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ARTICLE

Ultrasonic and Solvent free Synthesis of Regioselective Diastereomeric Adducts and Heterocyclic Products as Antibacterial Agents Using Quantum Chemical Computation

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ABSTRACT

Carboxylic acids bearing in α,β-position an oxirane ring functionality are, in fact, useful intermediates in the synthesis of biologically active compounds. Epoxidation of 4-(4-acetylamino/bromophenyl)-4-oxo-but-2-enoic acids *via* ultrasound and microwave conditions afforded the corresponding oxirane derivatives. Synthesis of heterocyclic compounds *via* ultrasonic epoxidation of α,β-unsaturated carboxylic acid afforded the regioselective diastereomeric adducts of camphor and considered as key steps for antibacterial activity of the synthesized heterocyclic compounds. The steric factor plays an important role in regioselectivity. The structures of newly synthesized compounds were elucidated by elemental analysis and spectroscopic data. Six synthesized compounds showed strong antibacterial activity against Gram-positive and Gram-negative bacteria.

KEYWORDS

Epoxide, Ultrasound, Microwave synthesis, Furanones, Pyridazinone, Oxazinones, HOMO energy.

INTRODUCTION

One strategy that potentially meets the goals of total synthesis and library production is multicomponent reaction (MCR) chemistry, in which three or more starting materials are brought together in a highly convergent approach to rapidly build up molecular structure and complexity [1-6]. According to this method, the products are formed in a single step and the diversity can be achieved simply by varying the reacting components. A large number of organic reactions can be carried out in a higher yield, shorter reaction time and milder conditions under sonication. On the other hand, ultrasonic reactions have been increasingly used as clean, green and environmentally benign routes for the preparation of organic compounds of synthetic and biological values, which is considered to be an important tool for green chemistry in terms of waste minimization and energy conservation [7-14]. Nevertheless, the use of ultrasound in heterocyclic system is not fully explored [15-17]. The synthesis of heterocyclic compounds are intriguing due to their unique bioactive structure and great potential for binding to biomolecules based on their inherent rigid chiral structure [18]. (*E*)-4-Aryl-4-oxo-2-butenoic acids

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showed antiproliferative activity against three human tumor cell lines in one-digit micromolar to submicromolar concentrations [19]. Stereoselective synthesis of α,β-epoxyesters is of considerable synthetic interest because a number of compounds can be obtained by the opening of the oxirane ring [20-22]. Carboxylic acids bearing in α,β-position an oxirane ring functionality are, in fact, useful intermediates in the synthesis of biologically active compounds [23] and activated double bond of (*E*)-4-aryl-4-oxo-2-butenoic acids [24]. The reactivity with diverse nucleophiles permits access to diverse intermediates [25-29]. Therefore, the starting material of epoxide will be directed to prepare the more interesting heterocyclic compounds of important biological activities.

EXPERIMENTAL

All melting points are corrected and were determined on a start electric melting point apparatus. Elemental analyses were carried out at the Micro-analytical Center, National Research Center, Cairo, Egypt. By Elementar Viro El Micro-analysis IR spectra (KBr, ν_{max}, cm^{-1}) were recorded on infrared spectrometer FT-IR 400D using OMNIC program and are reported frequency of absorption in terms of cm^{-1} and ^1H NMR spectra recorded on a Bruker spectrophotometer at 400 MHz using TMS as internal standard and with residual signals of the deuterated solvent δ = 7.26 ppm for $CDCl_3$ and δ 2.51 ppm for DMSO-d_6. ^{13}C NMR spectra were recorded on the same spectrometer at 100 MHz and referenced to solvent signals δ = 77 ppm for $CDCl_3$ and δ 39.50 ppm for DMSO-d_6. DEPT ^{13}C NMR spectroscopy were used where appropriate to aid the assignment of signals in the ^1H NMR and ^{13}C NMR spectra. The mass spectra were recorded on Shimadzu GCMS-QP-1000 EX mass spectrometer at 70 e.v using the electron ionization technique. Homogeneity of all compounds synthesized was checked by TLC.

Preparation of urea-H_2O_2 (UHP): In 100 mL pyrex flask 12 g urea and 34 mL hydrogen peroxide (30 %) were added together. The reaction mixture was stirred at 60 °C for 10 min. when cooled, it was transferred to crystallizing dish for slow evaporation [11].

General procedure for epoxidation (synthesis the compounds 1): A mixture of 4-(4-acetylamino/bromobenzoyl)-4-oxobut-2-enoic acids (0.02 mol) and urea-H_2O_2 (0.032 mol) dissolved in ethanol (20 mL) and aqueous solution of sodium hydroxides (0.4 mol, 4 %). The mixture was irradiated in water bath of ultrasonic cleaner at room temperature for 15 min. until all acids had disappeared as indicated by TLC. The mixture was extracted by ether and dried over anhydrous sodium sulfate. The residue was crystallized from proper solvent.

General procedure of synthesis the compounds 2 and 3: A mixture of the epoxides **1** (0.01 mol), active methylene precursor, *e.g.* R(+) camphor (0.01 mol), EtONa (8 mL) and ethanol (50 mL), the mixture was sonicated in the water bath of an ultrasonic cleaner under atmospheric conditions at room temperature for 25 min. After the completion of the reaction (monitored by TLC), the resulting precipitate was filtered and washed with ethanol to afford the pure product as solid in good to excellent yields. The reaction mixture was refluxed for 3 h, stirring 6 h, leave overnight 3 days and poured into ice/HCl, filter the crude product and washed by petroleum ether (b.p. 40-60 °C) and then crystallized.

