahydro-1-*H*-indene-1,5(7a*H*) dienes by Diels-Alder reaction [7]. The self-Diels-Alder reaction is useful for transformations of α, β-unsaturated ketones into cyclohexanones [5]. The Diels-Alder products such as cyclic and bicyclic methanones and imines possess significant biological activities [21–25, 31, 32]. Bicyclic ketones are used as starting materials for the synthesis of epoxy ketones [33], higher aromatic ketones, and nitriles [34]. These ketones possess important biological potential such as antimicrobial, antioxidant, insect antifeedant [35–37], cytotoxic [38], cardiotonic, antiarrhythmic, and antishock activities [39], and as fragrance ingredients [40] and anticonvulsants [41]. Recently, Thirunarayanan prepared some bicyclic methanones through a water-mediated Diels-Alder reaction catalyzed by fly-ash:H_2O catalyst and studied the antimicrobial, antioxidant, and insect antifeedant activities [35–37]. The literature review reveals that there is no information available about the water-mediated fly-ash catalyzed Diels-Alder[4+2] cycloaddition reaction for the synthesis of titled compounds. Hence the author attempted to synthesize of 2-(4-bromo-1-2-naphthyl)-3-(substituted phenyl) bicyclo[2.2.1] hepta-5-ene ketones by green chemical water mediated fly-ash catalyzed Diels-Alder[4+2] cycloaddition of *E*-(4-bromo-1-naphthyl)-2-propen-1-ones and cyclopentadiene under a cooling condition. The antimicrobial and antioxidant activities of these ketones have been evaluated using disc-diffusion [42] as well as the serial dilution method and diphenyl picryl hydrazyl (DPPH) radical scavenging [37] ability.

2. EXPERIMENTAL

2.1. *General*

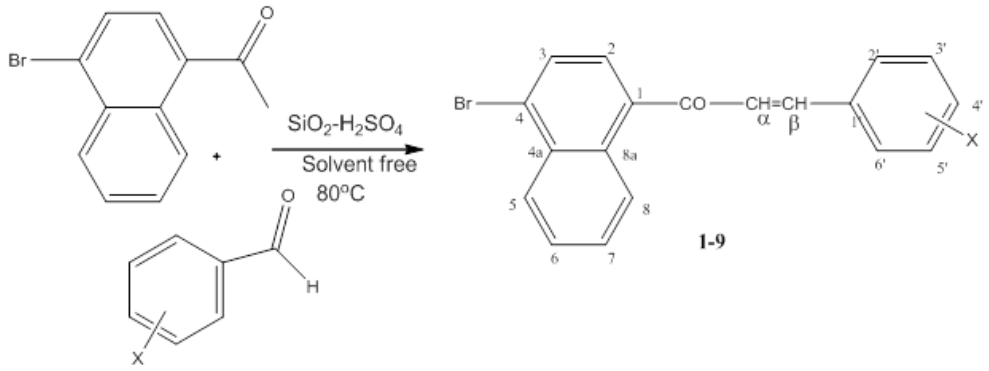
All chemicals were procured from Sigma-Aldrich and E-Merck. Fly-ash was collected from Thermal Power Plant-II, Neyveli Lignite Corporation (NLC), Neyveli, Tamil Nadu, India. The melting points of all bicyclo[2.2.1]heptene-2-ylmethanones were determined in open glass capillaries on a Mettler FP51 melting point apparatus and are uncorrected. Infrared (IR) spectra (KBr, 4000–400 cm^{-1}) were recorded on a Thermo Scientific Nicolet iS5, (USA) Fourier transform spectrophotometer. The nuclear magnetic resonance (NMR) spectra of selective compounds were recorded by 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 tetramethylsilane (TMS) as the internal standard. Electron impact and chemical ionization mode FAB^+ mass spectra were recorded with a Shimadzu GCMS-TQ8040 model spectrometer. The elemental analysis of all methanones was performed using a Thermo Finnigan Flash EA 1112 model elemental analyzer.

2.2. *Synthesis of 4-bromo-1-naphthyl chalcones*

The substituted styryl 4-bromo-1-naphthyl-ketones were synthesized by a literature method [43].

2.2.1. *General procedure for synthesis of 4-bromo-1-naphthyl ketone with benzaldehydes*

Equimolar quantities of 4-bromo-1-naphthyl ketone (2 mol), substituted benzaldehydes (2 mmol), and silica-sulfuric acid (1.5 g, equal to 4 mmol of H^+) were mixed thoroughly, placed in a 50 ml beaker, and closed with a watch glass (Scheme 1). The mixture was heated in an oven at 80 °C for 2–3.5 h. After complete conversion of the ketones as monitored by thin layer chromatogram (TLC), the mixture was cooled to room temperature. Dichloromethane (20–30 ml) was added and heated for 3–5 minutes. The reagent was removed by filtration. The filtrate was concentrated and the solid residue was recrystallized from ethanol to obtain the pure products as pale yellow glittering solid. The catalyst was recycled by washing the solid reagent remaining on the filter using ethyl acetate (20 ml) followed by drying in an oven at 50 °C for 2 h and it can be reused for another reaction run.



Entry	1	2	3	4	5	6	7	8	9
X	H	3-NH_2	3-Br	4-Cl	4-$N(CH_3)_2$	4-OH	4-OCH_3	4-CH_3	4-NO_2

Scheme 1. Synthesis of 4-bromo-1-naphthyl chalcones

The infrared carbonyl stretching frequencies of *s-cis* and *s-trans* conformers are assigned. Similarly the nuclear magnetic resonance chemical shifts (δ, ppm) of ethylene α, β protons and carbons are assigned. The characterization data of all chalcones are summarized as follows.

(2*E*)-1-(4-bromo-1-naphthyl)-3-phenyl-2-propen-1-one (1). Yield: 96%, m.p. 103–104 °C; IR (KBr, cm^{-1}): ν =1687 (CO *s-cis*), 1657 (CO *s-trans*), 984 (CH=CH). ^{1}H NMR ($CDCl_3$, ppm): δ = 8.249 (d,1H α), 8.364 (d,1H β), 7.192–7.864 (m, 11H Ar-H). ^{13}C NMR ($CDCl_3$, ppm): δ = 122.846 ($C_α$) 144.762 ($C_β$), 192.092 (CO), 136.954 (C_1), 129.816 (C_2), 129.907 (C_3), 128.218 (C_4), 129.907 (C_5), 126.437 (C_6), 127.300 (C_7), 125.816 (C_8), 133.00 (C_{4a}), 133.737 (C_{8a}), 137.201 (C_1'), 126.003 (C_2',C_6'), 128.665 (C_3',C_5'), 138.216 (C_4'). Analysis. Calcd. for $C_{19}H_{13}OBr$ (337.20): C, 67.67; H, 3.89. Found: C, 67.59; H 3.82(%).

(2*E*)-1-(4-bromo-1-naphthyl)-3-(3-aminophenyl)-2-propen-1-one (2). Yield: 92%, m.p. 72–73 °C; IR (KBr, cm^{-1}): ν = 1677 (CO *s-cis*), 1644 (CO *s-trans*), 996 (CH=CH), 3623 (-NH_2). ^{1}H NMR ($CDCl_3$, ppm): δ = 8.245 (d,1H α), 8.310 (d,1H β), 7.311–8.513 (m, 10H Ar-H), 4.623 (s, 2H–NH_2). ^{13}C NMR ($CDCl_3$, ppm): δ = 120.201 ($C_α$) 143.344 ($C_β$), 192.402 (CO), 136.421 (C_1), 126.000 (C_2), 128.980 (C_3), 127.410 (C_4), 128.418 (C_5), 126.317 (C_6), 128.300 (C_7), 127.816 (C_8), 133.744 (C_{4a}), 133.740 (C_{8a}), 132.452 (C_1'), 113.203 (C_2'), 147.209 (C_3'), 115.728 (C_4'), 130.174 (C_5'), 115.728 (C_6'). Analysis. Calcd. for $C_{19}H_{14}BrNO$ (337.20): C, 64.79; H, 4.01; N, 3.98. Found: C, 64.67: H, 3.98; N, 3.69(%).

