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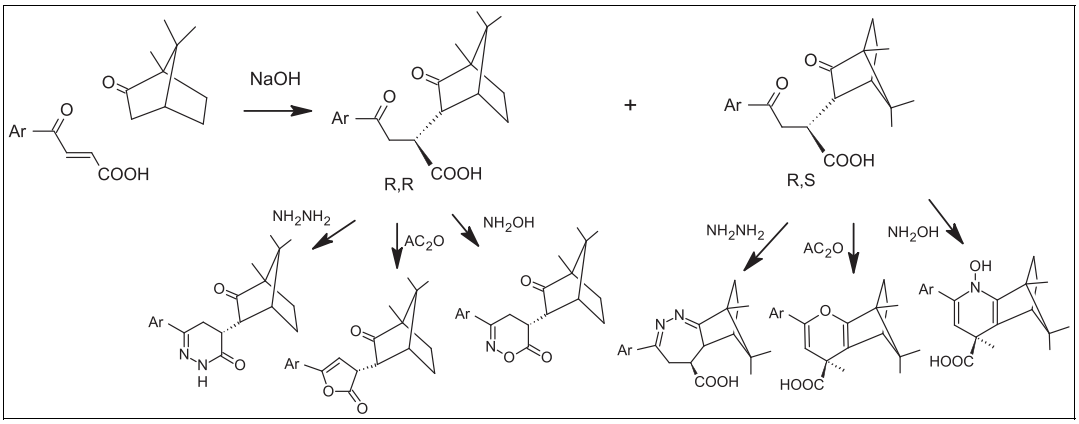

The reaction of 4-(4-acetylamino/bromophenyl)-4-oxobut-2-enoic acids with carbon nucleophiles afforded Michael adducts depending on the type of nucleophilic reagents and medium (acidic or basic). The adducts 2 and 3 were used as key starting materials to synthesize some heterocyclic compounds, which include pyridazinone, furanone, 1,2-oxazin-5-one, 1.2-diazapine, pyrane, and hydroxyl pyridine derivatives. The Steric factor plays an important role in regioselectivity. The structure of newly synthesized compounds was elucidated by elemental analysis and spectroscopic data.

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INTRODUCTION

(E)-4-aryl-4-oxo-2-butenoic acids have shown that the substitution pattern on the aroyl moiety influences the antiproliferative activity [1], and they have activated double bond, Half-wave reduction potentials (*E*1/2) [2], display good correlations with Hammett sigma value, and attempt to obtain good correlations using frontier orbitals of the molecules. Also, they have emerged the most promising drug candidates [3] that are selective for integrase S-1360 [4] and class of human immunodeficiency virus type1 integrase inhibitors [5]. Industrial application of the Diels–Alder reaction, Ifetroban sodium, was a selective thromboxane receptor antagonist investigated as an antiplatelet agent therapy in phase II clinical trials at Ifetroban sodium (BMS-180291) [6]. They are used as key starting materials because of their high electrophilicity, where the β-aroylacrylic acids react readily with nucleophiles including nitrogen and carbon nucleophiles to afford either cyclic or normal Michael adducts depending on the nature of the attacking nucleophiles and the reaction medium (neutral, basic, and acidic). As the Michael addition reaction may be considered an efficient tandem strategy for the construction of ring structures [7–9]. Therefore, these starting materials will be directed to prepare the more interesting heterocyclic compounds of important biological activities that bear 3(2H)-pyridazinone moiety [10].

RESULTS AND DISCUSSION

Reports from our laboratory [11–17] and others [18,19] revealed that the 4-aryl-4-oxobut-2-enoic acids are convenient poly electrophilic reagents in the synthesis of heterocycles, which for the addition reaction of nucleophililes, for example, carbon, nitrogen, sulfur, and phosphore occurs exclusively at the α-carbon electrophilic center of the carboxy precursors. Recently, the authors reported the behavior of 4-(4-acetylaminophenyl)-4-oxo-but-2-enoic acid (**1**) that was allowed to react with pyrazoles, for example, 3-methyl/phenyl-2-pyrazolen-5-one, barbituric acid, and quinazolinone derivatives in different reaction conditions [20] under Michael, aza-Michael, and Friedel–Crafts reaction conditions. In order to expand the potential of synthetic 4-aryl-4-oxo-but-2-enoic acids, the authors reported the behavior of 4-(4-acetylamino/bromophenyl)-4-oxobut-2-enoic acids (**1**) that was allowed to react with active methylene chiral precursor, for example, R(+)-camphor in the presence of sodium hydroxide (basic medium) under Michael reaction condition to afford the diastereomeric

