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Facile synthesis of new fused and non-fused heterocyclic systems from a γ-ketoacid

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ABSTRACT

The chemical reactivity of 4-(2-tetryl)-4-oxobut-2-enoic acid towards carbon, nitrogen, oxygen, sulfur nucleophiles and binucleophiles namely *o*-phenylenediamine, *o*-aminophenol, and *o*-aminothiophenol has been studied. The investigated nucleophilic reactions result in the formation of heterocyclic compounds with fused and non-fused systems namely, pyridazinone, tetrhydroquinoline, quinoxalone, oxazinone, thiazole and benzocoumarin.

1. Introduction

4-Aryl-4-oxobut-2-enoic acids (also considered as *β*-aroylacrylic acids), their derivatives represent an important class of compounds with wide spectrum of biological activities including antibacterial activity [1-5], anti-ulcer and cytoprotective properties [6,7], kynurenine-3-hydroxylase [8] and antiproliferative activity toward Human cervix carcinoma (HeLa) [9,10]. Moreover, the *β*-aroylacrylic acids have been attracting increasing attention in view of their high reactivity as building blocks for the synthesis of wide variety of compounds of various classes due to their selective transformations with different reagents.

In continuation of our previous works [11-19], the present work aimed at utilization of the reactivity of 4-(2-tetryl)-4-oxobut-2-enoic acid (**1**) towards different nucleophiles such as carbon, nitrogen, oxygen, sulfur nucleophiles and binucleophiles (*o*-phenylenediamine, *o*-aminophenol, and *o*-aminothiophenol) to construct mixed and non-mixed heterocyclic systems. Several electrophilic centers are present in acid (**1**) (α,β-unsaturated-γ-ketoacid), *viz* atoms C(2) and C(4) which are hopeful for many reaction routes with nucleophilic reagents.

2. Experimental

2.1. Instrumentation

All melting points were measured on a Gallenkamp melting point apparatus and are uncorrected. The infrared spectra were recorded using KBr disks on a Pye Unicam SP-3-300 infrared spectrophotometer. ^{1}H NMR experiments were run at 300 MHz on a Varian Mercury VX-300 NMR spectrometer using TMS as internal standard in deuterated chloroform ($CDCl_3$) or deuterated dimethylsulphoxide (DMSO-d_6). Chemical shifts δ are quoted. The mass spectra were recorded on Shimadzu GCMS-QP-1000EX Mass spectrometers at 70 eV. All the spectral measurements as well as elemental analyses were carried out at the Micro analytical Center of Cairo University. All the newly synthesized compounds gave satisfactory elemental analyses.

2.2. Synthesis

2.2.1. Reaction of 4-oxo-4-(5,6,7,8-tetrahydronaphthalen-2-yl)-but-2-enoic acid (1) [20] with cyclohexanone and / or camphor

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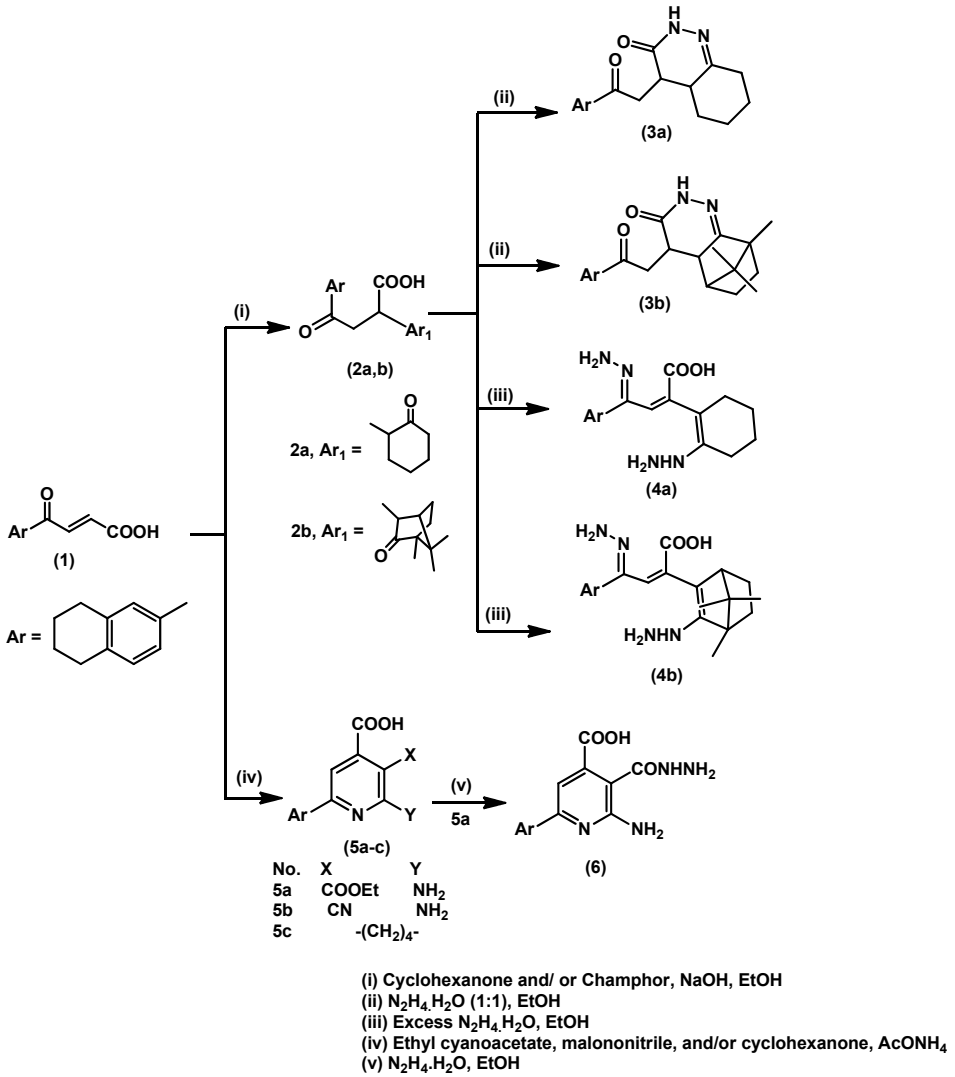


Scheme 1

A mixture of acid **1** (0.01 mmol, 2.30 g), cyclohexanone and/or camphor (0.01 mmol) in ethanol (30 mL) and 50% sodium hydroxide (2 mL) was stirred at reflux temperature for 6 h. The precipitated solid that formed after cooling was dissolved in water then acidified with hydrochloric acid. The crude solid product that deposited was collected by filtration and washed with water, dried and recrystallized from light petroleum ether (80-100 °C): ethanol (2:1) to give compound **2a**,**b** respectively (Scheme 1).