(2*E*)-1-(4-bromo-1-naphthyl)-3-(3-bromophenyl)-2-propen-1-one (3). Yield: 95%, m.p. 107–108 °C; IR (KBr, cm^{-1}): ν = 1681 (CO *s-cis*), 1658 (CO *s-trans*), 1025 (CH=CH). ^{1}H NMR ($CDCl_3$, ppm): δ = 8.309 (d,1H α), 8.335 (d,1H β), 7.515–8.052 (m, 10H Ar-H). ^{13}C NMR ($CDCl_3$, ppm): δ = 121.640 ($C_α$) 142.030 ($C_β$), 192.667 (CO), 137.020 (C_1), 127.736 (C_2), 129.480 (C_3), 123.280 (C_4), 128.750 (C_5), 126.737 (C_6), 128.098 (C_7), 134.690 (C_8), 134.989 (C_{4a}), 130.294 (C_{8a}), 140.437 (C_1'), 129.633 (C_2'), 128.280 (C_3'), 131.341 (C_4'), 130.294 (C_5'), 124.995 (C_6'). Analysis. Calcd. for $C_{19}H_{12}Br_2O$ (416.10): C, 54.84; H, 2.91. Found: C, 54.79; H, 2.83(%).

(2*E*)-1-(4-bromo-1-naphthyl)-3-(4-chlorophenyl)-2-propen-1-one (4) Yield: 96%, m.p. 100–101 °C; IR (KBr, cm^{-1}): ν = 1679 (CO *s-cis*), 1652 (CO *s-trans*), 1029 (CH=CH). ^{1}H NMR ($CDCl_3$, ppm): δ = 8.300 (d,1H α), 8.322 (d,1H β), 7.388–7.819 (m, 10H Ar-H). ^{13}C NMR ($CDCl_3$, ppm): δ = 121.306 ($C_α$) 143.725 ($C_β$), 186.601 (CO), 136.858 (C_1), 129.665 (C_2), 128.770 (C_3), 126.860 (C_4), 128.250 (C_5), 126.060 (C_6), 132.894 (C_7), 121.306 (C_8), 130.330 (C_{4a}), 130.772 (C_{8a}), 136.857 (C_1'), 127.956 (C_2', C_6'), 129.330 (C_3', C_5'), 136.888 (C_4'). Analysis. Calcd. for $C_{19}H_{12}BrClO$ (371.05): C, 61.40; H, 3.25. Found: C, 61.32; H, 3.22(%).

(2*E*)-1-(4-bromo-1-naphthyl)-3-(4-dimethylaminophenyl)-2-propen-1-one (5). Yield: 93%, m.p. 118–119 °C; IR (KBr, cm^{-1}): ν = 1672 (CO *s-cis*), 1631 (CO *s-trans*), 976 (CH=CH), 3576 (-NH_2). ^{1}H NMR ($CDCl_3$, ppm): δ = 8.122 (d,1H α), 8.199 (d,1H β), 7.636–8.319 (m, 10H Ar-H), 2.88 (s, 6H –$(CH_3)_2$). ^{13}C NMR ($CDCl_3$, ppm): δ = 118.800 ($C_α$) 141.300 ($C_β$), 190.200 (CO), 42.840 (CH_3), 135.00 (C_1), 129.724 (C_2), 127.994 (C_3), 129.091 (C_4), 130.144 (C_5), 128.947 (C_6), 128.527 (C_7), 124.720 (C_8), 130.149 (C_{4a}), 129.091 (C_{8a}), 124.720 (C_1'), 126.920 (C_2', C_6'), 114.417 (C_3', C_5'), 152.470 (C_4').

Analysis. Calcd. for $C_{21}H_{18}BrNO$ (380.27): C, 66.33; H, 4.77; N, 3.68. Found: C, 66.34; H, 4.67; N, 3.64(%).

(2*E*)-1-(4-bromo-1-naphthyl)-3-(4-hydroxyphenyl)-2-propen-1-one (6). Yield: 91%, m.p. 97–98 °C; IR (KBr, cm^{-1}): ν = 1671 (CO *s-cis*), 1635 (CO *s-trans*), 1015 (CH=CH), 3565 (–OH). ^{1}H NMR ($CDCl_3$, ppm): δ = 8.184 (d,1H α), 8.204 (d,1H β), 7.688–7.843 (m, 10H Ar-H), 4.752 (s, 1H –OH). ^{13}C NMR ($CDCl_3$, ppm): δ = 119.716 ($C_α$) 143.560 ($C_β$), 191.200 (CO), 134.521 (C_1), 128.533 (C_2), 130.055 (C_3), 128.533 (C_4), 130.299 (C_5), 128.340 (C_6), 132.144 (C_7), 124.924 (C_8), 132.144 (C_{4a}), 130.022 (C_{8a}), 130.032 (C_1'), 129.461 (C_2', C_6'), 116.992 (C_3', C_5'), 157.924 (C_4'). Analysis. Calcd. for $C_{19}H_{13}BrO_2$ (353.20): C, 64.61; H, 3.71. Found: C, 64.59; H, 3.69(%).

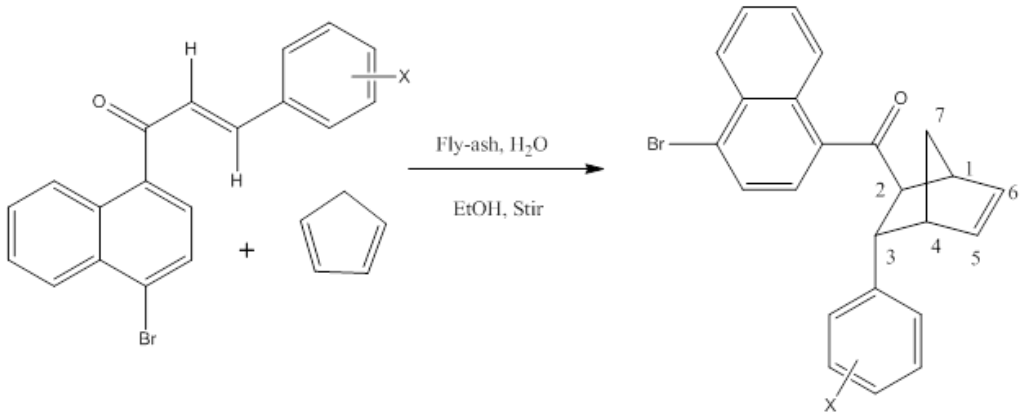
(2*E*)-1-(4-bromo-1-naphthyl)-3-(4-methoxyphenyl)-2-propen-1-one (7). Yield: 96%, m.p. 123–124 °C; IR (KBr, cm^{-1}): ν = 1685 (CO *s-cis*), 1641 (CO *s-trans*), 1024 (CH=CH). ^{1}H NMR ($CDCl_3$, ppm): δ = 8.213 (d,1H α), 8.337 (d,1H β), 7.053–7.824 (m, 10H Ar-H) 4.132 (s, 3H –OCH_3). ^{13}C NMR ($CDCl_3$, ppm): δ = 121.440 ($C_α$) 142.619 ($C_β$), 193.900 (CO), 53.810 (-OCH_3) 138.207 (C_1), 129.905 (C_2), 128.850 (C_3), 121.957 (C_4), 128.850 (C_5), 126.701 (C_6), 127.102 (C_7), 128.170 (C_8), 132.220 (C_{4a}), 130.599 (C_{8a}), 131.753 (C_1'), 127.102 (C_2', C_6'), 116.992 (C_3', C_5'), 163.446 (C_4'). Analysis. Calcd. for $C_{20}H_{15}BrO_2$ (367.23): C, 65.40; H, 4.12. Found: C, 65.39; H, 4.00(%).