(2R,3S,3R')-(+)-4-(4-(Acetylamino)phenyl)-3-hydroxy-2-(1,7,7-trimethylbicyclo[2,2,1]heptan-2-on-3-yl)-4-oxobutanoic acid (2a): White solid, 44 %, m.p.: 162-164 °C (ethanol). IR 1722, 1667 cm^{-1}. ^1H NMR spectrum (400 MHz, $CDCl_3$) δ: 0.94 (s, 3H, CH_3), 1.06 (s, 6H, $2CH_3$), 1.42-1.83 (m, 5H, $CHCH_2CH_2$, camphor moiety), 2.05 (s, 3H, CH_3CON-), 2.23 (dd, *J* = 14.2, 6.4 Hz, CHCO, camphor moiety), 2.91 (dd, *J* = 14.2, 7.8 Hz, 1H, CH-COO), 4, 92 (dd, *J* = 7.8, 6.4 Hz, CH(OH)-CO), 5.63 (bs, 1H, OH), 7.47-7.75 (m, 4ArH, aromatic protons), 11.5 (s, 1H, NH) and 12.2 (s, 1H, CO_2H) (acidic protons which exchanged in D_2O). Anal. calcd. (%) for $C_{22}H_{27}NO_6$: C, 65.83; H, 6.73. Found C, 65.86; H, 6.70. MS *m/z* 401 (M^+, 15).

(2R,3S,3R')-(+)-4-(4-Bromophenyl)-3-hydroxy-2-(1,7,7-trimethylbicyclo[2,2,1]heptan-2-on-3-yl)-4-oxobutanoic acid (2b): Colourless crystals, 32 %, m.p.: 146-148 °C (toluene). IR 1720, 1668 cm^{-1}.^1H NMR spectrum (400 MHz, $CDCl_3$) δ 0.91 (s, 3H, CH_3), 1.06 (s, 6H, $2CH_3$), 1.42-1.73 (m, 5H, $CHCH_2CH_2$, camphor moiety), 2.25 (s, 3H, CH_3CON-), 2.43 (dd, *J* = 13.7, 6.2 Hz, CHCO, camphor moiety), 2.91 (dd, *J* = 13.7, 7.5 Hz, 1H, CH-COO), 4, 84 (d, *J* = 7.5 Hz, CH (OH)-CO), 5.67 (bs, 1H, OH), 7.29-7.55 (m, 4ArH, aromatic protons), 12.2 (s, 1H, COOH) and ^{13}C NMR ($CDCl_3$) δ 22.8, 23.3, 28.3, 34.4, 38.6, 43.4, 58.4, 67.4, 102.3, 128.2, 129.2, 129.5, 134.4, 138.1, 155.7, 175.0, 183.2, 200.5. Anal. calcd. (%) for $C_{20}H_{23}O_5Br$ C, 56.87; H, 5.45. Found C, 56.83; H, 5.42. MS *m/z* 424 (M^++2, 20), 422 (M^+, 50).

(2S,3R,3R')-(-)-4-(4-(Acetylamino)phenyl)-3-hydroxy-2-(1,7,7-trimethylbicyclo[2,2,1]heptan-2-on-3-yl)-4-oxobutanoic acid (3a): Colourless crystals, 21 %, m.p.: 118-120 °C (pet. ether 80-100 °C). IR 1721, 1668 cm^{-1}. ^1H NMR spectrum (400 MHz, $CDCl_3$) δ 1.31 (s, 6H, $2CH_3$), 1.37-1.62 (m, 5H, $CHCH_2$-CH_2, camphor moiety), 1.76 (s, 3H, CH_3), 2.20 (s, 3H, CH_3CON-), 2.13 (dd, *J* = 16.0, 7.1 Hz, CHCO, camphor moiety), 2.61 (dd, *J* = 16.0, 7.9 Hz, 1H, CH-COO), 4.48 (d, *J* = 7.9, 7.1 Hz, CH (OH)-CO), 5.60 (bs, 1H, OH), 7.17-7.85 (m, 4ArH aromatic protons), 11.2 (s, 1H, NH) and 13.11 (s, 1H, COOH) and ^{13}C NMR ($CDCl_3$) δ 23.8, 25.4, 28.3, 32.0, 34.4, 37.1, 38.1, 39.4, 45.0, 58.4, 102.3, 108.2, 129.2, 129.5, 134.4, 138.1, 142.7, 145.0, 173.2, 198.5. Anal. calcd. (%) for $C_{22}H_{27}NO_6$: C, 65.83; H, 6.73. Found C, 65.83; H 6.72. MS *m/z* 401 (M^+, 45), 255 (99).

(2S, 3R, 3R')-(-)-4-(4-Bromophenyl)-3-hydroxy-2-(1,7,7-trimethylbicyclo[2,2,1]heptan-2-on-3-yl)-4-oxobutanoic acid (3b): Colourless crystals, 41 %, m.p.: 112-114 °C (pet. ether 80-100 °C). IR 1721, 1680 cm^{-1}.^1H NMR spectrum (400 MHz, $CDCl_3$) δ 1.06 (s, 3H, CH_3a), 1.2 (s, 3H, CH_3b), 1.83 (m, 4H, CH_2CH_2, camphor moiety), 1.78 (s, 3H, CH_3), 1.97 (m, 1H, CH, bridgehead methine, camphor moiety), 2.15 (dd, *J* = 15.6, 6.9 Hz), 2.65 (dd, *J* = 15.6, 7.8 Hz, 1H, CH-COO), 4.38 (d, *J* = 7.8 Hz, CH (OH)-CO), 5.87 (bs, 1H, OH), 7.72 -7.78 (m, 4ArH aromatic protons), 12.2 (s, 1H, COOH) and Anal. calcd. (%) for $C_{20}H_{23}O_5Br$: C, 56.87; H, 5.45. Found C, 56.86; H, 5.40. MS *m/z* 424 (M^++2, 17), 422 (M^+, 50), (154, 100).

Compounds 4 and 5: A mixture of compound **2** and/or **3** (0.01 mol) and acetic anhydride (9.4 mL, 0.1 mol) and then

refluxed on water bath for 2 h. The excess acetic anhydride was removed by distillation and the separated product was filtered, dried and were recrystallized.