4-Oxo-2-(2-oxocyclohexyl)-4-(5,6,7,8-tetrahydronaphthalen-2-yl)butanoic acid (**2a**): Color: Orange. Yield: 57 %. M.p.: 100-102 °C. FT-IR (KBr, ν, cm^{-1}): 2858-2660 (ν_{OH}), 1790 ($\nu_{C=O}$,cyclic ketone), 1708 ($\nu_{C=O}$, acid), 1679 ($\nu_{C=O}$, ketone), 1604 ($\nu_{C=C}$). ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm): 7.68-7.11 (m, 3H, Ar-H), 3.04-2.82 (m, 10H, tetrahydronaphthalene, cyclohexanone moiety, -CH_2CH-COOH), 2.31-1.27 (m, 10H, cyclohexanone moiety, tetrahydronaphthalene moiety). MS (EI, *m/z* (%)): 330 ([M+2]‡, 13.6), 216 (33.3), 159 (100.0), 131 (50.0).

4-Oxo-4-(5,6,7,8-tetrahydronaphthalen-2-yl)-2-(4,7,7-trimethyl-3-oxobicyclo[2.2.1]heptan-2-yl)butanoic acid (**2b**): Color: Yellow. Yield: 49 %. M.p.: 173 °C decomp. FT-IR (KBr, ν, cm^{-1}): 2858-2660 (ν_{OH}) , 1791 ($\nu_{C=O}$, cyclic ketone), 1708 ($\nu_{C=O}$, acid), 1678 ($\nu_{C=O}$, ketone). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 7.67-7.17 (m, 3H, Ar-H), 2.99-2.77 (m, 8H, tetrahydronaphthalene moiety, camphor moiety, -CH_2CH-COOH), 2.09-1.75 (m, 9H, camphor, tetrahydronaphthalene moiety), 1.24 (s, 3H, CH_3), 1.08 (s, 3H, CH_3), 1.03 (s, 3H, CH_3). MS (EI, *m/z* (%)): 384 ([M+2]‡, 3.7), 356 (4.8), 159 (100.0), 131 (22.7).

2.2.2. Reaction of Michael adducts (2a,b) with hydrazine hydrate

A mixture of Michael adduct **2a**,**b** (0.005 mmol, 1.89 g) and hydrazine hydrate (0.005 mmol, 0.25 mL) in ethanol (20 mL) was heated at reflux for 8 h. The solid product which was separated out on hot was collected, dried and recrystallized from *n*-butanol and/or dimethylformamide (DMF) to give compounds **3a**,**b**, respectively (Scheme 1).

4-(2-Oxo-2-(5,6,7,8-tetrahydronaphthalen-2-yl)ethyl)-4,4a,5,6,7,8-hexahydrocinnolin-3(2H)-one (**3a**): Color: Red. Yield: 32 %. M.p.: 201-202 °C. FT-IR (KBr, ν, cm^{-1}): 3334 (ν_{NH}), 1667 ($\nu_{C=O}$). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 7.82-7.01 (m, 3H, Ar-H), 6.87 (s, 1H, exchangeable, N*H*), 3.11-2.78 (m, 7H, tetrahdronaphthalene, pyridazinone moiety, -COCH_2), 2.31-1.27 (m, 13H, cyclohexanone moiety, tetrahydronaphthalene moiety, pyridazinone moiety).MS (EI, *m/z* (%)): 326 ([M+2]‡, 0.43),

325 ([M+1]$^{\cdot}$, 0.23), 324 (M$^{\cdot}$, 00.15), 159 (2.39), 131(3.29), 83 (18.04), 82 (13.34), 81 (16.37), 80 (100.0).

6-[2-Oxo-2-(5,6,7,8-tetrahydronaphthalen-2-yl)ethyl]-1,11, 11-trimethyl-3,4-diazatricyclo[6.2.1.02,7]undec-2-en-5-one (**3b**): Color: Red. Yield: 42 %. M.p.: 223 °C decomp. FT-IR (KBr, ν, cm^{-1}): 3341 (ν_{NH}), 1665 ($\nu_{C=O}$), 1608 ($\nu_{C=N}$). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 7.78-7.02 (m, 3H, Ar-H), 6.93 (s, 1H, exchangeable, N*H*), 3.30-2.57 (m, 7H, tetrahydronaphthalene, pyridazinone moiety, -COC*H*$_2$), 2.07-1.51 (m, 10H, camphor, tetrahydronaphthalene, pyridazinone moiety), 1.24 (s, 3H, C*H*$_3$), 1.08 (s, 3H, C*H*$_3$), 0.83 (s, 3H, C*H*$_3$). MS (EI, *m/z* (%)): 377 (M$^{\cdot}$, 2.73), 227 (100.0), 186 (9.56), 185 (5.19), 184 (2.19), 159 (21.58), 131 (53.83).

2.2.3. Reaction of Michael adducts (2a,b) with excessive hydrazine hydrate

A mixture of Michael adduct **2a**, **b** (1 g) and hydrazine hydrate (2 mL) in ethanol (20 mL) was heated at reflux for 3 h and left to cool. Then the mixture was poured in ice and acidified with hydrochloric acid. The crude solid product that deposited was collected by filtration and washed with water, dried and recrystallized from ethanol to afford compound **4a**,**b**, respectively (Scheme 1).

4-Hydrazono-2-(2-hydrazinocyclohex-1-enyl)-4-(5,6,7,8-tetra hydronaphthalen-2-yl)but-2-enoic acid (**4a**): Color: Pale red. Yield: 43 %. M.p.: 201-202 °C. FT-IR (KBr, ν, cm^{-1}): 3332 ($\nu_{NH,}$ ν_{NH2} & ν_{OH}), 1675 ($\nu_{C=O}$), 1606 ($\nu_{C=N}$). ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm): 8.85 (s, 2H, exchangeable, N*H*$_2$), 7.77-7.00 (m, 4H, Ar-H, C*H*=C-C=O), 3.04-2.70 (m, 4H, tetrahydronaphthalene moiety), 2.36-2.20 (br. s, 3H, exchangeable, -N*H*-N*H*$_2$), 1.79-1.62 (m, 4H, cyclohexenylhydrazine moiety), 1.44-1.27 (m, 8H, tetrahydro naphthalene, cyclohexenylhydrazine moiety). MS (EI, *m/z* (%)): 354 (M$^{\cdot}$, 100.0), 247 (61.3), 221 (41.9), 177 (27.4), 149 (14.5), 129 (12.9), 76 (64.5).