(2*E*)-1-(4-bromo-1-naphthyl)-3-(4-methylphenyl)-2-propen-1-one (8). Yield: 94%, m.p. 95–96 °C; IR(KBr, cm^{-1}): ν = 1676 (CO *s-cis*), 1642 (CO *s-trans*), 993 (CH=CH). ^{1}H NMR ($CDCl_3$, ppm): δ = 8.255 (d,1H α), 8.363 (d,1H β), 7.211–7.846 (m, 10H Ar-H) 2.574 (s, 3H –CH_3). ^{13}C NMR ($CDCl_3$, ppm): δ = 120.481 ($C_α$), 143.159 ($C_β$), 191.990 (CO), 25.300 (-CH_3) 137.252 (C_1), 129.791 (C_2), 131.095 (C_3), 128.804 (C_4), 130.214 (C_5), 128.610 (C_6), 132.294 (C_7), 122.610 (C_8), 130.214 (C_{4a}), 130.218 (C_{8a}), 137.252 (C_1'), 126.435 (C_2', C_6'), 129.791 (C_3', C_5'), 137.252 (C_4'). Analysis. Calcd. for $C_{20}H_{15}BrO$ (351.23): C, 68.39; H, 4.30. Found: C, 68.34: H, 3.99(%).

(2*E*)-1-(4-bromo-1-naphthyl)-3-(4-nitrophenyl)-2-propen-1-one (9). Yield: 94%, m. p. 116–117 °C; IR (KBr, cm^{-1}): ν = 1684 (CO *s-cis*), 1672 (CO *s-trans*), 1016 (CH=CH). ^{1}H NMR ($CDCl_3$, ppm): δ = 8.334 (d,1H α), 8.401 (d,1H β), 7.349–8.135 (m, 10H Ar-H). ^{13}C NMR ($CDCl_3$, ppm): δ = 123.433 ($C_α$) 145.183 ($C_β$), 193.552 (CO), 139.103 (C_1), 129.580 (C_2), 132.103 (C_3), 128.546 (C_4), 129.580 (C_5), 127.204 (C_6), 127.204 (C_7), 129.580 (C_8), 135.920 (C_{4a}), 132.103 (C_{8a}), 142.466 (C_1'), 127.598 (C_2', C_6'), 115.716 (C_3', C_5'), 148.499 (C_4'). Analysis. Calcd. for $C_{19}H_{12}BrNO_3$ (382.20): C, 59.71; H, 3.16; N, 3.66. Found: C, 59.68; H, 3.11; N, 3.58(%).

2.3. *General procedure for synthesis of (4-bromo-1-naphthyl)-(3-(substituted phenyl)bicyclo[2.2.1]hept-5-en-2-yl)methanones*

In a 100 ml conical flask, 2 mmol of 4-bromo-1-naphthyl chalcones 5 ml of ethanol, cyclopentadiene (2 mmol), and 0.4 g of fly-ash in 20 ml of water were taken and stirred for 6 h in an ice bath at a temperature of 0–4 °C (Scheme 2) and the reaction mixture was kept overnight.



Entry	10	11	12	13	14	15	16	17	18
X	H	3-NH_2	3-Br	4-Cl	4-$N(CH_3)_2$	4-OH	4-OCH_3	4-CH_3	4-NO_2

Scheme 2. Synthesis of (4-bromo-1-naphthyl)(3-(substituted phenyl)bicyclo[2.2.1] hept-5-en-2-yl) methanones

The completion of the reaction was monitored by thin layer chromatogram. Dichloromethane (10 ml) was added and the extract was separated by filtration. The filtrate was washed with water, and brine (10 ml), dried over anhydrous Na_2SO_4 and concentrated to give the solid product. The crude product was further purified by recrystallization with ethanol. The catalyst was washed with 5 ml of ethyl acetate and dried in a hot air oven at 110°C for 3 h. Then this catalyst was reused for further reaction runs.

2.4. *Measurement of antimicrobial activity*

The antimicrobial activities such as the antibacterial and antifungal activities, of prepared bicyclo[2.2.1]heptene-2-yl-methanones were evaluated using the disc-diffusion and serial dilution methods. The prepared bicyclo[2.2.1]heptene-2-yl-methanones subjected to evaluate the antimicrobial activities by measuring the zone of inhibition against bacterial and fungal strains. Three Gram-positive pathogenic strains (*Staphylococcus aureus*, *S. typhi*, and *Enterococcus faecalis*) and three Gram-negative strains (*Escherichia coli*, *Pseudomonas aeruginosa* and *Klebsiella pneumoniae*) were applied for evaluation of antimicrobial activities. The Bauer-Kirby [36] disc diffusion technique was adopted with a concentration of 250 μg/ml of with ampicillin and miconazole as standards.

2.4.1. *Measurement of antibacterial sensitivity by disc diffusion method*

The Bauer-Kirby [36] disc diffusion technique was adopted for antibacterial sensitivity assay measurements of all compounds. About 0.5 ml of the bacterial test compounds was spread uniformly over solidified Mueller-Hinton agar. Discs about 5 mm in diameter, made from Whatman No. 1 filter paper, were placed on the medium with potential inhibitor solution. The plates were incubated for 24 h at 37ºC upside down to prevent the collection of water droplets over the medium. Then the plates were examined and the diameters (mm) of zone of inhibition were measured. The results were recorded in triplicate.

2.4.2. *Measurement of antifungal sensitivity by disc diffusion method*

The Bauer-Kirby [36] disc diffusion technique was used for the measurement of antifungal activity of synthesized methanones. Sterilized potato dextrose agar medium was added to the Petri plates containing 1 ml of fungal strains. Uniform spreading of the agar on the plates was performed by means of clockwise and anti-clockwise rotation of the discs. The test sample was made by dissolving 15 mg of the methanones in 1 ml of dimethylsulfoxide (DMSO) solvent and applying it on the discs. This medium was solidified by incubation for 24 or 72 h at 25 or 28ºC. Then these plates were examined for the evaluation of antifungal activity by measuring the diameters (mm) of the zones of inhibition. Measurement results were recorded in triplicate.

2.5. *Antioxidant activity by radical scavenging method*

The diphenyl picryl hydrazyl (DPPH) radical scavenging activity technique [35] was used for the measurement of the 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 diphenyl picryl hydrazyl (DPPH) solution was prepared by dissolving 3.9 g of diphenyl picryl hydrazyl (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 diphenyl picryl hydrazyl (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 a UV–vis spectrophotometer (Shimadzu-1650) at 517 nm. A 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 the IC_{50} (μg/ml, concentration required to inhibit diphenyl picryl hydrazyl (DPPH) radical formation by 50%). α-Tocopherol was taken as a positive control. The radical scavenging activity was calculated as:

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

2.6. *Antimicrobial activity assay by dilution method*

2.6.1. *Antibacterial activity*

The Bauer-Kirby [36] disc diffusion experimental results of mm of maximum zone of inhibi-

tion in millimeters were compared with the potency of all ketones in standard drugs against bacterial and fungal strains by measuring the minimum inhibitory concentration (MIC) of test compounds using the two-fold serial dilution method.