adducts, 2-alkyl-4-aryl-4-oxo butanoic acids **3**, via the formation of carbanion in the cyclic moiety that added to the activated double bond of the acids **1**, which takes place under Michael reaction condition to afford diastereomeric Michael adducts **2** and **3** (Scheme 1).

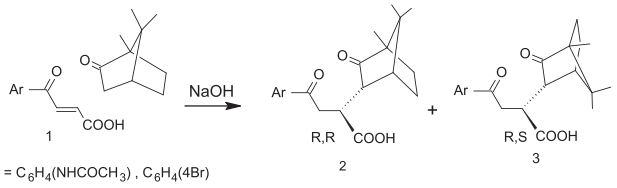
When the *(R,R)* acids **2** were allowed to react with hydrazine hydrate in boiling ethanol and/or hydroxylamine in boiling pyridine, either can be reacted directly or via their furanone derivatives **4**, they afforded pyridazinone derivatives **5** and oxazinone derivatives **6**, respectively (Scheme 2).

In the same manner, when the *(R,S)* acids **3** were allowed to react with hydrazine hydrate in boiling ethanol and hydroxyl amine in boiling pyridine, they afforded 1,2-diazapine **7** and pyridine **8** derivatives (Scheme 3). The regioselective products of 1,2-diazepine derivatives **6** were due to the ketonic group of the camphor moiety, which is more reactive than carboxylic group. In Scheme 2, the steric crowding of the bridged methyl group was outweigh the reactivity of carbonyl of camphor moiety and therefore, the isomers 2 could be preferred cyclization with the carboxylic group. The Steric factor plays an important role in the regioselectivity. So, the absence of steric crowding of bridged methyl group in camphor moiety of the acids **3** became a driving force to afford regioselective isomers **7**, **8**, and **9** instead of **5**, **6**, and **4**, respectively (Scheme 3).

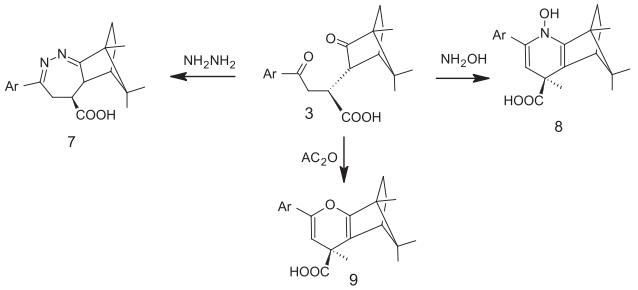
EXPERIMENTAL

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 Microanalysis (Germany), the IR spectra (KBr pellets, νmax/cm^{-1}) were recorded on infrared spectrometer FT-IR 400D using OMNIC program and reported frequency of absorption in terms of cm^{-1}, and ^{1}H-NMR spectra recorded on a Bruker spectrophotometer (Germany) 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 was used where appropriate to aid the assignment of signals in the ^{1}H-NMR and ^{13}C-NMR spectra. The mass spectra were recorded on Shimadzu GCMS-QP-1000 EX mass spectrometer (Japan) at 70 eV using the electron ionization technique. Homogeneity of all compounds synthesized was checked by TLC.