4-Hydrazono-4-(5,6,7,8-tetrahydronaphthalen-2-yl)-2-(3-hydrazino-4,7,7-trimethylbicyclo[2.2.1]hept-2-en-2-yl)but-2-enoic acid (**4b**): Color: Brown. Yield: 64 %. M.p.: 240-242 °C. FT-IR (KBr, ν, cm^{-1}): 3350 (br. $\nu_{NH,}$ $\nu_{NH2,}$ ν_{OH}), 1677 ($\nu_{C=O}$, α,β-unsaturated acid). ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm): 8.23 (s, 2H, exchangeable, N*H*$_2$), 7.78-6.99 (m, 4H, Ar-H, C*H*=C-C=O), 3.04-2.76 (m, 5H, tetrahydronaphthalene, camphor moiety), 2.23 (br. s, 3H, exchangeable, -N*H*-N*H*$_2$), 1.79 (m, 8H, tetrahydro naphthalene, camphor moiety), 1.27 (s, 3H, CH_3), 0.89 (s, 3H, CH_3), 0.87 (s, 3H, CH_3). MS (EI, *m/z* (%)): 408 (M$^{\cdot}$, 18.8), 364 (12.9), 227 (69.4), 226 (95.3), 225 (100.0), 174 (12.9), 173 (12.9), 165 (9.4), 160 (17.6), 159 (72.9).

2.2.4. Reaction of acid 1 with ethyl cyanoacetate, malononitrile and / or cyclohexanone in presence of ammonium acetate

A mixture of acid **1** (0.01 mmol, 2.30 g), ethyl cyanoacetate, malononitrile and / or cyclohexanone (0.01 mmol) and 5 g of ammonium acetate were fused in water bath for 3-5 h. Then the mixture was poured in ice, the crude solid product that deposited was collected by filtration and washed with water, dried and recrystallized from ethanol to give isonicotinic acid derivative **5a**, recrystallized from acetic acid to give isonicotinic acid derivative **5b** and/or recrystallized from benzene to give tetrahydroquinoline derivative **5c** (Scheme 1).

2-Amino-3-(ethoxycarbonyl)-6-(5,6,7,8-tetrahydronaphtha-len-2-yl)isonicotinic acid (**5a**): Color: Red. Yield: 56 %. M.p.: 200 °C decomp. FT-IR (KBr, ν, cm^{-1}): 3395($\nu_{OH,}$ ν_{NH2}), 1713 ($\nu_{C=O}$, ester), 1681 ($\nu_{C=O}$, acid), 1604 ($\nu_{C=C}$). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 7.70-7.15 (m, 4H, Ar-H), 4.91 (q, 2H, -C*H*$_2$-CH$_3$), 3.19 (s, 2H, exchangeable, NH_2), 2.73 (m, 4H, tetrahydronaphthalene moiety), 1.74 (m, 4H, tetrahydronaphthalene moiety), 1.24 (t, 3H, -CH$_2$C*H*$_3$). MS (EI, *m/z* (%)): 341 ([M+1]$^{\cdot}$, 2.9), 248 (4.7), 158 (14.1), 96(27.1), 55 (100.0).

2-Amino-3-cyano-6-(5,6,7,8-tetrahydronaphthalen-2-yl) iso-nicotinic acid (**5b**): Color: Pale green. Yield: 52 %. M.p.: 191-192 °C. FT-IR (KBr, ν, cm^{-1}): 3457 (ν_{OH}), 3345, 3210 (ν_{NH2}), 2209 ($\nu_{C\equiv N}$), 1699 ($\nu_{C=O}$, acid), 1678 ($\nu_{C=N}$), 1603 ($\nu_{C=C}$). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 7.78-7.23 (m, 4H, Ar-H), 3.30 (s, 2H, exchangeable, N*H*$_2$), 2.99 (m, 4H, tetrahdronaphthalene moiety), 1.75 (m, 4H, tetrahdronaphthalene moiety). MS (EI, *m/z* (%)): 294 ([M+1]$^{\cdot}$, 27.7), 280 (35.8), 226 (23.6), 127 (44.2), 110 (65.5), 76 (78.0), 56 (100.0).

2-(5,6,7,8-Tetrahydronaphthalen-2-yl)-5,6,7,8-tetrahydro quinoline-4-carboxylic acid (**5c**): Color: Pale brown. Yield: 67 %. M.p.: 183-185 °C. FT-IR (KBr, ν, cm^{-1}): 3386 (ν_{OH}), 1724 ($\nu_{C=O}$ acid), 1682 ($\nu_{C=N}$), 1603 ($\nu_{C=C}$). ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm): 7.65-7.16(m, 4H, Ar-H), 2.79 (m, 8H, tetrahdro naphthalene, cyclohexane moiety), 1.82 (m, 8H, cyclohaxane, tetrahdronaphthalene moiety). MS (EI, *m/z* (%)): 307 (M$^{\cdot}$, 34.2), 263 (34.2), 230 (21.1), 185 (34.2), 159 (100.0), 131(18.4), 129 (39.5), 91 (73.7).

2.2.5. 2-Amino-4-(carboxy)-6-(5,6,7,8-tetrahydro naphthalen-2-yl)nicotinohydrazide (6)

A mixture of isonicotinic acid derivative **5a** (0.005 mmol, 1.7 g) and hydrazine hydrate (0.005 mmol, 0.25 mL) in ethanol (20 mL) was refluxed for 14h, left to cool. The crude solid product that deposited after cooling was collected by filtration, dried and recrystallized from light petroleum ether (80-100°C): ethanol (3:1) to give compound **6** (Scheme 1). Color: Pale brown. Yield: 52 %. M.p.: 260 °C decomp. FT-IR (KBr, cm^{-1}): 3401 (ν_{OH}), 1713 ($\nu_{C=O,}$ acid), 1672 ($\nu_{C=O,}$ amide), 1613 ($\nu_{C=C}$). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 8.30 (s, 1H, exchangeable, N*H*), 7.72-7.03 (m, 4H, Ar-H), 3.68 (br.s, 4H, exchangeable, N*H*$_2$ & -NHN*H*$_2$), 2.81(m, 4H, tetrahydronaphthalene moiety), 1.65 (m, 4H, tetrahydronaphthalene moiety). MS (EI, *m/z* (%)): 325 ([M-1]$^{\cdot}$, 20.0), 226 (57.5), 159 (57.5), 127(57.5), 91 (75.0), 64 (100.0).