This procedure was applied for the seeded broth (10^{-6} to 10^{-7} cfu/ml). Test samples were taken at different concentrations of 200, 100, 50, 25, 12.5, 6.25, 3.13, 1.56, 0.78, and 0.39 μg/ml to find the minimum inhibitory concentration (MIC) by using seeded broth as the diluent. Similarly, the standard solution of ampicillin drug was prepared at concentrations of 200, 100, 50, 25.5, 6.25, 3.13, 1.56, 0.78, and 0.39 μg/ml of sterile distilled water and dimethylsulfoxide (DMSO) was maintained throughout the experiment simultaneously as control.

The study involves a series of 10 assay tubes to investigate the effect of the test compounds against each strain. First, 1.6 ml of seeded broth was transferred into the first assay tube and 0.4 ml of the test solution was added and then mixed thoroughly to obtain a concentration of 200 μg/ml. Next, 1 ml of seeded broth was transferred into the remaining nine assay tubes and then μg / ml of the content was pipetted out from the first assay tube and added to the second assay tube followed by thorough mixing. This type of dilution was repeated up to tenth assay tube serially. The same procedure was followed for standard drugs. Duplicates were also maintained under aseptic conditions.

The diluted samples of seeded broth tubes were kept in an incubator at 37 ± 1 °C for 24 h. After the incubation period, the concentrations of the assay tubes were altered using nutrient agar plates. The lowest concentration of the test samples gave good enough results for the complete inhibition of growth of the organism, which was taken as the minimum inhibitory concentration (MIC). The solvent control tube was simultaneously monitored for any inhibitory action. No inhibition was carried out for the sterile distilled water and dimethylsulfoxide (DMSO). The same procedure was employed for the measurement of antifungal activity of all compounds with their fungal strains.

In order to understand the results of the serial dilution method, the potency of synthesized compounds against the tested bacterial and fungal strains was calculated with respect to the reference (standards) using the following equation(1).

$$\text{Potency (\%)} = \frac{\text{MIC } (\mu\text{g/ml}) \text{ of reference compound}}{\text{MIC } (\mu\text{g/ml}) \text{ of tested compound}} \times 100 \quad (1)$$

3. RESULTS AND DISCUSSION

In our synthetic organic chemistry research laboratory, the author has attempted to synthesize (4-bromo-1-naphthyl) (3-(substituted phenyl)bicyclo[2.2.1]heptene-2-yl)methanone derivatives by an environmentally benign water-mediated fly-ash-catalyzed Diels-Alder reaction with cyclopentadiene as diene and (*E*)-4-bromo-1-naphthyl chalcones as dienophiles. This reaction gave positive results. Fly-ash contains oxides of Si, Al, Fe, Ca and organic muds as the main chemical components. The elemental analysis of lignite fly-ash (Class C fly-ash) indicates a composition of 15–45% SiO_2, 20–25% Al_2O_3, 6–15% Fe_2O_3, 15–40% CaO, and 0–5% C. During the reaction of diene and dienophiles, the chemical species present in the fly-ash catalyzed the [4+2] cycloaddition reaction. In this reaction, the obtained yield is more than 60%. The electron–donating group substituted chalcones gave a yield of more than 65%. The electron–withdrawing substituted chalcones gave a yield of 60%. This reaction was useful for synthesizing the Diels-Alder adduct by adopting the waste pollutant as catalyst. Also, no yield was observed without fly-ash catalyst in the reaction. The analytical data, physical constants and microanalysis data are presented in Table 1. The reusability of the catalyst in this reaction was studied in this cycloaddition with 2 mmol of 4-bromo-1-naphthylchalcone and 2 mmol of cyclopentadiene (compound **10**) and is presented in Table 2**.** The first run gave a product yield of 65%. The second and third runs gave 60 and 53%, respectively. The fourth and fifth runs gave 40%. The chalcone containing electron-donating substituents (OCH_3) gave a higher yield than electron-withdrawing (halogens and nitro) substituents. The effect of the catalyst on this reaction was studied by varying the catalyst quantity from 0.05 to 0.6 g. As the catalyst quantity increased from 0.05 to 0.4 g, the percentage of product increased from 58 to 65%. On further increasing the catalyst amount beyond 0.4 g, there was no increase in the percentage of product yielded. The effect of the catalyst loading is shown in Figure 1. The optimum quantity of catalyst loading was found to be 0.4 g of 4-bromo-1-naphthylchalcone substrate. The effect of solvents on this reaction (compound **10**) was studied with the same quantity of reactants with methanol, dichloromethane, dioxane, and tetrahydrofuran and is presented in Table 3. The higher yield was obtained in ethanol with fly-ash in water medium.

T a b l e 1

The physical constants and microanalysis data of (4-bromo-1-naphthyl)(3-(substituted phenyl) bicyclo[2.2.1]heptene-2-yl)methanone

Cpd	X	M. F.	MW	m.p. (°C)	Yield (%)	Microanalysis (%)		
						C	H	N
10	H	$C_{24}H_{19}BrO$	403	116–117	65	71.55 (71.47)	4.70 (4.75)	---
11	3-NH_2	$C_{24}H_{20}BrNO$	418	79–80	63	68.95 (68.91)	4.79 (4.82)	3.30 (3.35)
12	3-Br	$C_{24}H_8Br_2O$	482	112–113	61	59.72 (59.78)	3.71 (3.76)	–
13	4-Cl	$C_{24}H_8BrClO$	437	114–115	61	65.84 (65.85)	4.07 (4.14)	–
14	4-$N(CH_3)_2$	$C_{24}H_{24}BrNO$	445	122–123	63	69.95 (69.96)	5.39 (5.42)	3.14 (3.19)
15	4-OH	$C_{24}H_{19}BrO_2$	419	116–117	62	68.73 (68.75)	4.52 (4.57)	–
16	4-OCH_3	$C_{25}H_{21}BrO_2$	433	111–112	65	69.26 (69.29)	4.84 (4.88)	–
17	4-CH_3	$C_{25}H_{21}BrO$	417	103–104	64	71.93 (71.95)	5.02 (5.07)	–
18	4-NO_2	$C_{24}H_{18}BrNO_3$	448	117–118	61	64.27 (64.30)	3.99 (4.05)	3.10 (3.12)

Values in the parentheses are calculated

T a b l e 2

*The effect of reuse of the catalyst on the yield of the aqueous phase Diels-Alder reaction of styryl 4-bromo-1-naphthyl ketone and cyclopentadiene (compound **10**)*

Run	1	2	3	4	5
Yield (%)	65	60	53	40	40

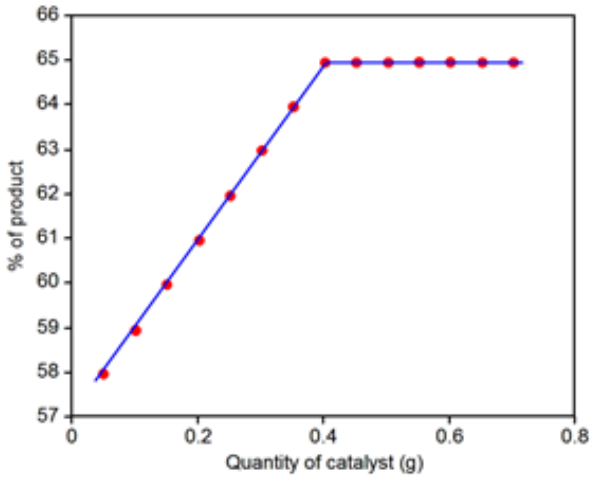


Fig. 1. The effect of catalyst loading

T a b l e 3

*The effect of solvents on the aqueous phase Diels-Alder reaction of styryl 4-bromo-1-naphthyl ketone and cyclopentadiene (compound **10**)*