N-(4-((8S)-(+)-1,3,5,6,7,8-Hexahydro-5,9,9-trimethyl-1-oxo-5,8-methanofuro[3,4-*b*]benzofuran-3-yl)phenyl)-acetamide (4a): Pale yellow solid crystal, 70 %, m.p.: 236-238 °C (dioxane). IR 1772, 1668 cm^{-1}. ^1H NMR spectrum (400 MHz, DMSO-d_6) δ 1.06 (s, 3H, CH_3a), 1.2 (s, 3H, CH_3b), 1.73 (m, 4H, CH_2CH_2, camphor moiety), 1.98 (s, 3H, CH_3), 2.25 (s, 3H, CH_3CON-), 2.43 (dd, *J* = 14.7, 7.4 Hz, CHCO, camphor moiety), 3.92 (s, CH, sterogenic methine proton fused furan), 7.47-7.75 (m, 4ArH aromatic protons), 11.4 (s, 1H, NH) and ^{13}C NMR (DMSO-d_6) δ 13.2, 18.3, 21.7, 23.9, 26.8, 38.4, 39.6, 46.6, 48.8, 50.2, 56.8, 129.7, 130.4, 131.8, 132.2, 136.2, 178.8, 195.7, 201.5, 213.4. Anal. calcd. (%) for $C_{22}H_{23}NO_4$: C, 72.32; H, 6.30. Found C, 72.30; H, 6.30. MS *m/z* 365 (M^+, 35), 150 (100).

(8S)-(+)-3-(4-Bromophenyl)-5,9,9-trimethyl-5,6,7,8-tetrahydro-5,8-methanofuro[3, 4-*b*]benzofuran-1-(3*H*)-one (4b): Yellow solid crystal, 73 %, m.p.: 216-218 °C (dioxane). IR 1780, 1700 cm^{-1}.^1H NMR spectrum (400 MHz, DMSO-d_6): δ 1.06 (s, 3H, CH_3a), 1.2 (s, 3H, CH_3b), 1.78 (s, 3H, CH_3), 1.80 (m, 4H, CH_2CH_2, camphor moiety), 2.56 (dd, *J* = 15.2, 7.0 Hz, CHCO, camphor moiety), 2.93 (dd, *J* = 15.2, 7.1 Hz, CH-COO, sterogenicmethine proton), 7.67-7.71 (m, 4ArH aromatic protons). Anal. calcd. (%) for $C_{20}H_{19}O_3Br$: C, 62.33; H, 4.93. Found C, 62.30; H, 4.94. MS *m/z* 387 (M^+ +2, 25), 385 (M^+, 75).

N-(4-((E)-2-((4R, 7S)-(-)-7,8,8-Trimethyl-2-oxo-4,5,6,7-tetrahydro-4,7-methanobenzofuran-3-(2*H*)-ylidene)-acetyl)phenyl)acetamide (5a): Pale yellow solid crystal, 80 %, m.p.: 250-252 °C (ethyl acetate). IR 1772, 1668 cm^{-1}; ^1H NMR spectrum (400 MHz, DMSO-d_6): δ 1.06 (s, 3H, CH_3a), 1.2 (s, 3H, CH_3b), 1.73 (m, 4H, CH_2CH_2, camphor moiety), 1.98 (s, 3H, CH_3), 2.25 (s, 3H, CH_3CON-), 2.43 (dd, *J* = 16.2, 7.4 Hz, CHCO, camphor moiety), 2.92 (dd, *J* = 16.2, 7.4 Hz, CH-COO, sterogenic methine proton), 7.47-7.75 (m, 4ArH aromatic protons), 11.2 (s, 1H, NH) and Anal. calcd. (%) for $C_{22}H_{23}NO_4$: C 72.32, H 6.30; Found C 72.30, H 6.30. MS *m/z* 365 (M^+, 100).

(4R,7S,*E*)-(-)-3-(2-(4-Bromophenyl)-2-oxoethylidene)-7,8,8-trimethyl-4,5,6,7-tetrahydro-4,7-methanobenzofuran-2-(3*H*)-one (5b): Off white crystals, 80 %, m.p.: 232-234 °C (dioxane). IR 1779, 1694 cm^{-1}. ^1H NMR spectrum (400 MHz, DMSO-d_6): δ 1.06 (s, 3H, CH_3a), 1.2 (s, 3H, CH_3b), 1.78 (s, 3H, CH_3), 1.80 (m, 4H, CH_2CH_2, camphor moiety), 2.56 (dd, *J* = 15.6, 7.0 Hz, CHCO, camphor moiety), 2.93 (dd, *J* = 15.6, 7.0 Hz, CH-COO, sterogenic methine proton), 7.67-7.71 (m, 4ArH aromatic protons) and ^{13}C NMR (DMSO-d_6) δ 22.8, 23.3, 28.3, 34.4, 38.6, 43.4, 67.4, 102.3, 128.2, 129.2, 129.5, 131.3, 134.4, 138.1, 155.7, 175.0, 183.2, 200.5. Anal. calcd. (%) for $C_{20}H_{19}O_3Br$: C, 62.33; H, 4.93. Found C, 62.30; H, 4.94. MS *m/z* 387 (M^+ +2, 23), 385 (M^+, 45), 205 (100).

Compounds 6: A mixture of cmpound **2** (0.01 mol) and hydrazine hydrate (0.01 mol) in ethanol (30 mL) was heated under reflux for 5 h. The reaction mixture was allowed to cool and the separated product was filtered, dried and were recrystallized from ethanol.

N-(4-((9S)-(+)-1,2,4a,6,7,8,9,9b-Octahydro-6,10,10-trimethyl-1-oxo-6,9-methanobenzofuro[2,3-d]pyridazin-4-yl)phenyl)acetamide (6a): Off white crystals, 75 %, m.p.: 196-198 °C (ethanol). IR 3362, 1710 and 1676 cm^{-1}.^1H NMR (400 MHz, DMSO-d_6): δ 0.94 (s, 3H, CH_3a), 1.17 (s, 3H, CH_3b), 1.26 (s, 3H, CH_3), 1.48-1.71 (m, 4H, $2CH_2$), 1.87 (m, 1H, methine bridgehead), 3.36 (d, *J* = 7.8 Hz, 1H, CH-CO), 4, 82 (d, *J* = 7.8 Hz, CH (O)-C=N), 7.48-7.56 (m, 4H, Ar-H), 12.34 (bs, 2H, 2NH of acetamido and pyridazine moieties) and ^{13}C NMR (DMSO-d_6) δ 11.8, 18.3, 18.7, 21.9, 26.8, 37.3, 38.4, 39.6, 44.6, 45.8, 48.2, 56.8, 129.7, 130.4, 131.8, 136.2, 178.8, 195.7, 201.5, 213.4. Anal. calcd. (%) for $C_{22}H_{25}N_3O_3$: C, 69.65; H, 6.59. Found C, 69.65; H, 6.58. MS: *m/z* 379 (M^+, 100).