Scheme 1



Scheme 3

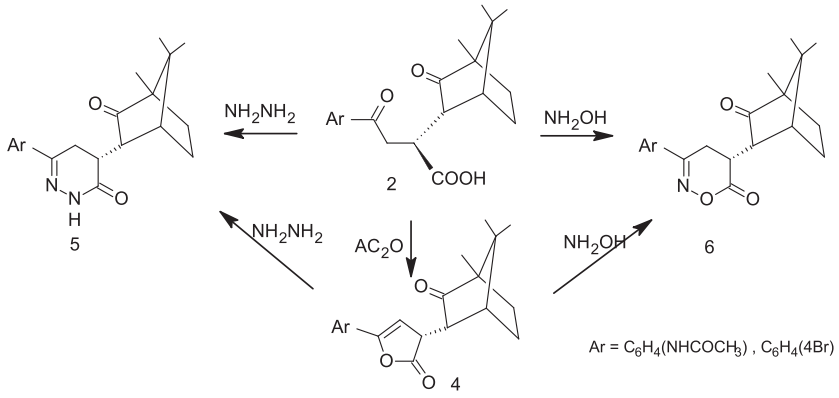


General procedure of starting material in literature [11].

General procedure of synthesis the compounds 2 and 3. A mixture of 4-(4-acetylamino/bromobenzoyl)-4-oxobut-2-enoic acids **1** (0.01 mol) and active methylene precursor, for example, R(+) camphor (0.01 mol), (50%)NaOH (8 mL), and ethanol (50 mL) was refluxed for 3 h and left overnight for 3 days. The reaction mixture was poured into ice/HCl, filtered the crude product, and washed by petroleum ether (bp 40–60°C), and then crystallized.

***(2R,3R)*4-(4-(Acetylamino)phenyl)-2-(1,7,7-trimethylbicyclo [2,2,1]heptan-2-on-3-yl)-4-oxobutanoic acid (2a)**. Melting point 162–164°C. IR(KBr pellets, νmax/cm^{-1}) 1668, 1720 (C = O). ^{1}H-NMR spectrum ($CDCl_3$): δ 1.06 (s, 3H, CH_3a), 1.2 (s, 3H, CH_3b), 1.73 (m, 5H, $CHCH_2CH_2$, camphor moiety), 1.98 (s, 3H, CH_3), 2.25 (s, 3H,CH_3CON-), 2.43 (dd, CHCO, camphor moiety), 2.71

Scheme 2



(dd, 1Ha and 1Hb methylene protons, CH_2-C=O, diastereotopic protons), 2,92 (m, CH-COO, sterogenic methine proton), multiplet at 7.47–7.75 assigned for 4ArH aromatic protons, and singlet at 8.5 and 13.2 (an acidic protons which exchanged in D_2O). *Anal.* Calcd for $C_{22}H_{27}NO_5$: C 68.57, H 7.01; found: C 68.46, H 7.00. MS: m/z 385[M].

***(2R,3R)*4-(4-Bromophenyl)-2-(1,7,7-trimethylbicyclo[2,2,1]heptan-2-on-3-yl)-4-oxobutanoic acid (2b)**. Melting point 144–148°C. IR (KBr pellets, νmax/cm^{-1}) 1680, 1720 (C=O). ^{1}H-NMR spectrum ($CDCl_3$): δ 1.06 (s, 3H, CH_3a), 1.2 (s, 3H, CH_3b), 1.78 (s, 3H, CH_3), 1.80 (m, 5H, $CHCH_2CH_2$, camphor moiety), 2.56 (dd, CHCO, camphor moiety), 2.78 (dd, 1Ha, (J = 15.2 Hz, J = 7.2 Hz), and 1Hb methylene protons, CH_2-C=O, diastereotopic protons, 2.93 (m, CH-COO, stereogenic methine proton), multiplet at 7.67–7.71 assigned for 4ArH aromatic protons, singlet at 10.7 (an acidic proton which exchanged in D_2O), and ^{13}C-NMR δ 22.8 (CH_3), 23.3 (CH_3), 28.3 (CH_3), 34.4 (CH_2), 38.6 (C), 43.4 (CH_2), 58.4 (CH_2), 67.4 (C), 102.3 (CH), 128.2 (CH), 129.2 (2CH), 129.5 (2CH), 134.4 (CH), 138.1 (C), 155.7 (C), 175.0 (C), 183.2 (C), and 200.5 (C). *Anal.* Calcd for $C_{20}H_{23}O_4Br$ C 58.96, H 5.65; found: C 58.93, H 5.62. MS: m/z 408[M^++2], 406[M^+].