Solvent	Ethanol	Methanol	Dichloromethane	Dioxane	Tetrahydro furan
Yield (%)	65	63	62	60	62

In this experiment, the obtained products exist as single enantiomers. The synthesized ketones were characterized by their analytical data, physical constants (Table 1), and spectroscopic data, as follows. Based on earlier reports [1, 3, 4, 9, 21–25], the norbornyl ring exists as 1*S*, 2*S*, 3*S*, and 4*R* geometries. The chemical shift (δ, ppm) of the C-1 proton is found to be around 3.75 as a double doublet. The chemical shift (δ, ppm) of the C-2 proton is around 3.55 as triplets. The chemical shift (δ, ppm) of the C-3 proton is around 3.4 as triplets. The chemical shift (δ, ppm) of the C-4 proton is around 2.6 as double doublets. The chemical shift (δ, ppm) of C-5 and C-6 protons is around 6.5 as doublets. The chemical shifts (δ, ppm) of C-7 and C-7′ protons are around the ranges of 1.8 and 1.6 as a doublet of doublets. The spectroscopic data of the synthesized Diels-Alder adducts are summarized below.

(4-Bromonaphthalen-1-yl)((1S,2S,3S,4R)-3-phenylbicyclo[2.2.1]hept-5-en-2-yl)methanone (10). IR (KBr, cm^{-1}): ν 3069, 2885, 1687, 1514, 1344, 1172, 1082, 993, 711, 690, 585, 484; ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 3.738 (dd, 1H, $H_{1,4}$, J = 6.4 and 4.0 Hz), 3.510 (t, 1H, H_2, J = 16 Hz), 3.481 (t, 1H, H_3, J = 17 Hz), 2.635 (dd, 1H, H_4, J = 4.0 and 4.8 Hz), 6.572 (d, 1H, $H_{5,6}$, J = 16.5 Hz), 1.845 (dd, 1H, H_7, J = 8.0 and 6.0 Hz), 1.612 (dd, 1H, $H_{7'}$, J = 6 and 4 Hz), 7.176–8.917 (m, 11H, Ar–H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 196.37 (CO), 47.12 ($C_{1,4}$), 53.81 (C_2), 45.07 (C_3), 134.43 (C_6), 136.17 (C_6), 46.37 (C_7), 124.37–147.81 (Ar–C); MS (EI): *m/z* 403 [M^+], 405 [M^{2+}], 325, 246, 232, 204, 197, 169, 154, 126, 92, 77, 28.

((1S, 2S, 3S, 4R)-3-(3-Aminophenyl)bicyclo [2.2.1] hept-5-en-2-yl)(4-bromonaphthalen-1-yl)methanone (11). IR (KBr, cm^{-1}): ν 3427, 3086, 2918, 1662, 1593, 1525, 1442, 1357, 1300, 1168, 1039, 837, 734, 466; ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 3.754 (dd, 1H, H_1, J = 6.8 and 4.0 Hz), 3.481 (t, 1H, H_2, J = 16 Hz), 3.407 (t, 1H, H_3, J = 17 Hz), 2.655 (dd, 1H, H_4, J = 4.0 and 6.0 Hz), 6.417 (d, 1H, $H_{5,6}$, J = 16.5 Hz), 1.759 (dd, 1H, H_7, J = 8 and 6 Hz), 1.636 (dd, 1H, $H_{7'}$, J = 6.4 and 4.0 Hz), 6.317 (s, 2H, NH_2), 6.653–9.173 (m, 10H, Ar–H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 197.28 (CO), 46.83 ($C_{1,4}$), 53.85 (C_2), 45.77 (C_3), 134.26 (C_6), 136.19 (C_6), 45.32 (C_7), 113.17–149.76 (Ar–C); MS (EI): *m/z* 418 [M^+], 420 [M^{2+}], 401, 391, 325, 232, 246, 204, 154, 92, 91, 77, 26, 16.

(4-Bromonaphthalen-1-yl)((1S,2S,3S,4R)-3-(3-bromophenyl)bicyclo[2.2.1]hept-5-en-2-yl)methanone (12). IR (KBr, cm^{-1}): ν 3082, 2916, 1664, 1593, 1521, 1442, 1359, 1168, 1041, 831, 732, 470; ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 3.716 (dd, 1H, H_1, J = 6.4 and 4.0 Hz), 3.521 (t, 1H, H_2, J = 15.5 Hz), 3.443 (t, 1H, H_3, J = 17 Hz), 2.729 (dd, 1H, H_4, J = 5.2 and 6.4 Hz), 6.481 (d, 1H, $H_{5,6}$, J = 17 Hz), 1.812 (dd, 1H, H_7, J = 6.4 and 6.0 Hz), 1.640 (dd, 1H, $H_{7'}$, J = 8.0 and 6.4 Hz), 7.217–9.071 (m, 10H, Ar–H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 198.32 (CO), 47.12 ($C_{1,4}$), 53.21 (C_2), 44.68 (C_3), 135.27 (C_6), 136.14 (C_6), 46.11 (C_7), 126.31–149.71 (Ar–C); MS (EI): *m/z* 482 [M^+], 484 [M^{2+}], 486 [M^{4+}], 402, 325, 322, 275, 247, 232, 204, 196, 154, 126, 120, 92, 79, 77, 28.

(4-Bromonaphthalen-1-yl)((1S,2S,3S,4R)-3-(4-chlorophenyl)bicyclo[2.2.1]hept-5-en-2-yl)methanone (13). IR (KBr, cm^{-1}): ν 3020, 2924, 1638, 1479, 1330, 1174, 1078, 997, 815, 804, 601, 489; ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 3.727 (dd, 1H, H_1, J = 4.0 and 6.4 Hz), 3.571 (t, 1H, H_2, J = 15 Hz), 3.461 (t, 1H, H_3, J = 17 Hz), 2.762 (dd, 1H, H_4, J = 4.0 and 6.4 Hz), 6.617 (d, 1H, $H_{5,6}$, J = 17 Hz), 1.769 (dd, 1H, H_7, J = 6.0 and 4.0 Hz), 1.684 (dd, 1H, $H_{7'}$, J = 6.0 and 4.0 Hz), 7.271–9.371 (m, 10H, Ar–H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 197.92 (CO), 46.73 ($C_{1,4}$), 53.24 (C_2), 45.73 (C_3), 134.28 (C_6), 136.27 (C_6), 46.34 (C_7), 126.72–145.72 (Ar–C); MS (EI): *m/z* 437 [M^+], 441 [M^{4+}], 420 [M^{2+}], 402, 357, 325, 323, 204, 126, 120, 111, 92, 89, 77, 35, 28.