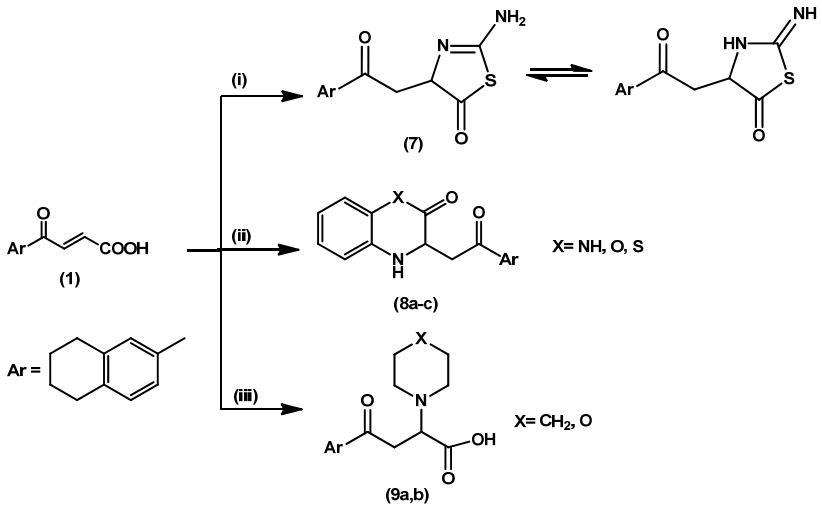
2.2.6. 2-Amino-4-(2-oxo-2-(5,6,7,8-tetrahydronaphthalen-2-yl)ethyl)thiazol-5(4H)-one (7)

A mixture of acid **1** (0.01 mmol, 2.30 g) and thiourea (0.01 mmol, 0.76 g) in dry ethanol (20 mL) with 2 drops of glacial acetic acid was refluxed for 4h, left to cool, the precipitated solid was collected, dried and recrystallized from ethanol to afford compound **7** (Scheme 2). Color: Pale yellow. Yield: 83 %. M.p.: 192-193 °C. FT-IR (KBr, ν, cm^{-1}): 3381, 3273 (ν_{NH}), 1672 ($\nu_{C=O}$ acid), 1610 ($\nu_{C=C}$). ^{1}H NMR spectrum (300 MHz, DMSO-d_6, δ, ppm): 8.95 (s, 1H, N*H*, D_2O-exchangeable), 8.79 (s, 1H, N*H*, D_2O-exchangeable), 7.69-7.19 (m, 3H, Ar-H), 7.03 (br.s 2H, N*H*$_2$, D_2O-exchangeable), 4.39 (dd, 1H, $j_{vic,cis}$ = 10.8 Hz, $J_{vic,tr.}$ = 3.3 Hz, H_c), 3.89 (dd, 1H, $J_{gem.}$ = 18.6 Hz, $J_{vic,tr}$ = 3.0 Hz, H_a) 3.40(dd, 1H, $J_{gem.}$ = 18.6 Hz, $J_{vic,cis}$ = 10.8 Hz, H_b), 2.78 (m, 4H, tetrahydro naphthalene moiety), 1.75 (m, 4H, tetrahydronaphthalene moiety). MS (EI, *m/z* (%)): 288 (M$^{\cdot}$, 27.3), 159 (100.0), 131 (30.3), 129 (79.8).

2.2.7. Reaction of acid 1 with o-phenylendiamine, o-amino phenol and /or o-aminothiophenol

A mixture of acid **1** (0.01 mmol, 2.30 g) and *o*-phenylenediamine, *o*-aminophenol and / or *o*-aminothiophenol (0.01 mmol) in ethanol (20 ml) containing few drops of glacial acetic acid, was heated at reflux for 4-7h. After cooling, the precipitated solid was collected, dried and recrystallized from DMF, ethanol and/or benzene:ethanol (2:1) to give compounds **8a**,**b** and **c** (Scheme 2).

3-(2-Oxo-2-(5,6,7,8-tetrahydro-naphthalen-2-yl)ethyl)-3,4-dihydroquinoxalin-2(1H)-one (**8a**): Color: Reddish brown. Yield: 73 %. M.p.: >300 °C. FT-IR (KBr, ν, cm^{-1}): 3349 (ν_{NH}), 1724 ($\nu_{C=O,}$ quinoxalinone), 1676 ($\nu_{C=O,}$ ketone), 1603 ($\nu_{C=C}$).



Scheme 2

^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 8.56 (s, 1H, exchangeable, -CON*H*), 7.68-6.54 (m, 7H, Ar-H), 4.26 (s, 1H, exchangeable, N*H*), 4.05 (t, 1H, quinoxalinone moiety), 3.15 (d, 2H, C*H*$_2$CO), 2.79 (m, 4H, tetrahydronaphthalene moiety), 1.68 (m, 4H, tetrahydronaphthalene moiety). MS (EI, *m/z* (%)): 320 (M‡, 42.9), 285 (35.7), 179(28.6), 159 (42.9), 149 (50.0), 55 (100.0).

3-(2-Oxo-2-(5,6,7,8-tetrahydronaphthalen-2-yl)ethyl)-3,4-dihydrobenzo[b][1,4]oxazin-2-one (**8b**): Color: Dark brown. Yield: 34 %. M.p.: 181 °C decomp. FT-IR (KBr, ν, cm^{-1}): 3338 (ν_{NH}), 1713 ($\nu_{C=O}$ oxazinone), 1678 ($\nu_{C=O}$ ketone), 1603 ($\nu_{C=C}$). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 7.72-6.65 (m, 7H, Ar-H), 4.32 (s, 1H, exchangeable, N*H*), 4.00 (t, 1H, oxazinone moiety), 3.20 (d, 2H, -C*H*$_2$CO), 2.82 (m, 4H, tetrahydronaphthalene moiety), 1.64 (m, 4H, tetrahydronaphthalene moiety). MS (EI, *m/z* (%)): 324 ([M+3]‡, 23.5), 303 (76.5), 275 (35.3), 254 (23.5), 185(58.8), 159 (88.2), 129(23.5), 91(64.7), 63 (100.0).

3-(2-Oxo-2-(5,6,7,8-tetrahydronaphthalen-2-yl)ethyl)-3,4-dihydrobenzo[b][1,4]thiazin-2-one (**8c**): Color: Pale brown. Yield: 32%. M.p.: 252 decomp. FT-IR (KBr, ν, cm^{-1}): 3375 (ν_{NH}), 1713 ($\nu_{C=O}$, thiazinone), 1678 ($\nu_{C=O}$, ketone), 1608($\nu_{C=C}$). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 7.59-6.32 (m, 7H, Ar-H), 4.30 (s, 1H, exchangeable, N*H*), 4.08 (t, 1H, thiazinone moiety), 3.21 (d, 2H, -C*H*$_2$CO), 2.80 (m, 4H, tetrahdronaphthalene moiety), 1.60 (m, 4H, tetrahdronaphthalene moiety). MS (EI, *m/z* (%)): 337 (M‡, 35.7), 277 (42.9), 262 (64.3), 228 (50.0), 211 (50.0), 191 (50.0), 177 (57.1), 164 (64.3), 155 (50.0), 148 (100.0), 138 (57.1), 124 (71.4).