***(2R,3S)*4-(4-(Acetylamino)phenyl)-2-(1,7,7-trimethylbicyclo[2,2,1]heptan-2-on-3-yl)-4-oxobutanoic acid (3a)**. Melting point 148–150°C. IR (KBr pellets, νmax/cm^{-1}) 1668, 1720 (C=O). ^{1}H-NMR spectrum ($CDCl_3$): δ 1.31 (s, 6H, $2CH_3$), 1.82 (m, 5H, $CHCH_2CH_2$, camphor moiety), 1.76 (s, 3H, CH_3), 2.20 (s, 3H, CH_3CON-), 2.43 (dd, CHCO, camphor moiety), 2.71 (dd, 1Ha, (J = 15.2Hz, J = 7.2Hz), and 1Hb methylene protons, CH_2-C=O, diastereotopic protons, 2.92 (m, CH-COO, sterogenic methine proton), multiplet at 7.47–7.75 assigned for 4ArH aromatic protons, singlet at 11.2 and 13.11 (an acidic proton which exchanged in D_2O), and ^{13}C-NMR δ 23.8 (CH_3), 25.4 (CH_3), 28.3 (CH_3), 32.0 (CH_3), 34.4 (CH_2), 37.1 (CH_2), 38.1 (C), 39.4 (CH_2), 45.0 (C), 58.4 (CH), 102.3 (CH), 108.2 (CH), 129.2 (2CH),129.5 (2CH), 134.4 (C), 138.1 (C), 142.7 (C), 145.0 (C), 173.2 (C), and 198.5 (C).

***(2R,3S)*4-(4-Bromophenyl)-2-(1,7,7-trimethylbicyclo[2,2,1]heptan-2-on-3-yl)-4-oxobutanoic acid (3b)**. Melting point 136–138°C. IR (KBr pellets, νmax/cm^{-1}) 1680, 1720 (C=O). ^{1}H-NMR spectrum ($CDCl_3$): 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), 2.73(dd, CHCO, camphor moiety), 3.01(dd, 1Ha, (J = 15.2 Hz, J = 7.2Hz), and 1Hb methylene protons, CH_2-C=O, (J = 15.2Hz, J = 5.1Hz), diastereotopic protons, 3.22 (m, CH-COO, sterogenic methine proton, J = 7.2, J = 5.1), multiplet at 7.72–7.78 assigned for 4ArH aromatic protons, and singlet at 11.2 (an acidic proton which exchanged in D_2O). *Anal.* Calcd for $C_{20}H_{23}O_4Br$: C 59.11, H 7.01; found: C 59.26,H 7.09. MS: m/z 408[M + 2], 406[M], 307, 198, 154, 105, 96.

Compounds 4. A mixture of **2** (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 re-crystallized from mixed toluene–ethanol.

***5-(4-(Acetylamino)phenyl)-3-(1,7,7-trimethylbicyclo[2,2,1]heptan-2-on-3-yl)-2(3H)*furanone (4a)**. Melting point 220–222°C. IR (KBr pellets, νmax/cm^{-1}) 1668, 1772 (C=O). ^{1}H-NMR spectrum ($CDCl_3$): δ 1.06 (s, 3H, CH_3a), 1.2 (s, 3H, CH_3b),1.73 (m, 5H, $CHCH_2CH_2$, camphor moiety), 1.98 (s, 3H,CH_3), 2.25 (s, 3H, CH_3CON-), 2.43 (dd, CHCO, camphor moiety), 2.92 (dd, CH-COO, sterogenic methine proton), 5.4 (s, 1H, furanone proton), multiplet at 7.47–7.75 assigned for 4ArH aromatic protons, singlet at 13.2 (an acidic proton (NH) which exchanged in D_2O) and ^{13}C-NMR δ 13.2 (CH_3), 18.3 (CH_3), 21.7 (CH_3), 23.9 (CH_2), 26.8 (CH_2), 38.4 (CH_3), 39.6 (CH), 46.6 (CH), 48.8 (CH), 50.2 (C), 56.8 (C), 129.7 (C), 130.4 (2CH), 131.8 (2CH), 132.2 (CH), 136.2 (C), 178.8 (C), 195.7 (C), 201.5 (C), and 213.4 (C). *Anal.* Calcd for $C_{22}H_{25}NO_4$: C 71.93, H 6.81; found: C 71.86,H 6.70. MS: m/z 367[M].