(4-Bromonaphthalen-1-yl)((1S,2S,3S,4R)-3-(4-(dimethylamino)phenyl)bicyclo[2.2.1]hept-5-en-2-yl) methanone (14). IR (KBr, cm^{-1}): ν 2924, 2864, 1631, 1471, 1332, 1174, 1081, 997, 815, 707, 599, 491; ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 3.715 (dd, 1H, H_1, J = 6.4 and 4.0 Hz), 3.441 (t, 1H, H_2, J = 16 Hz), 3.664 (t, 1H, H_3, J = 16.5 Hz), 2.499 (dd, 1H, H_4, J = 6.0 and 4.8 Hz), 6.417 (d, 1H, $H_{5,6}$, J = 16 Hz), 1.834 (dd, 1H, H_7, J = 6.4 and 4.0 Hz), 1.647 (dd, 1H, $H_{7'}$, J = 6.0 and 4.0 Hz), 3.178 (s, 3H, CH_3), 7.172–9.301 (m, 10H, Ar–H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 196.73 (CO), 46.92 ($C_{1,4}$), 53.14 (C_2), 44.94 (C_3), 135.71 (C_6), 136.28 (C_6), 46.32 (C_7), 45.32 (CH_3), 112.37–149.37 (Ar–C); MS (EI): *m/z* 445 [M^+], 447 [M^{2+}], 430, 401, 366, 325, 240, 232, 204, 126, 120, 92, 79, 77, 29, 15.

(4-Bromonaphthalen-1-yl)((1S,2S,3S,4R)-3-(4-hydroxyphenyl)bicyclo[2.2.1]hept-5-en-2-yl)methanone (15). IR (KBr, cm^{-1}): ν 3433, 3020, 2922, 1639, 1487, 1336, 1172, 1078, 997, 813, 702, 597, 489; ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 3.709 (dd, 1H, H_1, J = 8.0 and 4.0 Hz), 3.527 (t, 1H, H_2, J = 17 Hz), 3.592 (t, 1H, H_3, J = 16.5 Hz), 2.723 (dd, 1H, H_4, J = 6.4 and 4.0 Hz), 6.371 (d,

1H, $H_{5,6}$, J = 16.5 Hz), 1.796 (dd, 1H, H_7, J = 8.0 and 6.4 Hz), 1.628 (dd, 1H, $H_{7'}$, J = 4.8 and 6.0 Hz), 5.714 (s, 1H, OH), 6.671–8.927 (m, 10H, Ar–H); ^{13}C NMR (100MHz, $CDCl_3$, ppm): δ 197.22 (CO), 46.63 ($C_{1,4}$), 53.61 (C_2), 45.73 (C_3), 135.26 (C_6), 136.64 (C_6), 46.38 (C_7), 115.96–158.32 (Ar–C); MS (EI): *m/z* 419 [M^+], 421 [M^{2+}], 401, 325, 246, 232, 213, 204, 185, 154, 126, 92, 77, 28.

(4-Bromonaphthalen-1-yl)((1S,2S,3S,4R)-3-(4-methoxyphenyl)bicyclo[2.2.1]hept-5-en-2-yl)methanone (16). IR (KBr, cm^{-1}): ν 3024, 2922, 1643, 1487, 1334, 1170, 1076, 997, 813, 702, 599, 489; ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 3.668 (dd, 1H, H_1, J = 6.0 and 4.0 Hz), 3.492 (t, 1H, H_2, J =16 Hz), 3.367 (t, 1H, H_3, J = 16 Hz), 2.744 (dd, 1H, H_4, J = 6.0 and 4.0 Hz), 6.470 (d, 1H, $H_{5,6}$, J = 16 Hz), 1.823 (dd, 1H, H_7, J = 8.0 and 6.4 Hz), 1.642 (dd, 1H, $H_{7'}$, J = 6.8 and 4.8 Hz), 3.932 (s, 3H, OCH_3), 6.857–9.091 (m, 10H, Ar–H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 196.24 (CO), 46.74 ($C_{1,4}$), 53.51 (C_2), 45.62 (C_3), 135.38 (C_6), 136.24 (C_6), 46.12 (C_7), 59.34 (OCH_3), 112.97–152.74 (Ar–C); MS (EI): *m/z* 433 [M^+], 435 [M^{2+}], 417, 353, 325, 277, 232, 204, 126, 120, 107, 92, 91, 79, 28, 31, 15.

(4-Bromonaphthalen-1-yl)((1S,2S,3S,4R)-3-(4-methylphenyl)bicyclo[2.2.1]hept-5-en-2-yl)methanone(17). IR (KBr, cm^{-1}): ν 3035, 2866, 1683, 1597, 1465, 1317, 1190, 1085, 999, 898, 694, 563, 482; ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 3.755 (dd, 1H, H_1, J = 6.4 and 4.0 Hz), 3.507 (t, 1H, H_2, J = 16.5 Hz), 3.417 (t, 1H, H_3, J = 17 Hz), 2.735 (dd, 1H, H_4, J = 8.0 and 4.8 Hz), 6.451 (d, 1H, $H_{5,6}$, J = 18 Hz), 1.797 (dd, 1H, H_7, J = 8.0 and 4.0 Hz), 1.618 (dd, 1H, $H_{7'}$, J = 6.4 and 4.0 Hz), 2.417 (s, 3H, CH_3), 7.273–9.186 (m, 10H, Ar–H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 197.38 (CO), 47.13 ($C_{1,4}$), 53.17 (C_2), 45.36 (C_3), 135.26 (C_6), 136.74 (C_6), 46.93 (C_7), 23.76 (CH_3), 125.98–140.22 (Ar–C); MS (EI): *m/z* 417 [M^+], 419 [M^{2+}], 401, 337, 325, 233, 211, 204, 183, 126, 92, 91, 77, 28, 15.

(4-Bromonaphthalen-1-yl)((1S,2S,3S,4R)-3-(4-nitrophenyl)bicyclo[2.2.1]hept-5-en-2-yl)methanone (18). IR (KBr, cm^{-1}): ν 3072, 3030, 2877, 1610, 1517, 1316, 1166, 1082, 989, 690, 569, 480; ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 3.771 (dd, 1H, H_1, J = 8.0 and 5.6 Hz), 3.534 (t, 1H, H_2, J = 16 Hz), 3.441 (t, 1H, H_3, J = 17 Hz), 2.762 (dd, 1H, H_4, J = 6.0 and 7.2 Hz), 6.420 (d, 1H, $H_{5,6}$, J = 16.5 Hz), 1.791 (dd, 1H, H_7, J = 6.0 and 8.0 Hz), 1.592 (dd, 1H, $H_{7'}$, J = 8.0 and 4.0 Hz), 7.631–9.140 (m, 10H, Ar–H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 198.64 (CO), 47.32 ($C_{1,4}$), 53.22 (C_2), 44.68 (C_3), 134.44 (C_6), 135.33 (C_6), 46.52 (C_7), 123.11–148.59 (Ar–C); MS (EI): *m/z* 448 [M^+], 450 [M^{2+}], 401, 368, 325, 242, 232, 214, 205, 154, 126, 122, 92, 91, 77, 46, 27.

3.1. *Antibacterial activity of ketones by disc diffusion method*

The disc diffusion technique was followed using the Bauer-Kirby [36] method at a concentration of 250 μg ml^{-1} with ampicillin used as the standard drug. The measured antibacterial activities of all methanones are presented in Table 4. The zone of inhibition in millimeters is shown in Figure 2. Methanones **3** and **4** showed excellent antibacterial activity against all bacterial strains.