2.2.8. Reaction of acid 1 with piperidine and/or morpholin

A mixture of acid **1** (0.01 mmol, 2.3 g) and piperidine and/or morpholin (0.01 mmol) in ethanol (20 mL) was heated at reflux temperature for 14-19 h, left to cool, the precipitated solid was collected, dried and recrystallized from ethanol and/or diluted dioxane to give compound **9a**,**b**, respectively (Scheme 2).

4-Oxo-2-(piperidin-1-yl)-4-(5,6,7,8-tetrahydronaphthalen-2-yl)butanoic acid (**9a**): Color: Yellow crystals. Yield: 47 %. M.p.: 162 °C decomp. FT-IR (KBr, ν, cm^{-1}): 3400 (ν_{OH}), (1730 ($\nu_{C=O}$, acid), 1678 ($\nu_{C=O}$, ketone), 1604 ($\nu_{C=C}$). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 7.47-7.09 (m, 3H, Ar-H), 4.12 (t, 1H, CH$_2$-C*H*-N-), 3.02 (d, 2H, C*H*$_2$-CH-N-), 2.83 (m, 4H, tetrahydronaphthalene moiety), 2.20 (t, 4H, piperidine moiety), 1.58 (m, 10H, tetrahydro naphthalene, piperidine moiety). MS (EI, *m/z* (%)): 314 ([M-1]‡, 18.5), 290 (44.4), 264 (25.9), 236 (55.6), 224 (37.0), 215(25.9), 159 (66.7), 144 (55.6), 129 (81.5), 118 (74.1), 64 (100.0).

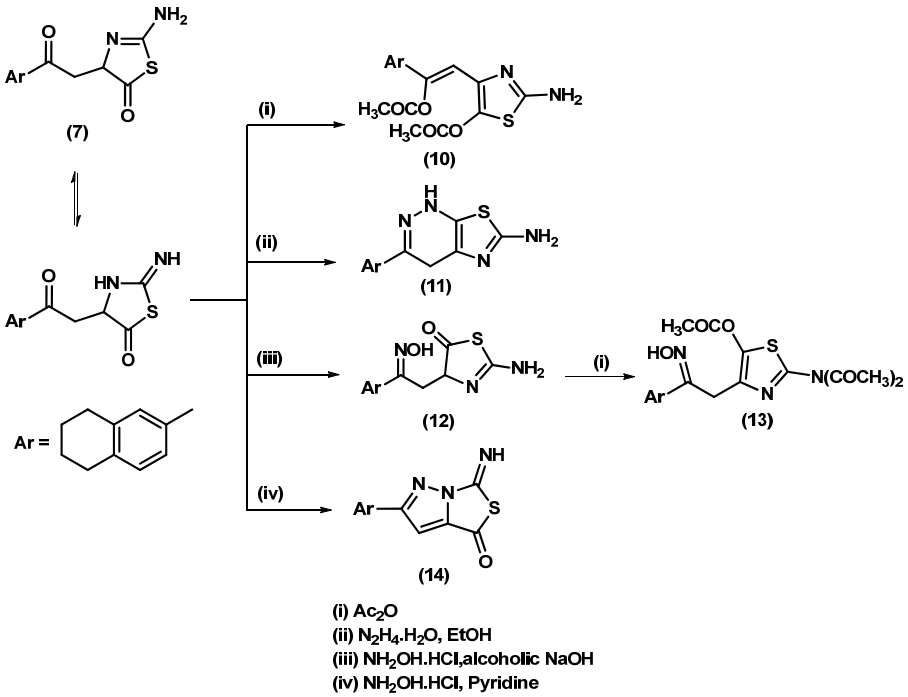
2-Morpholino-4-oxo-4-(5,6,7,8-tetrahydronaphthalen-2-yl) butanoic acid (**9b**): Color: Pale brown. Yield: 49 %. M.p.: > 300°C. FT-IR (KBr, ν, cm^{-1}): 3424 (ν_{OH}), 1707 ($\nu_{C=O}$, acid), 1679 ($\nu_{C=O}$, ketone), 1603 ($\nu_{C=C}$). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 7.50-7.10 (m, 3H, Ar-H), 4.00 (t, 1H, CH$_2$-C*H*-N-), 3.56 (t, 4H, morpholine moiety), 2.98 (d, 2H, C*H*$_2$-CH-N-), 2.79 (m, 4H, tetrahydronaphthalene moiety), 2.35 (t, 4H, morpholine moiety), 1.63 (m, 4H, tetrahydronaphthalene moiety). MS (EI, *m/z* (%)): 317 (M‡, 18.2), 185 (45.5), 159 (100.0), 129(54.5), 91(40.9), 57 (77.3).

2.2.9. 2-[5-(acetyloxy)-2-amino-1,3-thiazol-4-yl]-1-(5,6,7,8-tetrahydronaphthalen-2-yl)vinyl acetate (10)

A solution of thiazolone **7** (0.005 mmol, 1.44 g) in acetic anhydride (10 mL) was refluxed on water bath for 10 h, then poured into ice/cold water with stirring. The crude solid product that deposited was collected by filtration, washed with water, dried and recrystallized from aqueous dioxane to give compound **10** (Scheme 3). Color: Pale yellow. Yield: 43 %. M.p.: 147 °C decomp. FT-IR (KBr, ν, cm^{-1}): 3244, 3197 (ν_{NH2}), 1764, 1707 ($\nu_{C=O}$ esters). ^{1}H NMR (300 MHz, CDCl$_3$, δ, ppm): 7.66-7.10 (m, 3H, ArH), 6.78 (s, 1H, C*H*=C-OCOCH$_3$), 4.26 (s, 2H, NH$_2$, D$_2$O-exchangeable), 3.03-2.23 (m, 4H, tetrahydronaphthalene moiety), 1.82 (s, 6H, -2COCH$_3$), 1.49-1.33 (m, 4H, tetrahydro naphthalene moiety). MS (EI, *m/z* (%)): 374 ([M+2]‡, 17.49), 373 ([M+1]‡, 13.39), 372 ([M]‡, 12.31), 159 (16.41), 131 (14.25), 129 (17.09), 80 (81.64), 64 (100.0).

2.2.10. 3-(5,6,7,8-Tetrahydronaphthalen-2-yl)-1,4-dihydrothiazolo[5,4-c]pyridazin-6-amine (11)

A mixture of thiazolone **7** (0.005 mmol, 1.44 g) and hydrazine hydrate (0.005 mmol, 0.25 mL) in ethanol (20 mL) was heated at reflux temperature for 3 h left to cool the solid product was collected, dried and recrystallized from DMF to give compound **11** (Scheme 3). Color: Red. Yield: 60%. M.p.: 238 °C decomp. FT-IR (KBr, ν, cm^{-1}): 3414 & 3310 (ν_{NH2}, $\nu_{NH)}$,1658 ($\nu_{C=N}$).