(9S)-(+)-4-(4-Bromophenyl)-6,10,10-trimethyl-4a,6,7,8,9,9b-hexahydro-6,9-methanobenzofuro[2,3-d]pyridazin-1-(2*H*)-one (6b): Off white crystals, 75 %, m.p.: 184-186 °C (ethanol). IR 3345, 1710, 1690 cm^{-1}.^1H NMR (DMSO-d_6) δ 1.1 (s, 3H, CH_3), 1.16 (s, 3H, CH_3), 1.26 (s, 3H, CH_3), 1.59-1.71 (m, 4H, $2CH_2$), 1.98 (t, *J* = 5.7 Hz, 1H, methine bridgehead), 3.83 (d, *J* = 7.9 Hz, 1H, CH-CO), 4, 27 (d, *J* = 7.9 Hz, CH (O)-C=N), 7.68-7.80 (m, 4H, Ar-H), 11.34 (brs, 1H, NH) and Anal. calcd. (%) for $C_{20}H_{21}N_2O_2Br$: C, 60.00; H, 5.25. Found C, 60.02; H, 5.27. MS *m/z* 402 (M^++2, 21), 400 (M^+, 61), 250 (100).

Compounds 7: A mixture of compound **2** (0.01 mol) and hydroxylamine (1.03 g; 0.015 mol) in pyridine (20 mL) and then refluxed for 3 h. The reaction mixture was poured onto ice/HCl and the separated solid was filtered, dried and were recrystallized from dioxane.

N-(4-((9S)-(+)-4a,6,7,8,9,9b-Hexahydro-6,10,10-trimethyl-1-oxo-1*H*-6,9-methanobenzofuro[2,3-d][1,2]-oxazin-4-yl)phenyl)acetamide (7a): Off white crystals, 65 %, m.p.: 212-214 °C (dioxane). IR 3362, 1718, 1676 cm^{-1}.^1H NMR (400 MHz, DMSO-d_6) δ 0.94 (s, 3H, CH_3a), 1.17 (s, 3H, CH_3b), 1.26 (s, 3H, CH_3), 1.48-1.71 (m, 4H, $2CH_2$), 1.87 (m, 1H, methine bridgehead), 3.31 (d, *J* = 7.2 Hz, 1H, CH-CO), 4, 92 (d, *J* = 7.2 Hz, CH (O)-C=N), 7.52-7.61 (m, 4H, Ar-H), 12.34 (brs, 1H, NH of acetamido moiety) and Anal. calcd. (%) for $C_{22}H_{24}N_2O_4$: C, 69.47; H, 6.31. Found C, 69.45; H, 6.32. MS: *m/z* 380 (M^+, 55), 252 (100).

(9S)-(+)-4-(4-Bromophenyl)-6,10,10-trimethyl-4a,6,7,8,9,9b-hexahydro-1*H*-6,9-methanobenzofuro[2,3-d]-[1,2]oxazin-1-one (7b): Off white crystals, 66 %, m.p.: 192-194 °C (dioxane). IR 1710, 1690 cm^{-1}.^1H NMR (DMSO-d_6) δ 1.1 (s, 3H, CH_3a), 1.16 (s, 3H, CH_3b), 1.26 (s, 3H, CH_3), 1.59-1.71 (m, 4H, $2CH_2$), 1.98 (t, *J* = 6.1 Hz, 1H, methine), 3.27 (d, *J* = 8.1 Hz, 1H, CH-CO), 4, 37 (d, *J* = 8.1 Hz, CH (O)-C=N), 7.71-7.79 (m, 4H, Ar-H) and ^{13}C NMR (DMSO-d_6) δ 11.8, 18.3, 18.7, 21.9, 26.8, 37.3, 38.4, 44.6, 45.8, 48.2, 56.8, 129.7, 130.4, 131.8, 136.2, 178.8, 195.7, 213.4. Anal. calcd. (%) for $C_{20}H_{20}NO_3Br$: C, 59.85; H, 4.98. Found C, 59.86; H, 4.96. MS *m/z* 403 (M^+, 60), 401 (M^+, 100), 250 (66).

Compounds 8: A mixture of compound **3** (0.01 mol) and hydrazine hydrate (0.01 mol) in ethanol (30 mL) and was heated under reflux for 5 h. The reaction mixture was allowed to cool and the separated product was filtered, dried and were recrystallized from ethanol.

N-(4-(5-((1S,3R,4S)-(-)-3-Hydroxy-4,7,7-trimethyl-bicyclo[2.2.1]heptan-2-yl)-6-oxo-1,6-dihydropyridazin-3-yl)phenyl)acetamide (8a): White solid, 67 %, m.p.: 196-198

°C (ethanol). IR 3334, 1710, 1668 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ 1.12 (s, 3H, CH_3a), 1.23 (s, 3H, CH_3b), 1.30 (s, 3H, CH_3), 2.25 (s, 3H, CH_3CO), 1.52-1.78 (m, 5H, CH-CH_2-CH_2), 3.00 (m, 1H, attached camph), 3.24 (d, *J* = 7.3 Hz, 1H, CHOH), 5.72 (bs, 1H, OH), 7.48-7.56 (m, 5H, Ar-H), 10.35 (s, 1H, NH pyridazinone moiety), 12.34 (s, 1H, NH of acetamido moiety) and ^{13}C NMR (DMSO-d_6) δ 11.8, 18.3, 18.7, 21.9, 26.8, 37.3, 38.4, 39.6, 44.6, 45.8, 48.2, 56.8, 129.7, 130.4, 131.8, 136.2, 178.8, 195.7, 201.5, 213.4. Anal. calcd. (%) for $C_{22}H_{27}N_3O_3$: C, 69.29; H 7.08; Found C, 69.29; H 7.00. MS *m/z* 381 (M+, 12), 267 (100), 175 (37), 137 (56).