T a b l e 4

Antibacterial, antifungal and antioxidant activities of (4-bromo-1-naphthyl)-(3-(substituted phenyl) bicyclo[2.2.1]hept-5-en-2-yl)methanones

Cpd	X	Antibacterial activity (zone of inhibition, mm)					Antifungal activity (zone of inhibition, mm)		Antioxidant activity
		Gram-positive bacteria			Gram-negative bacteria				
		B. subtilis	*M. luteus*	*S. aureus*	*E. coli*	*P. aeruginosa*	*A. niger*	*P. spp*	
10	H	7	8	7	7	8	7	10	17.71 ± 1.18
11	3-NH_2	8	7	7	7	8	7	10	14.53 ± 1.94
12	3-Br	13	15	12	12	10	8	9	19.58 ± 1.09
13	4-Cl	11	14	10	11	9	8	9	21.65 ± 1.54
14	4-$N(CH_3)_2$	7	7	7	6	7	10	9	21.45 ± 1.64
15	4-OH	6	6	8	7	7	7	7	37.95 ± 1.24
16	4-OCH_3	8	6	7	7	8	7	9	35.56 ± 1.65
17	4-CH_3	9	7	7	7	6	9	7	22.44±1.62
18	4-NO_2	6	7	–	6	7	12	12	11.04 ± 1.82
Ampicillin		16	19	14	17	13	–	–	39.14 ± 1.57
Miconazole		–	–	–	–	–	14	13	(DPPH)

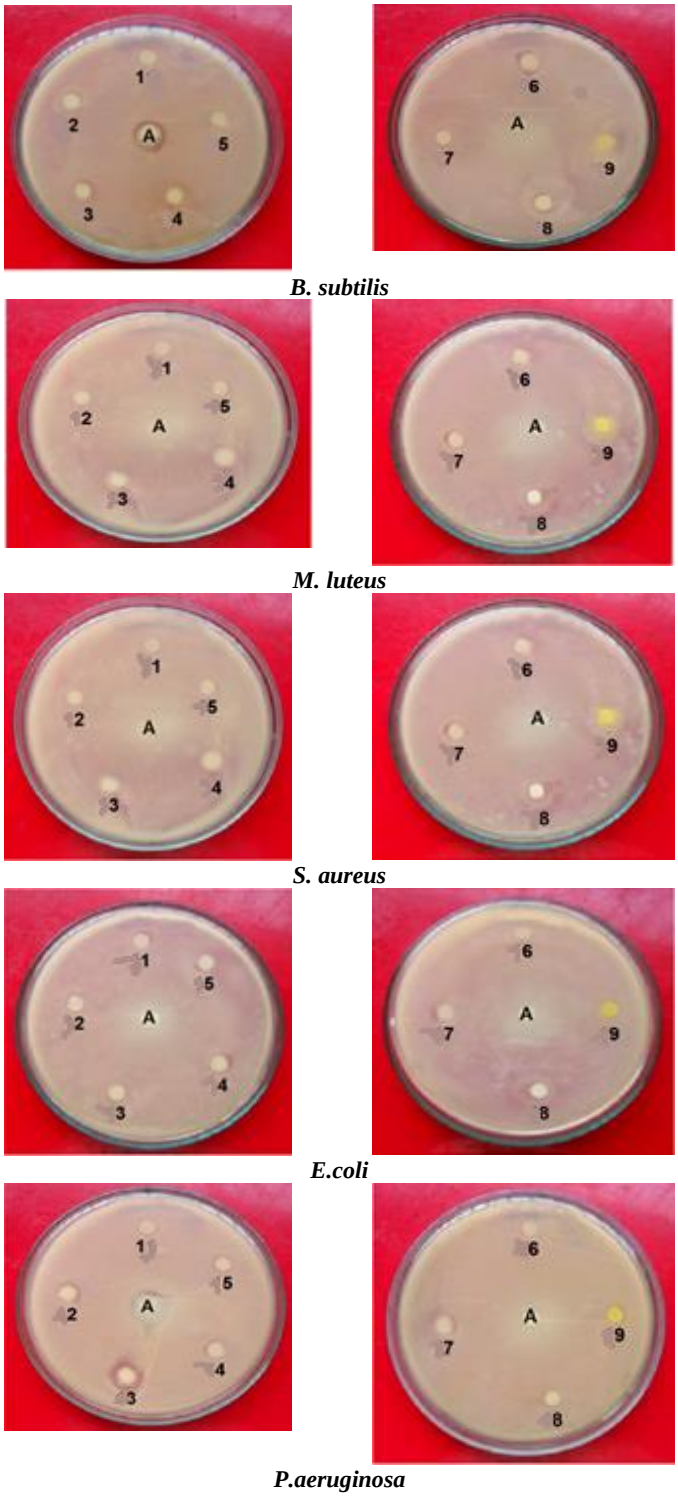


Fig. 2. Antibacterial activity as millimeters of zone of inhibition of (4-bromo-1-naphthyl)-(3-(substituted phenyl)bicyclo[2.2.1]hept-5-en-2-yl)methanones

Compounds containing H-, amino-, dimethylamino-, methoxy- and methyl-substitutions (**1**, **2**, **5**, **7** and **8**) showed moderate antibacterial activity against *Bacillus subtilis* bacterial strains. The nitro- and hydroxy-substituted methanones (**6** and **9**) showed the least activity against *B. subtilis* bacterial strains. Compounds containing hydroxy and methoxy substituents (**6** and **7**) show poor antibacterial activity against the *Micrococcus luteus* bacterial strain. With regard to compound **9**, nitro substitution was inactive against *S. aureus* strain. Dimethylamino- and nitro-substituted methanones show poor antibacterial activity against *E. coli* strain. Methanone with methyl substitution (**8**) shows the least antibacterial activity against *P. aeruginosa* bacterial strain.

3.2. *Antifungal sensitivity assay of ketones by disc diffusion method*

The observed antifungal activities of all prepared bicyclic methanones are presented in Table 4. The zones of inhibition of methanones with fungal strains in Petri plates are shown in Figure 3. The nitro-substituted compound methanone **9** showed excellent antifungal activity against *Aspergillus niger* and *P. spp* fungal strains. Dimethylamino- and methyl-substituted methanones (**5** and **9**) showed moderate activity against *A. niger* fungal strain. The parent- and amino-, hydroxy-, and methoxy-substituted compounds (**1**, **2**, **6,** and **7**) showed the least antifungal activity. The parent methanone and amino- and nitro-substituted compounds (**1**, **2**, and **9**) showed excellent antifungal activity against *P. spp* fungal strain. Compounds containing halogens- and dimethylamino- and methoxy-substitutions (**3**–**5** and **7**) showed good antifungal activities against *Pen. spp* fungal strain. Hydroxy- and methyl-substituted methanones (**6** and **9**) showed the least antifungal activity against *Pen. sp* strain.

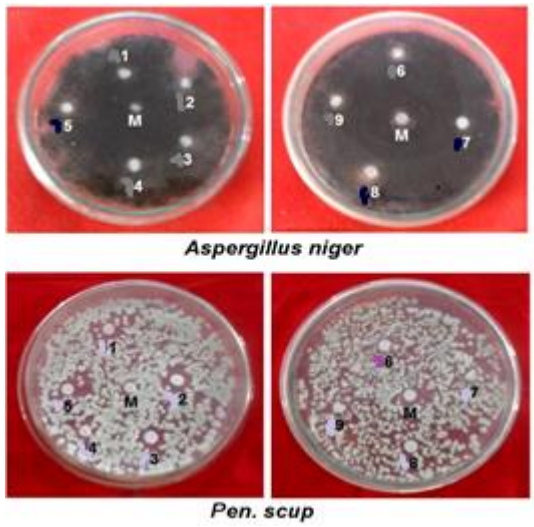


Fig. 3. Antifungal activity as millimeters of zone of inhibition of (4-bromo-1-naphthyl)-(3-(substituted phenyl)bicyclo[2.2.1]hept-5-en-2-yl)methanones

3.3. *Antimicrobial activities by serial dilution method*

The antimicrobial assay of prepared methanones was measured by the serial dilution method. In this method, the minimum inhibitory concentration (MIC) values and the percentage potency of all compounds against the microbial strains were measured. For the dilution concentration of 1.5–0.3 μg/ml, the observed statistical data are presented in Table 5 and the potency diagram is illustrated in Figure 4.