Scheme 3

^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 8.01 (s, 1H, N*H*, D_2O-exchangeable), 7.80-7.08 (m, 3H, ArH), 4.20 (s, 2H, NH_2, D_2O-exchangeable), 2.82-2.72 (m, 4H, tetrahydronaphthalene moiety), 2.44(s, 2H, pyridazine moiety), 1.90-1.70 (m, 4H, tetrahydronaphthalene moiety). MS (EI, *m/z* (%)): 284 ($M^{\ddagger}$, 10.0), 283 ($[M-1]^{\ddagger}$, 20.0), 228 (20.0), 157 (23.3), 131(73.3), 114 (46.7), 64 (100.0).

2.2.11. 2-Amino-4-(2-(hydroxyimino)-2-(5,6,7,8-tetrahydro naphthalen-2-yl)ethyl)thiazol-5(4H)-one (12)

A mixture of thiazolone **7** (0.005 mmol, 1.44 g) and hydroxylamine hydrochloride (0.005 mmol, 0.35 g) and NaOH (0.02 mmol, 0.8 g) in ethanol (20 mL) was refluxed for 8 h. The solid product that deposited on hot was collected by filtration, dried and recrystallized with DMF to give compound **12** (Scheme 3). Color: Pale brown. Yield: 15 %. M.p.: > 300 °C. FT-IR (KBr, ν, cm^{-1}): 3369 (ν_{OH} & ν_{NH2}), 1674 ($\nu_{C=O}$), 1599 ($\nu_{C=N}$). ^{1}H NMR spectrum (300 MHz, DMSO-d_6, δ, ppm): 7.77-7.56 (m, 3H, ArH), 4.36 (s, 2H, N*H*$_2$, D_2O-exchangeable), 3.85 (s, 2H, N=C-C*H*$_2$), 2.85-2.78 (m, 4H, tetrahydronaphthalene moiety), 2.52 (s, 1H, CH, thiazolone moiety), 2.31 (s, 1H, OH, D_2O-exchangeable), 1.66-1.54 (m, 4H, tetrahydronaphthalene moiety). MS (EI, *m/z* (%)): 305 ($[M+2]^{\ddagger}$, 12.2), 258 (14.6), 199 (12.2), 159(100.0), 144 (24.4), 129 (43.9), 115 (34.1), 98 (43.9).

2.2.12. 2-Diacetylamino-4-(2-(hydroxyimino)-2-(5,6,7,8-tetrahydronaphthalen-2-yl)ethyl)thiazol-5-yl acetate (13)

A mixture of compound **12** (0.25 g) and acetic anhydride (10 mL) was heated at reflux for 2h, Then poured in ice/cold water with stirring. The crude solid product that deposited was collected by filtration, washed with water, dried and recrystallized from dioxane to give compound **13** (Scheme 3). Color: Black. Yield: 42 %. M.p.: 263 °C decomp. FT-IR (KBr, ν, cm^{-1}): 3438 (ν_{OH}), 1766 ($\nu_{C=O}$ ester), 1716 ($\nu_{C=O}$ imide), 1605 ($\nu_{C=C}$). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 7.72-7.23 (m, 3H, Ar-H), 4.05 (s, 2H, NOH=C-C*H*$_2$), 2.80-2.69 (m, 4H, tetrahydronaphthalene moiety), 2.26 (s, 1H, O*H*, D_2O-exchangeable), 2.20 (s, 6H, -N(COC*H*$_3$)$_2$), 1.98 (s, 3H, C*H*$_3$COO), 1.67-1.60 (m, 4H, tetrahydronaphthalene moiety). MS (EI, *m/z* (%)): 370 ($[M-OCOCH_3]^{\ddagger}$, 31.6), 233 (31.6), 227 (42.1), 186 (36.8), 162 (36.8), 129 (47.4), 121 (68.4), 105 (31.6), 55 (100.0).

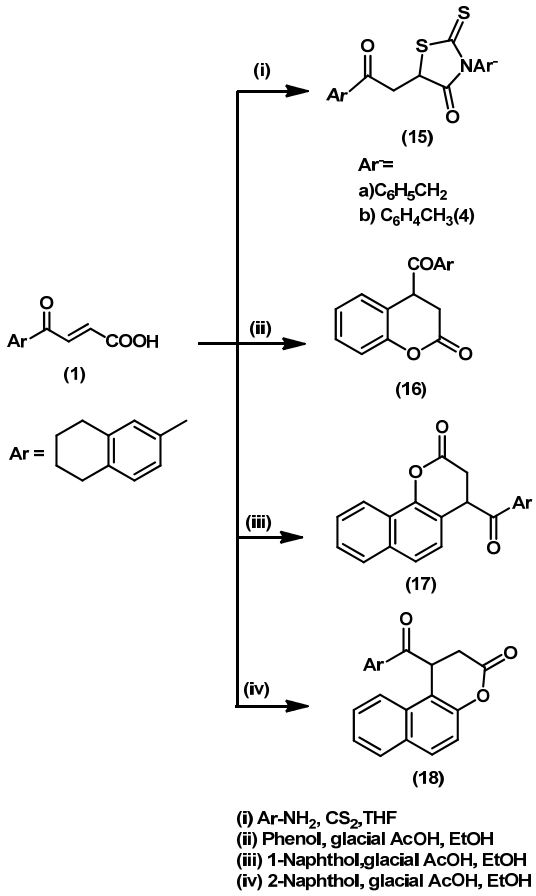
2.2.13. 6-Imino-2-(5,6,7,8-tetrahydronaphthalen-2-yl) pyrazolo[1,5-c]thiazol-4(6H)-one (14)

A mixture of thiazolone **7** (0.005 mmol, 1.44 g) and hydroxylamine hydrochloride (0.005 mmol, 0.35 g) in pyridine (15 mL) was refluxed for 6 h. Then the reaction mixture was poured into cold water the crude product that deposited was filtered off, washed with water, dried and recrystallized from ethanol to give compound **14** (Scheme 3). Color: Pale green. Yield: 45 %. M.p.: 193-195 °C. FT-IR (KBr, ν, cm^{-1}): 3285 (ν_{NH}), 1706 ($\nu_{C=O}$), 1640 ($\nu_{C=N}$), 1607 ($\nu_{C=C}$). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 7.25-6.99 (m, 4H, Ar-H), 4.50 (s, 1H, N*H*, D_2O-exchangeable), 2.81-2.72 (m, 4H, tetrahydronaphthalene moiety), 1.65-1.58 (m, 4H, tetrahydronaphthalene moiety). MS (EI, *m/z* (%)): 281 ($M-2]^{\ddagger}$, 84.2), 280 (68.4), 265 (42.1), 238 (47.4), 224 (36.8), 210 (47.4), 194 (42.1), 177 (26.2), 128 (68.4), 112 (42.1), 96 (63.2), 54 (100.0).