6-(4-Bromophenyl)-4-((1S, 3R,4S)-(-)-3-hydroxy-4,7,7-trimethylbicyclo[2.2.1]heptan-2-yl)pyridazin-3-(2*H*)-one (8b): Colourless crystals, 82 %, m.p.: 184-186 °C (ethanol). IR 1708 cm^{-1}.^1H NMR (400 MHz, DMSO-d_6) δ 1.12 (s, 3H, CH_3a), 1.23 (s, 3H, CH_3b), 1.30 (s, 3H, CH_3), 1.52-1.78 (m, 5H, CH-CH_2-CH_2), 3.00 (m, 1H, attached camph), 3.24 (d, *J* = 5.7 Hz, 1H, CHOH), 5.72 (bs, 1H, OH), 7.48-7.56 (m, 5H, Ar-H), 11.05 (s, 1H, NH pyridazinone moiety). Anal. calcd. (%) for $C_{20}H_{23}N_2O_2Br$: C, 59.70; H, 5.72. Found C, 59.75; H, 5.72. MS *m/z* 402 (M^+, 22), 251 (100), 175 (77), 156 (47).

Compounds 9: A mixture of compound **3** (0.01 mol) and hydroxylamine (1.03 g; 0.015 mol) in pyridine (20 mL) and then refluxed for 3 h. The reaction mixture was poured onto ice/HCl and the separated solid was filtered, dried and were recrystallized from ethanol.

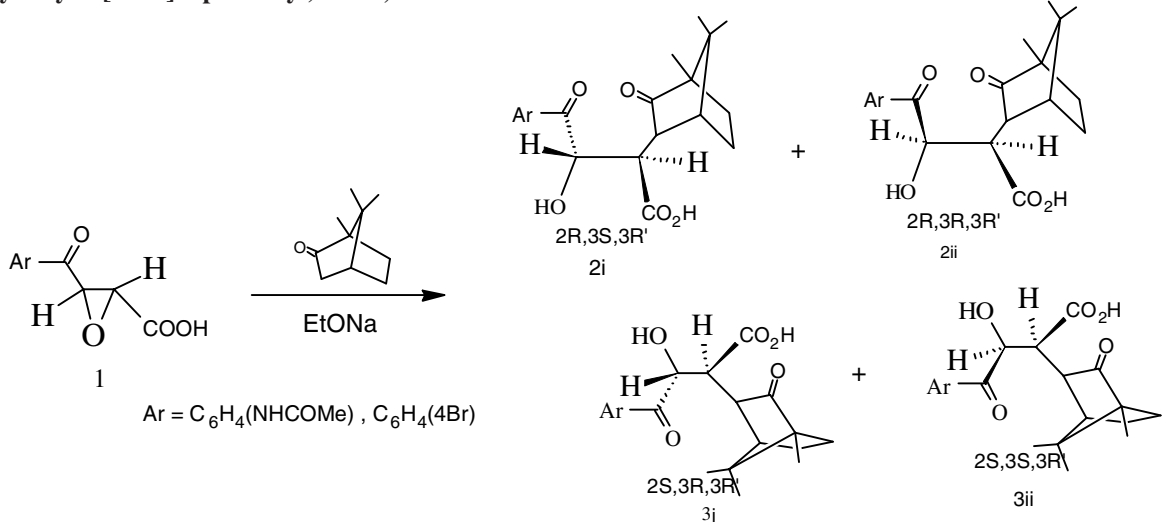
N-(4-(5-((1S,3R,4S)-(-)-3-Hydroxy-4,7,7-trimethylbicyclo[2.2.1]heptan-2-yl)-6-oxo-6*H*-1,2-oxazin-3-yl)-phenyl)acetamide (9a): Colourless crystals, 70 %, m.p.: 234-236 °C (ethanol). IR 3420, 1710, 1676 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ 1.12 (s, 3H, CH_3a), 1.23 (s, 3H, CH_3b), 1.30 (s, 3H, CH_3), 2.25 (s, 3H, CH_3CO), 1.52-1.78 (m, 5H, CH-CH_2-CH_2), 3.00 (m, 1H, attached camph), 3.24 (m, 1H, CHOH), 5.72 (bs, 1H, OH), 7.48-7.56 (m, 5H, Ar-H), 12.34 (s, 1H, NH of acetamido moiety) and ^{13}C NMR (DMSO-d_6) δ 11.8, 18.3, 18.7, 21.9, 26.8, 37.3, 38.4, 39.6, 44.6, 45.8, 48.2, 56.8, 129.7, 130.4, 131.8, 136.2, 178.8, 195.7, 201.5, 213.4. Anal. calcd. (%) for $C_{22}H_{26}N_2O_4$: C, 69.11; H, 6.81. Found C, 69.17; H, 6.81. MS *m/z* 382 (M^+, 100).

3-(4-Bromophenyl)-5-((1S, 3R,4S)-(-)-3-hydroxy-4,7,7-trimethylbicyclo[2.2.1]heptan-2-yl)-6*H*-1,2-oxazin-6-one (9b): Colourless crystal, 74 %, m.p.: 218-220 °C (ethanol). IR 3412, 1720 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ 1.12 (s, 3H, CH_3a), 1.23 (s, 3H, CH_3b), 1.30 (s, 3H, CH_3), 1.52-1.78 (m, 5H, CH-CH_2-CH_2), 3.00 (m, 1H, attached camph), 3.24 (d, *J* = 3.7 Hz, 1H, CHOH), 5.72 (bs, 1H, OH acidic proton exchangeable), 7.48-7.56 (m, 5H, Ar-H). Anal. calcd. (%) for $C_{20}H_{22}NO_3Br$: C, 59.55; H, 5.46. Found C, 59.38; H 5.37. MS *m/z* 403 (M+, 45), 251 (100), 175 (68), 156 (54).