***5-(4-Bromophenyl)-3-(1,7,7-trimethylbicyclo[2,2,1]heptan-2-on-3-yl)-2(3H)*furanone (4b)**. Melting point 208–210°C. IR (KBr pellets, νmax/cm^{-1}) 1700, 1780 (C=O). ^{1}H-NMR spectrum ($CDCl_3$): δ 1.06 (s,3H,CH_3a), 1.2 (s, 3H, CH_3b), 1.78 (s,3H,CH_3), 1.80 (m, 5H, $CHCH_2CH_2$, camphor moiety), 2.56 (dd, CHCO, camphor moiety), 2.93 (dd, CH-COO, sterogenic methine proton), 5.4 (s,1H,furanone proton), multiplet at 7.67–7.71 assigned for 4ArH aromatic protons, and ^{13}C-NMR δ 22.8 (CH_3), 23.3 (CH_3), 28.3 (CH_3), 34.4 (CH_2), 38.6 (C), 43.4 (CH_2), 67.4 (C), 102.3 (CH), 128.2 (CH), 129.2 (2CH), 129.5 (2CH), 131.3 (CH), 134.4 (CH),138.1 (C), 155.7 (C), 175.0 (C), 183.2 (C),and 200.5 (C). *Anal.* Calcd for $C_{20}H_{21}O_3Br$: C 61.85, H 5.41; found: C 61.86, H 5.44. MS: m/z 389[M^+ +2], 387[M^+].

Compounds 5. A mixture of **2** (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.

6-(4-Acetylaminophenyl)-4-(1,7,7-trimethyl-3-oxo-bicyclo[2,2,1]hepta-2-yl)-2,3,4,5-tetrahydro-3-oxopyridazine (5a). Melting point 196–198°C. IR (KBr pellets, νmax/cm^{-1}) 1676, 1710 (C=O), 3362 (N-H). ^{1}H-NMR (DMSO-*d6)*: 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), 2.56 (2dd, 1Ha, and 1Hb methylene protons, CH_2-C=N, diastereotopic protons in pyridazinone moiety), 3.17 (dd, CH-,sterogenic methine proton), 3.25 (m, 1H, attached, camph), 7.48–7.56 (m, 4H, Ar-H), 12.34 (brs, 2H, 2NH of acetamido and pyridazine moieties), and ^{13}C-NMR δ 11.8 (CH_3), 18.3 (CH_3), 18.7 (CH_3), 21.9 (CH_2), 26.8 (CH_2), 37.3 (CH_2), 38.4 (CH_3), 39.6 (CH), 44.6 (CH), 45.8 (CH), 48.2 (C), 56.8 (C), 129.7 (C), 130.4 (2CH), 131.8 (2CH), 136.2 (C), 178.8 (C), 195.7 (C), 201.5 (C), and 213.4 (C). *Anal.* Calcd for $C_{22}H_{27}N_3O_3$: C 69.29,H 7.08; found: C 69.15, H 7.00. MS: m/z 381[M], 267,175,137.

6-(4-Bromophenyl)-4-(1,7,7-trimethyl-3-oxo-bicyclo[2,2,1]hepta-2-yl)-2,3,4,5-tetrahydro-3-oxopyridazine (5b). Melting point 184–186°C. IR(KBr pellets, νmax/cm^{-1}) 1690, 1710 (C=O), 3345 (N-H). ^{1}H-NMR (DMSO-*d6)*: 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, 1H, methine bridgehead), 2.75 (dd, 1Ha, (J = 15.2, J = 7.9), and 1Hb methylene protons, CH_2-C=O, diastereotopic protons, 3.17 (dd, CH-COO, sterogenic methine proton), 3.25 (m,1H,attached), 7.68–7.80 (m, 4H, Ar-H), 11.34 (brs,1H,NH), and ^{13}C-NMR δ 11.8 (CH_3), 18.3 (CH_3), 18.7 (CH_3), 21.9 (CH_2), 26.8 (CH_2), 37.3 (CH_2), 38.4 (CH), 44.6 (CH), 45.8 (CH), 48.2 (C), 56.8 (C),129.7 (C), 130.4 (2CH), 131.8 (2CH), 136.2 (C), 178.8 (C),195.7 (C), and 213.4 (C).