2.2.14. Reaction of acid 1 with benzylamine and/or p-toluidine in presence of carbon disulphide

To a solution of benzylamine and/or *p*-toulidine (0.015 mmol) in THF (20 mL) and carbon disulphide (0.03 mmol, 2.28 mL), compound **1** (0.01 mmol, 2.3 g) was added and continuously stirred at room temperature for 4h, the crude product was filtered off, dried and recrystallized from ethanol, to give compounds **15a**,**b**, respectively (Scheme 4).

3-Benzyl-5-(2-oxo-2-(5,6,7,8-tetrahydronaphthalen-2-yl) ethyl)-2-thioxothiazolidin-4-one (**15a**): Color: Yellow crystals. Yield: 43 %. M.p.: 184-186 °C. FT-IR (KBr, ν, cm^{-1}): 1724 ($\nu_{C=O}$, thiazolidinone), 1677 ($\nu_{C=O}$, ketone), 1603 ($\nu_{C=C}$).



Scheme 4

^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 7.65-7.06 (m, 8H, Ar-H), 4.50 (s, 2H, -NCH_2), 4.02 (dd, 1H, $j_{vic,cis}$= 10.6 Hz, $J_{vic,tr.}$ = 3.0 Hz, H_c, thioxothiazolidinone moiety), 3.67 (dd, 1H, $J_{gem.}$ = 18.8 Hz, $J_{vic,tr}$ = 3.0 Hz, H_a, COCH_2), 3.30 (dd, 1H, $J_{gem.}$ = 18.8 Hz, $J_{vic,cis}$ = 10.6 Hz, H_b, COCH_2), 2.82 (m, 4H, tetrahydronaphthalene moiety), 1.67 (m, 4H, tetrahydronaphthalene moiety). MS (EI, *m/z* (%)): 304 ([M-C_6H_5-CH_2-]$^{\bullet+}$, 1.29), 172 (0.99), 159 (45.05), 131 (13.25), 91 (100.0).

5-(2-Oxo-2-(5,6,7,8-tetrahydronaphthalen-2-yl)ethyl)-2-thioxo-3-p-tolylthiazolidin-4-one (**15b**): Color: Brownish yellow. Yield: 64 %. M.p.: 222 °C decomp. FT-IR (KBr, ν, cm^{-1}): 1730($\nu_{C=O}$, thiazolidinone), 1677($\nu_{C=O}$, ketone), 1603 ($\nu_{C=C}$). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 7.73-7.00 (m, 7H, Ar-H), 4.05 (dd, 1H, $j_{vic,cis}$ = 10.3 Hz, $J_{vic,tr.}$ = 3.1 Hz, H_c, thiazolidinone moiety), 3.69 (dd, J_{gem} = 18.4 Hz, $J_{vic,tr}$ = 3.1 Hz, 1H, H_a, COCH_2), 3.41 (dd, $J_{gem.}$ = 18.4 Hz, $J_{vic,cis}$ = 10.3 Hz, 1H, H_b, COCH_2), 2.85 (m, 4H, tetrahydronaphthalene moiety), 2.41 (s, 3H, CH_3), 1.65 (m, 4H, tetrahydronaphthalene moiety). MS (EI, *m/z* (%)): 304 ([M-$C_6H_4CH_3$ (4)]$^{\bullet+}$, 0.65), 159 (100.0), 131 (17.05), 91 (17.05).

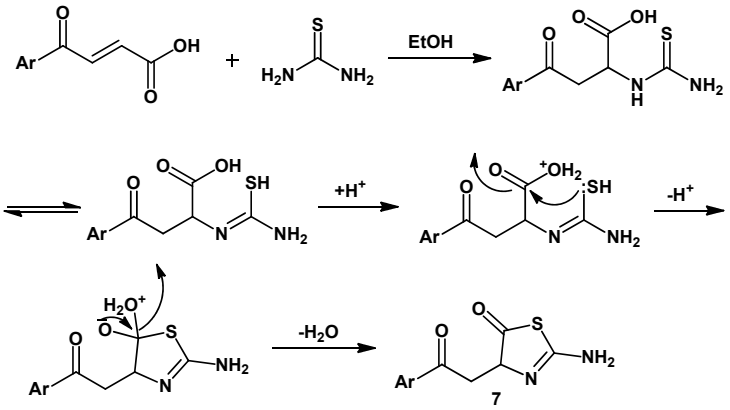
2.2.15. Reaction of acid 1 with phenol, α- and / or β-naphthols

To a solution of acid **1** (0.005 mmol, 1.15 g) in ethanol (30 mL), phenol α- and/or β-naphthols (0.005 mmol) and (1 mL) of glacial acetic acid was added. The mixture reaction was refluxed for 4 h. left to cool the precipitated solid was filtered off, dried and recrystallized from diluted dioxane & benzene and/or dioxane to give compounds **16-18**, respectively (Scheme 4).

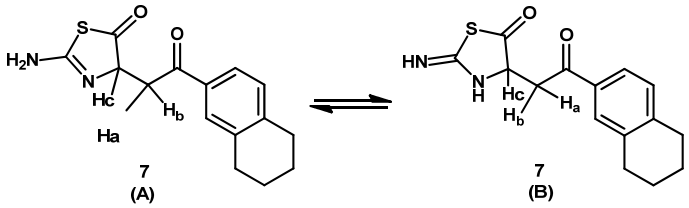
4-(1,2,3,4-Tetrahydronaphthalene-6-carbonyl)-3,4-dihydro chromen-2-one (**16**): Color: Brown. Yield: 42%. M.p.: 152 °C decomp. FT-IR (KBr, ν, cm^{-1}): 1730 ($\nu_{C=O}$, coumarin), 1679 ($\nu_{C=O}$, ketone), 1604 ($\nu_{C=C}$). ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm): 7.62-7.13 (m, 7H, Ar-H), 4.02 (t, 1H, coumarin moiety), 2.79 (d, 2H, coumarin moiety), 1.80 (m, 4H, tetrahydronaphthalene moiety), 1.25 (m, 4H, tetrahydronaphthalene moiety). MS (EI, *m/z* (%)): 306 (M$^{\bullet+}$, 20.98), 159 (100.0), 147 (20.40), 131 (3.74), 119 (6.90).