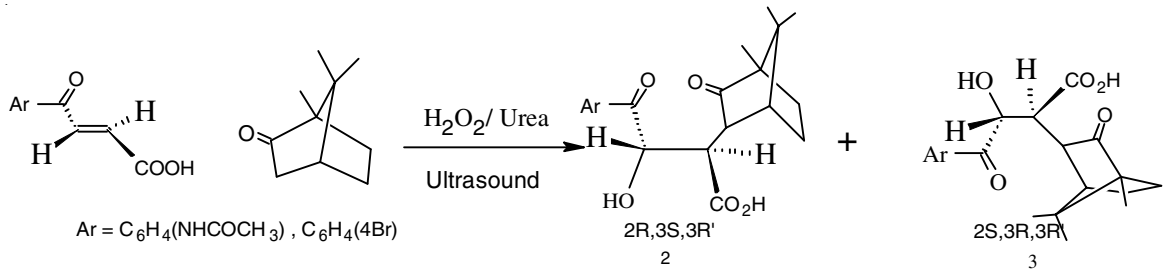
RESULTS AND DISCUSSION

Recently, the authors reported the behaviour of 4-(4-acetylaminophenyl)-4-oxo-2-butenoic and 4-(4-bromophenyl)-4-oxo-2-butenoic acids (**1**) toward some electrophilic and nucleophilic reagents. They were allowed to react with carbon and nitrogen nucleophiles, *e.g.* reactive aromatic hydrocarbons, 3-methyl-2-pyrazolen-5-one, 3-phenyl-2-pyrazolen-5-one, barbituric acid, quinazolinone derivatives and (1R,4R)(+)-camphor in different reaction conditions [30-37] under Michael, aza-Michael and Friedel-Crafts reaction conditions. Synthesis of the diastereomeric Michael adducts [38] have been thought us to make the reaction of the (+)-camphor with their epoxides [39]. The mechanism of epoxidation *via* reaction of urea and hydrogen peroxide within ultrasound basic conditions was outlined in **Scheme-I**. The regioselectivity of the oxirane derivatives (**1**) in position α toward the carboxylic group played an important role to yield the four diastereomeric adducts. Experimentally, the authors isolated two diastereomeric adducts only (**Scheme-II**). The *anti* aroyl and carboxylic groups for **2i** and **3i** isomers were more favoured than *syn* isomers **2ii** and **3ii**. The repulsion force of aroyl and carboxylic groups is outweigh the intramolecular hydrogen bond in *syn* isomers. This explain why the two diastereomers **2ii** (2R,3R,3R') and **3ii** (2S,3S,3R') are not isolated. On the other hands, the energy gaps between HOMO and LUMO values are reflected the lower stability of these isomers (Fig. 1).

Aryl groups effected on the pecentage yield of products. The yield of isomer **2i** (2R,3S,3R') in case of acetamido benzoyl derivative (**2a**) was 44 % otherwise the bromo benzoyl derivative (**2b**) was 32 % that a *vice versa* in case of isomer **3i** (2S,3R,3R'). The isomer **3a** was 21 % than **3b** 41 %. The charge density of the acetyl amino group in **3a** was allowed to



Scheme-I



Scheme-II

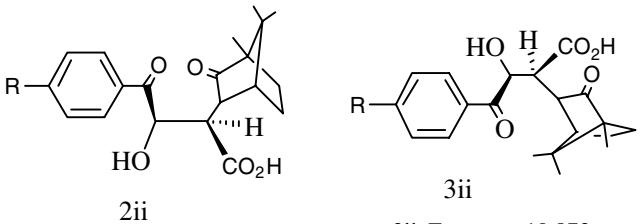


Fig. 1

afraid of attack the tag dimethyl groups of R(+)camphor precursor (maximum repulsion) and so, it afforded low % yield (21 %). The presence of hydroxyl group in the products **2** and **3** afforded the interested products. It reflected that the reactivity of the diastereomeric products **2** and **3** when they investigated within the electrophilic and nucleophilic reagents.

The ^{1}H NMR for the adducts **2** and **3** (Fig. 2) are correspond to the experimental results. The ^{1}H NMR (DMSO-d_6) of the adduct **2a**, δ ppm, (*J*, Hz): reveals at 2.23(dd, *J* = 14.2, 6.4 Hz, CHCO, camphor moiety), 2.91(dd, *J* = 14.2, 7.8 Hz, 1H, CH-COO), 4,92(dd, *J* = 7.8, 6.4 Hz, CH(OH)-CO) and the adduct **3a**, δ ppm, (*J*, Hz): reveals at 2.13(dd, *J* = 16.0, 7.1 Hz, CHCO, camphor moiety), 2.61(dd, *J* = 16.0, 7.9 Hz, 1H, CH-COO), 4.48 (d, *J* = 7.9, 7.1 Hz, CH(OH)-CO) corresponds to (Fig. 1a and 1b). On the other hand, the application of one-pot multicomponent reactions (MCRs) and microwave-assisted has been demonstrated to offer smooth reaction conditions, higher overall yield and afforded new products when they are compared to classical synthetic methodologies [18-21]. In one pot reaction of 4-aryl-4-oxo-2-butenoic acids, camphor, urea, hydrogen peroxide at pH 12, under microwave irradiation (W 250 and T 150 °C) afforded furanone (**4**) and arylidine (**5**). The mechanism of one pot syntheses of furanone derivatives **4** and **5** is known to be through the formation of the epoxide product *via* the reaction α,β-unsaturated ketones and urea hydrogen peroxide reagent(UHP) and it reacts with active methylene containing ketones using catalytic amount of strong bases like sodium hydroxide, triethylamine or piperidine (10 %). This reaction is followed by condensation, cyclization and dehydra-tion to afford the corresponding furanone derivatives **4** and **5** (**Scheme-III**). When the (2R,3S,3R') acids (**2**) and/or (2S,3R,3R') acids (**3**) were allowed to react with sodium ethoxide in ethanol, at stirring 6 h afforded the furanone derivatives (**4**) and (**5**), respectively (**Scheme-IV**). The steric crowding due to the bridged methyl group was outweigh the reactivity of carbonyl of camphor moiety. Therefore, the isomers **2** can be preferred cyclization with the carboxylic group affording furanone (**4**). The reactivity of ketonic group the camphor moiety is more than carboxylic group that lead to afford furanone (**5**). The presence of the camphoryl moiety in the (2S,3R,3R') acids (**3**) did not allow to afford the corresponding furanone. The reaction of the acids (**3**) had to go E_{1CB} followed by cyclization within the carboxylic group. Moreover, the absence of steric crowding of bridged methyl group in camphor moiety of the acids (**3**) became a driving force to afford regioselective isomers **5** (**Scheme-IV**).