Anal. Calcd for $C_{20}H_{23}N_2O_2Br$: C 59.70,H 5.72; found: C 59.65, H 5.67. MS: m/z 402[M], 251,175,156.

Compounds 6. A mixture of **2** (0.01 mol) and hydroxyl amine (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.

3-(4-Acetylaminophenyl)-5-(1,7,7-trimethyl-3-oxo-bicyclo[2,2,1] hepta-2-yl)- 4,5,6-trihydro-1,2-oxazin-6-one (6a). Melting point 212–214°C. IR (KBr pellets, νmax/cm^{-1}) 1676, 1710 (C=O), 3362 (N-H). ^{1}H-NMR(DMSO-*d6)*: 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), 2.56 (2dd, 1Ha, and 1Hb methylene protons, CH_2-C=N, diastereotopic protons in oxazinone moiety), 3.17 (dd, CHCOO, sterogenic methine proton), 3.25 (m, 1H, attached, camph), 7.52–7.61 (m, 4H, Ar-H), 12.34 (brs, 1H, NH of acetamido moiety), and ^{13}C-NMR δ 11.8 (CH_3), 18.3 (CH_3), 18.7 (CH_3), 21.9 (CH_2), 26.8 (CH_2), 37.3 (CH_2), 38.4 (CH_3), 39.6 (CH), 44.6 (CH), 45.8 (CH), 48.2 (C), 56.8 (C), 129.7 (C), 130.4 (2CH), 131.8 (2CH), 136.2 (C), 178.8 (C), 195.7 (C), 201.5 (C), 213.4 (C). *Anal.* Calcd for $C_{22}H_{26}N_2O_4$: C 69.11, H 6.81; found: C 69.05, H 6.72. MS: m/z 382[M], 267,175,137.

3-(4-Bromophenyl)-5-(1,7,7-trimethyl-3-oxo-bicyclo[2,2,1] hepta-2-yl)-4,5,6-trihydro-1,2-oxazin-6-one (6b). Melting poinr 192–194°C. IR (KBr pellets, νmax/cm^{-1}) 1690, 1710 (C=O), 3331 (N-H). ^{1}H-NMR (DMSO-*d6)*: 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, 1H, methine), 2.75 (dd,1Ha, (J=15.2, J=7.9), and 1Hb methylene protons, CH_2-C=O, (J=15.2, J=2.4) diastereotopic protons, 3.17 (dd, CH-COO, sterogenic methine proton J=9.7Hz, J=7.9Hz, J=2.4Hz), 3.25 (m, 1H, attached, J=9.7Hz), 7.71–7.79 (m, 4H, Ar-H), and ^{13}C-NMR δ 11.8 (CH_3), 18.3 (CH_3), 18.7 (CH_3), 21.9 (CH_2), 26.8 (CH_2), 37.3 (CH_2), 38.4 (CH), 44.6 (CH), 45.8 (CH), 48.2 (C), 56.8 (C), 129.7 (C), 130.4 (2CH), 131.8 (2CH), 136.2 (C), 178.8 (C), 195.7 (C), and 213.4 (C). *Anal.* Calcd for $C_{20}H_{22}NO_3Br$: C 59.55, H 5.46; found: C 59.47, H 5.40. MS: m/z 403[M], 251,175,156.

Compounds 7. A mixture of **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.