4-(1,2,3,4-Tetrahydronaphthalene-7-carbonyl)-3,4-dihydro benzo[h]chromen-2-one (**17**): Color: Brownish yellow. Yield: 31 %. M.p.: > 300 °C. FT-IR (KBr, ν, cm^{-1}): 1724 ($\nu_{C=O}$ coumarin), 1677 ($\nu_{C=O}$ ketone), 1603 ($\nu_{C=C}$). ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm): 7.90-7.22 (m, 9H, Ar-H), 4.32 (t, 1H, coumarin moiety), 2.82 (d, 2H, coumarin moiety), 2.06 (m, 4H, tetrahydronapht halene moiety), 1.58 (m, 4H, tetrahydronaphthalene moiety). MS (EI, *m/z* (%)): 356 (M$^{\bullet+}$, 23.1), 230 (20.5), 184 (25.1), 159 (100.0), 131 (42.2), 91 (53.1).

1-(1,2,3,4-Tetrahydronaphthalene-7-carbonyl)-1,2-di-hydro benzo[f]chromen-3-one (**18**): Color: Pale brown. Yield: 30 %. M.p.: > 300 °C. FT-IR (KBr, ν, cm^{-1}): 1738 ($\nu_{C=O}$ coumarin), 1679 ($\nu_{C=O}$ ketone), 1603 ($\nu_{C=C}$). ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm): 7.85-7.09 (m, 9H, ArH), 4.52 (t, 1H, chromenone moiety), 2.77 (d, 2H, chromenone moiety), 2.10 (m, 4H, tetrahydro naphthalene moiety), 1.64 (m, 4H, tetrahydronaphthalene moiety). MS (EI, *m/z* (%)): 356 (M$^{\bullet+}$, 3.1), 230 (17.4), 184 (15.1), 159 (100.0), 131 (31.8), 91 (33.7).



Scheme 5



Scheme 6

3. Results and discussion

3.1. Chemistry

When acid **1** was submitted to react with cyclohexanone and/or camphor in the presence of alcoholic sodium hydroxide, it underwent carba-Michael addition to yield 4-oxobutanoic acid derivatives **2a**,**b**, respectively. Michael adduct **2a**,**b** has been allowed to react with hydrazine hydrate in 1:1 molar ratio in boiling ethanol to afford the pyridazinone derivatives, **3a**,**b**. On the other hand, when the reaction was conducted in the presence of excessive hydrazine hydrate it yielded the bis-hydrazone derivative, followed by dehydrogenation to yield the more thermodynamically stable products **4a**,**b**.

As a part of our programme involving utility of 4-(2-tetryl)-4-oxo-but-2-enoic acid (**1**) in the synthesis of some interesting heterocyclic compounds, the authors sought to investigate the behaviour of the acid **1** with ethyl cyanoacetate, malononitrile and/or cyclohexanone in the presence of ammonium acetate as basic catalyst. The isolated products have been identified as 2-amino-3-ethoxycarbonyl-6-(tetryl-2-yl)-pyridine-4-carboxy-lic acid (**5a**), 2-amino-6-tetryl-3-cyano-4-carboxylic acid (**5b**) and 2-(2-tetryl)-4-carboxy-5,6,7,8-tetrhydroquinoline (**5c**), respectively. When the enaminoester **5a** reacted with hydrazine hydrate in boiling ethanol, the corresponding hydrazide **6** (Scheme 1) was obtained.

2-Amino-4-(2-oxo-2-(5,6,7,8-tetrahydronaphthalen-2-yl) ethyl)thiazol-5(4H)-one (**7**) was obtained when acid **1** was allowed to react with thiourea, as nitrogen nucleophile, in boiling ethanol. Plausible mechanism of the reaction is shown in Scheme 5.

The ^{1}H NMR spectrum of product **7** revealed that it is present in solution, in dynamic equilibrium of two forms (A) and (B) with a ratio of 54.65 and 45.35%, respectively (Scheme 6).

The very thorough study of ^{1}H NMR spectrum of compound **7** showed a multiplet due to the presence of two diastereotopic protons of methylene group flanked between the carbonyl functionality of the tetroyl moiety and the methine group of thiazole nucleus. Due to the non-equivalence of protons Ha and Hb, they undergo geminal coupling with each other and each line of the two doublets couples with the stereogenic proton Hc to give the multiplet. The stereogenic proton Hc undergoes the vicinal coupling with the two diastereotopic protons Ha and Hb to give d × d signal.

Refluxing acid 1 with bidentate nucleophiles namely o-phenylenediamine, *o*-aminophenol and/or *o*-aminothiophenol in alcohol afforded satisfactory yields of quinoxalone (**8a**), 3(2-tetroylmethyl)3,4-dihydrobenzo-1,4-oxazin-2-one (**8b**) and (**8c**), respectively. Acid **1** added amines (piperidine and/or morpholine,) to the more reactive vinylic carbon (alpha carbon to the carboxyl group) to produce the α-amino-γ-ketoacids **9a**,**b** (Scheme 2).

The structure of 2-aminothiazolone **7** was chemically verified *via* acetylating with acetic anhydride in which all active OH hydrogens have been acetylated to afford derivative **10** (Scheme 3). The reaction of thiazole derivative **7** with hydrazine hydrate in boiling ethanol resulted in annulation reaction and afforded the thiazolopyridazine derivative **11** as a bicyclic fused heterocyclic system. Interactions of thiazole derivative **7** with hydroxyl amine hydrochloride in boiling ethanol in the presence of NaOH and/or in boiling pyridine yield the corresponding oxime **12** and pyrazolothiazole **14** as a second bicyclic fused heterocycle. Acetylation of oxime **12** *via* acetic anhydride yielded the acetoxy derivative **13** [21-23].

Thiazole derivatives represent an important class of heterocyclic compounds with expected biological activity and have considerable chemical and pharmacological importance. Particularly, they are useful as anticonvulsant activity [24], antimicrobial [25,26], anticancer [27] and anti-inflammatory [28]. This prompted us to synthesize new thiazole derivatives bearing a tetryl moiety with the aim of decreasing polarity of the thiazole derivatives. Thus, when acid **1** was submitted to react with ammonium benzyldithiocarbamate, and 4-tolyldithio carbamate in tetrahydrofuran, the corresponding 2-thioxo-1,3-thiazolidin-4-one derivatives **15a** and **15b** were obtained

(Scheme 4). The present work describes the reaction of 4-(2-tetryl)-4-oxo-but-2-enoic acid (**1**) with phenol, α and / or β-naphthols in ethanol containing drops of glacial acetic acid to give 4-tetroyl-3,4-dihydrocoumarine **16**, 4(2-tetryoyl)-3,4-dihydrobenzocoumarine derivatives **17** and **18**, respectively.

4. Conclusion

γ-Ketoacids could be utilized in heterocyclic synthesis of fused and non-fused systems *via* facile reactions with different mono and bi-dentate carbon, nitrogen, oxygen, sulfur nucleophiles.

Acknowledgement

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