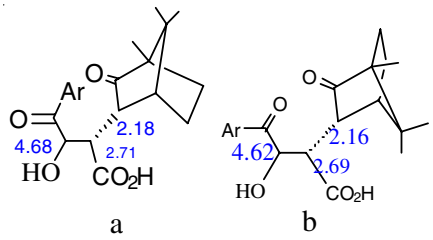
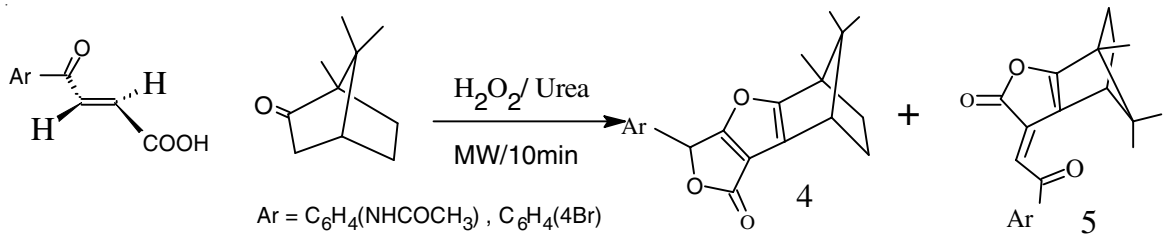


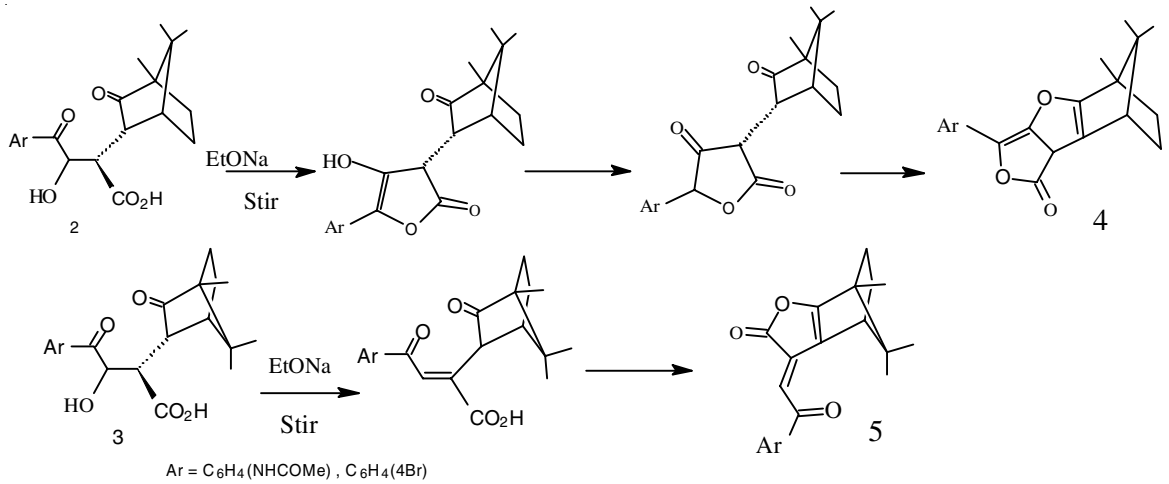
Fig. 2

Moreover, when the (2R,3S,3R')-(+) acids (**2**) were allowed to react with hydrazine hydrate in boiling ethanol and/or hydroxylamine in boiling pyridine, either can be reacted directly or *via* their furanone derivatives (**4**), they afforded furo[2,3-*d*]pyridazin-3(2H)-one derivatives (**6**) and furo[2,3-*d*]oxazin-6-one derivatives (**7**), respectively (**Scheme-V**).

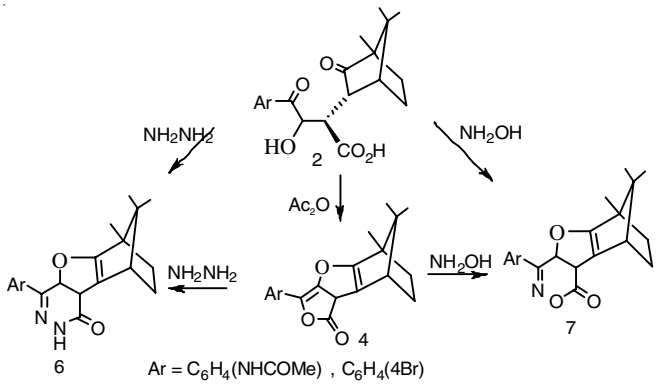
When the (2S,3R,3R')-(-) acids (**3**) were allowed to react with hydrazine hydrate in boiling ethanol and hydroxyl amine in boiling pyridine, afforded the pyridazinone **(8)** and 2,1-oxazinone **(9)** derivatives respectively (**Scheme-VI**). The authors can be expected the spiro products (**10**) and (**11**) respectively



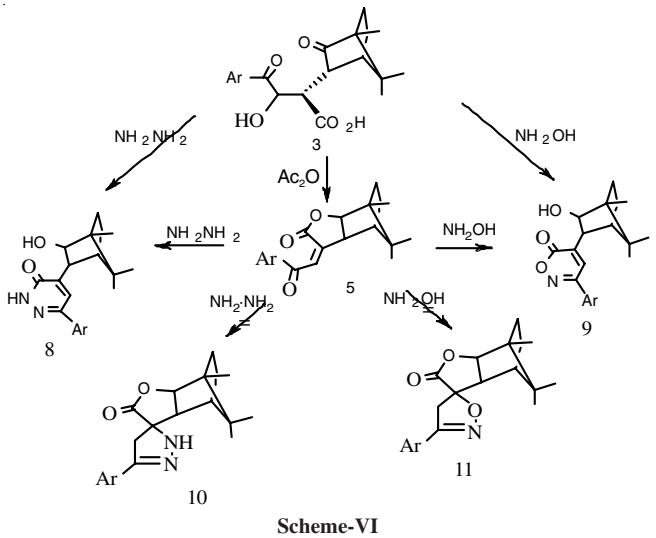
Scheme-III



Scheme-IV



Scheme-V



Scheme-VI

but, the steric crowding due to the bridged methyl group was outweigh and so, the reaction of isomers 3 with hydrazine hydrate and/or hydroxylamine can be preferred the 1, 2 addition followed by the cyclization with lactonic group.