3-(4-Acetylaminophenyl)-1,7,7-trimethyl-3-oxo-bicyclo[2,2,1] heptan[2,3-c] 1,2-diazepine-5-carboxylic acid (7a). Melting point 196–198°C. IR (KBr pellets, νmax/cm^{-1}) 1668, 1710 (C=O). ^{1}H-NMR (DMSO-*d6)*: 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_2-CH_2), 2.56 (dd, 1Ha, and 1Hb methylene protons, CH_2-C=N), 3.17 (dd, CHCOO, sterogenic methine proton,), 3.00 (m, 1H, attached, camph), 7.48-7.56 (m, 4H, Ar-H), 12.34 (s, 1H, NH of acetamido moiety), and ^{13}C-NMR δ 11.8 (CH_3), 18.3 (CH_3), 18.7 (CH_3), 21.9 (CH_2), 26.8 (CH_2), 37.3 (CH_2), 38.4 (CH_3), 39.6 (CH), 44.6 (CH), 45.8 (CH), 48.2 (C), 56.8 (C), 129.7 (C), 130.4 (2CH), 131.8 (2CH), 136.2 (C), 178.8 (C), 195.7 (C), 201.5 (C),and 213.4 (C). *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], 267,175,137.

3-(4-Bromophenyl)-1,7,7-trimethyl-3-oxo-bicyclo[2,2,1]heptan [2,3-c] 1,2-diazepine-5-carboxlic acid (7b). Melting point 184–186°C. IR (KBr pellets, νmax/cm^{-1}) 1708 (C=O). ^{1}H-NMR (DMSO-*d6)*: 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, 1H, methine bridgehead), 2.75 (dd, 1Ha, (J=15.2Hz, J=7.9Hz), and 1Hb methylene protons, CH_2-C=O, 3.17 (dd, CH-COO, sterogenic methine proton), 3.25 (m, 1H, attached), 7.68–7.80 (m, 4H, Ar-H), 8.2 (bs, 1H, CO_2H), and ^{13}C-NMR δ 11.8 (CH_3), 18.3 (CH_3), 18.7 (CH_3), 21.9 (CH_2), 26.8 (CH_2), 37.3 (CH_2), 38.4 (CH), 44.6 (CH), 45.8 (CH), 48.2 (C), 56.8 (C), 129.7 (C), 130.4 (2CH), 131.8 (2CH), 136.2 (C), 178.8 (C), 195.7 (C), and 213.4 (C). *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], 251,175,156.

Compounds 8. A mixture of **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 from mix toluene–ethanol.

***2-(4-(Acetylamino)phenyl)-1,7,7-trimethylbicyclo[2,2,1]heptan [2,3-b] (4H)*pyran-4-carboxylic acid (8a)**. Melting point 150–152°C. IR (KBr pellets, νmax/cm^{-1}) 1712 (C=O). ^{1}H-NMR spectrum ($CDCl_3$): δ 1.11 (s, 3H, CH_3a),1.22 (s, 3H, CH_3b), 1.73 (m, 5H, $CHCH_2CH_2$, camphor moiety), 1.98 (s, 3H, CH_3), 2.25 (s, 3H, CH_3CON-), 2.43 (dd, CHCO, camphor moiety), 2,92 (dd, CH-COO, sterogenic methine proton), 5.4 (s, 1H, furanone proton), multiplet at 7.47–7.75 assigned for 4ArH aromatic protons, singlet 10.8, 13.2 (brs, 2H, an acidic protons COOH and NH which exchanged in D_2O), and ^{13}C-NMR δ 13.2 (CH_3), 18.3 (CH_3), 21.7 (CH_3), 23.9 (CH_2), 26.8 (CH_2), 38.4 (CH_3), 39.6 (CH), 46.6 (CH), 48.8 (CH), 50.2 (C), 56.8 (C), 129.7 (C), 130.4 (2CH), 131.8 (2CH), 132.2 (CH), 136.2 (C),178.8 (C), 195.7 (C), 201.5 (C), and 213.4 (C). *Anal.* Calcd for $C_{22}H_{25}NO_4$: C 71.93, H 6.81; found: C 71.97,H 6.81. MS: m/z 367[M].