3.3.1. *Antibacterial activity*

From Table 5, methanone **4** shows the maximum potency (90%) and compound **2** shows the minimum potency (10%) against *B. subtilis* strain. The electron-withdrawing 4-chloro substituted methanone maximizes the potency, the electron-donating 4-methoxy substitution produces good activity, and the amino group reduces the potency to the minimum for *B. subtilis*. Ketone **3** shows maximum potency (92%) and compounds **2** and **6** show minimum potencies (15%) against *M. luteus* strain. The compounds **1**, **4**, and **5** show more than 50% antibacterial potency against this strain. The ketones **7–9** show less than 50% potency against *M. luteus* strain. The bromo-substituted compound shows maximum MIC-potency values and the amino substitution shows the minimum MIC-potency values against *M. luteus* strain. Methanones **3** and **4** show maximum (90%) potencies against *S. aureus* bacterial strain. Compounds **1**, **2**, and **7** show more than 50% potency and the ketones **5**, **6**, **8** and **9** show less than 50% potency against *S. aureus* strain. Here the electron-withdrawing 3-chloro, 3-bromo substituents were enhanced and 4-hydroxy and 2-nitro substituents reduced the antibacterial activities (30%) against *S. aureus* strain. Methanone **4** showed more than 100% potency (102%) and ketone **8** showed the lowest potency (15%) of antibacterial activity against *E. coli* strain. These potencies correspond to the methanones containing the electron-withdrawing 4-chloro and electron-donating 4-methyl substituents. The remaining methanones, **1–3**, **5**, **6** and **7**, showed more than 50% potency of antibacterial activity against *E. coli* strain. Ketone **4** showed maximum potency (95%) against *P. aeruginosa* bacterial strain. This observation is attributed to the fact that the electron-withdrawing 4-chloro substituent enhanced the maximum potency and the electron-donating 4-nitro substituent reduced the potency to less than 50%. The compounds **1–3**, **5–7** and **8** showed more than 50% potency against *P. aeruginosa* bacterial strain.

T a b l e 5

The antibacterial and antifungal activities of (4-bromo-1-naphthyl)-(3-(substituted phenyl) bicyclo[2.2.1]hept-5-en-2-yl)methanones by serial method

Cpd	X	Antibacterial activity MIC-potency					Antifungal activity MIC-potency	
		Gram-positive bacteria			Gram-negative bacteria			
		B. subtilis	*M. luteus*	*S. aureus*	*E. coli*	*P. aeruginosa*	*A. niger*	*P. spp.*
10	H	60	70	55	71	65	80	75
11	3-NH_2	10	15	60	63	55	85	90
12	3-Br	75	92	90	95	80	65	80
13	4-Cl	90	88	90	102	95	60	75
14	4-$N(CH_3)_2$	15	60	35	63	70	80	90
15	4-OH	20	15	30	55	50	70	80
16	4-OCH_3	40	30	85	90	65	85	90
17	4-CH_3	35	20	40	15	80	90	95
18	4-NO_2	38	25	30	40	45	95	95
Ampicillin		18	18	18	18	18	–	–
Miconazole		–	–	–	–	–	15	15

3.3.2. *Antifungal activity*

The prepared methanone **9** showed the maximum potency (95%) and all other ketones showed more than 50% potency against *A. niger* fungal strain. The electron-withdrawing 4-methyl and 4-nitro substituents enhanced the maximum antifungal potency against *A. niger* strain. The compounds **8** and **9** showed maximum potency (95%) against *Penicillium spp.* fungal strain. All compounds showed more than 50% potency against *Penicillium spp.* strain. The electron-withdrawing nitro-substituents and amino-substituents enhanced the maximum antifungal potency.

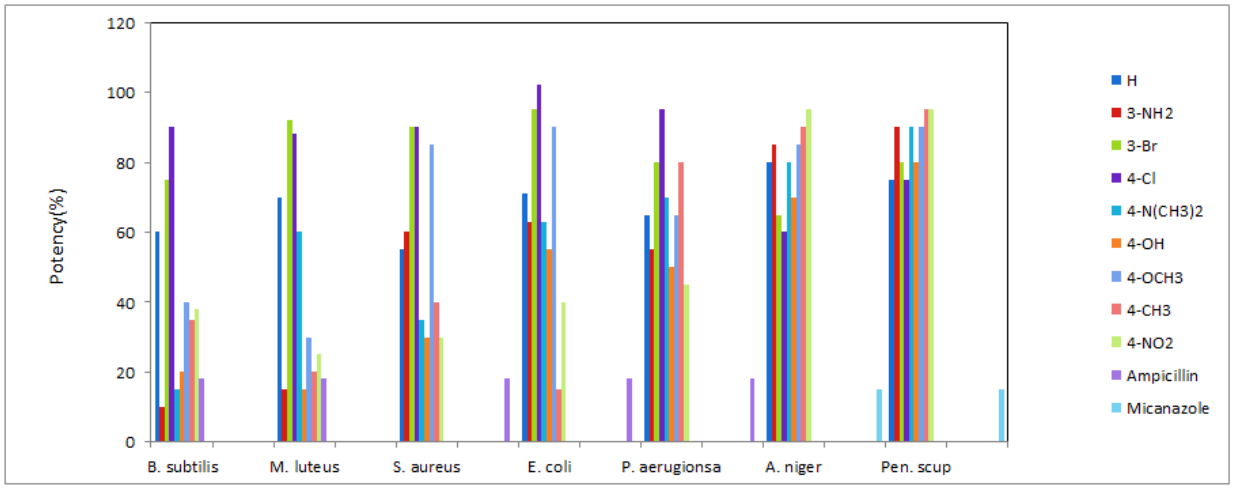


Fig. 4. Potency diagram of antibacterial and antifungal activities of (4-bromo-1-naphthyl)-(3-(substituted phenyl)bicyclo[2.2.1] hept-5-en-2-yl)methanones found by the serial method

3.4. *Antioxidant activity*

The antioxidant activities of synthesized (4-bromo-1-naphthyl)-(3-(substituted phenyl)bicycle [2.2.1]hept-5-en-2-yl)methanones were measured using the diphenyl picryl hydrazyl (DPPH) radical scavenging method [35]. The observed antioxidant activities of methanones are presented in Table 4. From Table 4, it can be seen that the hydroxyl- and methoxy-substituted methanones (**6** and **7**) showed significant antioxidant activity.

4. CONCLUSIONS

Totally nine (4-bromo-1-naphthyl)(3-(substituted phenyl)bicyclo[2.2.1]hept-5-en-2-yl)methanones were synthesized by an environmentally benign water-mediated Diels-Alder [4+2] cycloaddition reaction between 4-bromo-1-naphthyl chalcones and cyclopentadiene under cooling conditions. The yields of the synthesized ketones were more than 60%. The synthesized ketones were characterized by their physical constants and spectroscopic data. The antimicrobial activities of these synthesized ketones were studied by disc diffusion and the serial dilution method. From the disc diffusion technique, it was found that the methanol derivatives possessing halogens, dimethylamino, nitro, methyl, amino, and H substituents showed very good antibacterial activity. The nitro, amino, dimethylamino, parent and methoxy substituents present in methanones showed excellent, very good, and good antifungal activities against the fungal strains. From the serial dilution method, it was found that the electron-withdrawing bromo-, chloro- and nitro-substituted compounds showed maximum antibacterial and antifungal potency against the bacterial and fungal strains.

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