Antibacterial activity evaluation

Filter paper disc-diffusion method: The newly synthesized heterocyclic compounds listed in Table-1 were tested for their antibacterial activity against Gram positive bacteria [*Staphylococcus aureus* (ATCC 25923) and *Bacillus cereus* (ATCC 10987)], Gram negative bacteria [*Serratia marcesens* (ATCC 274) and *Proteus mirabilis* (SM514)]. The preliminary screening of the investigated compounds was performed using the filter paper disc-diffusion method. The most active compounds were **1**, **3**, **5** and **7** which were strongly inhibitory to all or some of the tested bacteria. The highly antibacterial activity for the compounds **1**, **3**, **5** and **7** by quantum chemical parameter are due to the presence of the activated double bond that can be inhibit the enzyme of bacteria. The rest of compounds showed moderate activities against the tested bacteria (Table-1).

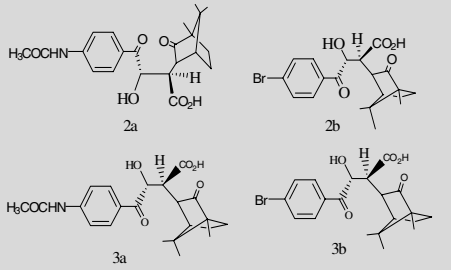
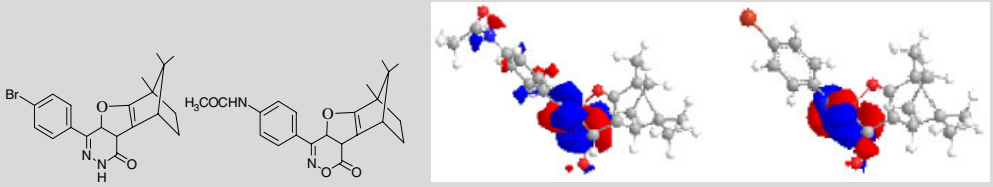
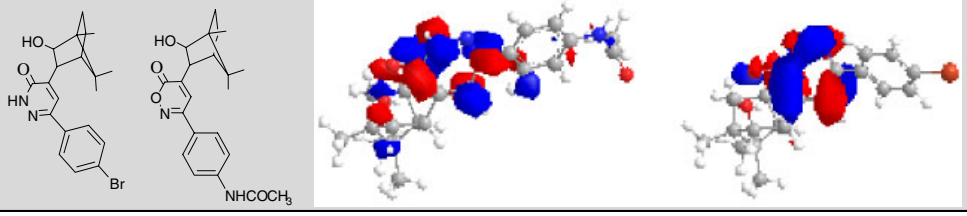
TABLE-1
ANTIBACTERIAL ACTIVITY OF
THE SYNTHESIZED COMPOUNDS

Compd. No.	Inhibition zone (mm)			
	Gram-positive		Gram-negative	
	S. aureus	*B. cereus*	*S. marcesens*	*P. mirabilis*
1a	16	16	15	18
1b	18	17	17	16
2a	11	11	10	10
2b	11	10	09	11
3a	13	12	11	12
3b	14	12	11	12
4a	09	08	07	08
4b	12	10	11	08
5a	17	15	20	18
5b	16	15	16	16
6a	09	08	09	10
6b	07	07	08	11
7a	15	15	16	17
7b	17	16	18	14
8a	09	08	09	07
8b	09	07	08	05
Chloramphenicol®	18	19	22	21
Ampicillin®	19	22	24	20

The sensitivity of microorganisms to the tested compounds is identified in the following manner: Highly sensitive = Inhibition zone 15-20 mm; Moderately sensitive = Inhibition zone 10-15 mm; Slightly sensitive = Inhibition zone 5-10 mm; Not sensitive = Inhibition zone 0-5 mm; Each results represents the average of triplicate readings.

From Tables 1 and 2, the lowest values of HOMO energy becomes high antibacterial activity and are accorded with Rizk *et al.* data [39]. The authors can explained the heterocyclic

TABLE-2
CHEMICAL STRUCTURE OF THE SYNTHESIZED COMPOUNDS, THEIR ELECTRON DISTRIBUTION SITES AND E_{HOMO} VALUES

ompound number	Chemical structure and electron distribution sites	HOMO energy values
2, 3		**2a:** E_{HOMO} = -8.883 E_{LUMO} = -5.996 **2b:** E_{HOMO} = -10.224 E_{LUMO} = -6.000 **3a:** E_{HOMO} = -9.743 E_{LUMO} = -4.883 **3b:** E_{HOMO} = -10.356 E_{LUMO} = -5.526
4, 5		**4a:** E_{HOMO} = -8.691 E_{LUMO} = -7.853 **4b:** E_{HOMO} = -7.170 E_{LUMO} = - 6.392 **5a:** E_{HOMO} = -11.268 E_{LUMO} = -5.751 **5b:** E_{HOMO} = -11.410 E_{LUMO} = - 5.392
6, 7		**6a:** E_{HOMO} = -4.883 E_{LUMO} = -2.874 **6b:** E_{HOMO} = -5.343 E_{LUMO} = -2.833 **7a:** E_{HOMO} = -6.656 E_{LUMO} = -3.073 **7b:** E_{HOMO} = -6.656 E_{LUMO} = -3.543
8, 9		**8a:** E_{HOMO} = -2.125 E_{LUMO} = -1.184 **8b:** E_{HOMO} = -2.645 E_{LUMO} = -1.125 **9a:** E_{HOMO} = -3.935 E_{LUMO} = - 1.965 **9b:** E_{HOMO} = -4.035 E_{LUMO} = - 1.978

products **8** and **9** *versus* **10** and **11** *via* the energy gaps of the pyridazinone derivatives **8** and oxazinone derivatives **9** do not exceed (ΔE = 2 ev) (Table-2) that refer to the more stability of these derivatives than the spiro products **10** and **11** (ΔE = 4.1 ev).

Conclusion

The authors have demonstrated a facile and efficient method for the preparation of the two important diastereomeric adducts **2**, **3** and furanone **4**, **5** *via* epoxide (**1**) under ultrasonic and microwave conditions. The adducts **2** and **3** afforded heterocyclic moieties *via* treatment with electrophilic and nucleophilic reagents. A new furanone (**5**), act as chalcone derivatives that afforded highly antibacterial activity due to activated double bonds as enzymatic inhibitor. The compounds have high E_{HOMO} exhibited high antibacterial activities.

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