***2-(4-Bromophenyl)-1,7,7-trimethylbicyclo[2,2,1]heptan[2,3-b](4H)*pyran-4-carboxylic acid (8b)**. Melting point 164–166°C. IR (KBr pellets, νmax/cm^{-1}) 1715 (C=O). ^{1}H-NMR spectrum ($CDCl_3$): δ 1.10 (s, 3H, CH_3a), 1.20 (s, 3H, CH_3b), 1.82 (s, 3H, CH_3), 1.98 (m, 5H, $CHCH_2CH_2$, camphor moiety), 2,93 (dd, CH-COO, sterogenic methine proton), 6.2 (s, 1H, pyrane proton), multiplet at 7.67–7.71 assigned for 4ArH aromatic protons, 11.2 (s, 1H, COOH), and ^{13}C-NMR δ 22.8 (CH_3),23.3 (CH_3), 28.3 (CH_3), 34.4 (CH_2), 38.6 (C), 43.4 (CH_2), 67.4 (C), 102.3 (CH), 128.2 (CH), 129.2 (2CH), 129.5 (2CH), 131.3 (CH), 134.4 (CH), 138.1 (C), 155.7 (C), 175.0 (C), 183.2 (C), and 200.5 (C). *Anal.* Calcd for $C_{20}H_{21}O_3Br$: C 61.85, H 5.41; found: C 61.73, H 5.32. MS: m/z 389[M^+ +2], 387[M^+].

Compounds 9. A mixture of **3** (0.01 mol) and hydroxyl amine (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.

2-(4-(Acetylamino)phenyl)-1-(hydroxy)-1,7,7-trimethylbicyclo [2,2,1]heptan[2,3-b]1,4-dihydropyridine-4-carboxylic acid (9a). Melting point 234–236°C. IR (KBr pellets, νmax/cm^{-1}) 1676, 1710 (C=O), 3420 (O-H). ^{1}H-NMR (DMSO-*d6)*: 1.12 (s, 3H, CH_3a),1.19 (s, 3H, CH_3b), 1.31(s, 3H, CH_3.), 1.58–1.84 (m, 4H, $2CH_2$), 2.01 (m, 1H, methine bridgehead), 2.56 (s, 3H, CH_3), 3.17 (s, 1H, CHCOO), 4.4 (s, 1H, proton of pyridine moiety), 4.8 (brs, 1H, OH), 7.52–7.61 (m, 4H, Ar-H), 11.8 (brs, 2H, NH of acetamido moiety and -COOH), and ^{13}C-NMR δ 11.8 (CH_3), 18.3 (CH_3), 18.7 (CH_3), 21.9 (CH_2), 26.8 (CH_2), 37.3 (CH_2),

38.4 (CH_3), 39.6 (CH), 44.6 (CH), 45.8 (CH), 48.2 (C), 56.8 (C), 129.7 (C), 130.4 (2CH), 131.8 (2CH), 136.2 (C), 178.8 (C), 195.7 (C), 201.5 (C), and 213.4 (C). *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], 267,175,137.

2-(4-Bromophenyl)-1-(hydroxyl)-1,7,7-trimethylbicyclo[2,2,1] heptan[2,3-b]1,4-dihydro)pyridine-4-carboxylic acid (9b). Melting point 218–220°C. IR (KBr pellets, νmax/cm^{-1}) 1710 (C = O), 3412 (O-H). ^{1}H-NMR (DMSO-*d6)*: 1.12 (s, 3H, CH_3a), 1.19 (s, 3H, CH_3b), 1.31 (s, 3H, CH_3.), 1.58–1.84 (m, 4H, $2CH_2$), 2.01 (m, 1H, methine bridgehead), 3.17(s, 1H, CHCOO), 4.4 (s, 1H, proton of pyridine moiety), 4.8 (brs, 1H,OH), 7.52–7.61 (m, 4H, Ar-H), 11.2 (s, 1H, COOH), and ^{13}C-NMR δ 11.8 (CH_3), 18.3 (CH_3), 18.7 (CH_3), 21.9 (CH_2), 26.8 (CH_2), 37.3 (CH_2), 38.4 (CH), 44.6 (CH), 45.8 (CH), 48.2 (C), 56.8 (C), 129.7 (C), 130.4 (2CH), 131.8(2CH), 136.2 (C), 178.8 (C), 195.7 (C), and 213.4 (C). *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], 251,175,156.

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