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Aza-and carba-Michael Adducts as Building Blocks in Heterocyclic Synthesis

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Abstract – The present work deals with the reaction of 4-(4-bromo phenyl oxobut-2-enoic acid **1** with nitrogen and carbon nucleophiles afforded aza-and carb-Michael adducts **2, 3, 6, 9, 10, 11, 12, 13, 14** depending on the type of reagents and medium (neutral or basic) . The adducts **2** are used as a key starting materials to synthesize some hetrocycles include furanone **15**, oxazinone **16** and pyridazinone **17** derivatives .The behavior of the latter compounds towards different electrophilic and nucleophilic reagents were investigated.Hydrazinoysis of the carba- Michael adduct **6** afforded tetrahydrobenzo1,2-diazapene derivatives **7, 8.** The structure of the newly synthesized compounds were elucidated by elemental analysis and spectroscopic data

Keywords – 4- Bromo phenyl oxobut-2-enoic acid, Pyrazolone, Quinazolinone, Pyridoquinazoline quinoxaline, Furanone, oxazinone, Tetrahydroquinoline, 1, 2-Benzodiazapine, Pyridazinone

1. Introduction

β-aroylacrylic acids have an antiproliferative action against the human cervix carcinoma (Hela cells) [1], cytostatic activity used as an aid to study and determine factors affecting the human eye's UV filters [2], as aspergillus controller [3] and inhibitors of phospholipase [4]. Morever they have a marked increase in vitro-activity against gram positive bacteria [5] and anticancer [6]. They are used a key starting material due to their high electrophilicity, where the β-aroylacrylic acids react readily with nucleophilies including nitrogen and carbon nucleophiles afford either cyclic or normal Michael adducts depending on the nature of the attacking nucleophiles and the reaction medium (neutral,basic,acidic). As the Michael addition reaction may be considered an efficient tandem strategy for the construction of ring structures [7]-[9]. Therefore, this starting material will be directed to prepare the more interesting heterocyclic compounds of important biological activities which bearing 3 (2H)-pyridazinone moiety [10].

2. Materials and Method

All melting points are uncorrected and were determined on a Stuart electric melting point apparatus. Elemental analyses were carried out at the Micro analytical Center, National Research Center, Cairo, Egypt. By Elementar Viro El Microanalysis IR spectra (KBr) were recorded on infrared spectrometer FT-IR 400D using OMNIC program and are reported frequency of absorption in terms of cm^{-1} and H-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 CDC l3 and δ 2.51 ppm for DMSO-d6. C-NMR spectra were recorded on the same spectrometer at 100 MHz and referenced to solvent signals δ = 77 ppm for CDCl3 and δ 39.50 ppm for DMSO-d6.DEPT 135 NMR spectroscopy were used where appropriate to aid the assignment of signals in the H and 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.

2.1. General Procedure of starting Material in literature [11]

2.1.1. Compounds 2a-c

A mixture of 3-(4-bromobenzoyl)-prop-2-enoic acid (2.55 g; 0.01 mol) and 3, 5-dimethylpyrazole, 3-methyl and/or phenylpyrazol-2-en-5-one (0.01 mol) in 50 mL ethanol was.refluxed for 3 h. The reaction mixture was allowed to cool and the crude product was washed by petroleum ether (Boiling point: 40- 60 ^{0}C), and then, crystallized from toluene to give compounds 2

2.1.2. 4-(p-bromophenyl)-2-(3,5-dimethylpyrazol-1-yl)-4-oxobutanoic acid (2a))

Yield 83%. Melting point 165-167 ^{0}C. IR (KBr) 1680, 1720 (CO). 1HNMR spectrum (CDCl3) : δ 2.06 (s,3H,CH3), 2.20 (s,3H,CH3), 3.81(2dd,1Ha, (J=15.2, J=7.2) and 1Hb methylene protons, CH2-C=O, (J=15.2, J=5.1) diastereotopic protons), 4, 8 (dd,CH-COO,sterogenic methine proton , J=7.2, J=5.1), multiplet at 7.47 – 7.75 assigned for 4ArH aromatic protons, singlet 13.2 an acidic proton which exchanged in D_2O and 13C-NMR δ 13.8 (CH3), 21.3 (CH3), 34.4 (CH2) , 58.4 (CH), 102.3 (CH), 128.2 (CH), 129.2 (CH) ,129.5 (CH), 134.4(C), 138.1(C), 142.7(C), 145.0 (C), 173.2(C), 198.5(C). Anal.Calc. for C15H15BrN2O3:C51.30, H 4.31; found: C51.26, H 4.29. MS: m/z 353[M+2], 351[M], 307, 198, 154, 105, 96.

2.1.3. 4-(p-bromophenyl)-2-(3-methyl-5-oxo-4, 5-dihydropyrazol-1-yl)-4-oxobutanoic acid (2b)

Yield 74 %.Mp 180-181 ^{0}C. IR (KBr) 1617, 1630 (C=N), 1667, 1691, 1705(CO). 1HNMR spectrum (CDCl3) : δ 2.10(s,3H,CH3),2.09(s,2H,CH2),3.73 (2dd,1Ha, (J=15.2,

J=7.2) and 1Hb methylene protons , CH2-C=O, (J=15.2, J=5.1) diastereotopic protons), 4, 90 (dd,CH-COO,sterogenic methine proton , J=7.2, J=5.1) , 7.47 – 7.74 (m, 4H, 4ArH aromatic protons), 12.8 (brs,1H,OH, an acidic proton which exchanged in D2O) and 13C-NMR δ 16.8 (CH3), 34.7 (CH2) ,44.4 (CH),53.4 (CH),128.9 (C), 131.2 (CH) , 132.5 (CH) , 135.4(C),154.8(C),171.7(C),199.0 (C). Anal.Calc. for C14H13BrN2O4:C47.61, H 3.71; found: C 47.54, H 3.89.

2.1.4. 4-(p-bromophenyl)-2-(3-phenyl-5-oxo-4, 5-dihydropyrazol-1-yl)-4-oxobutanoic acid (2c)

Yield 81 %. Mp 169-171 ^{0}C. IR(KBr) 1630 (C=N), 1681, 1722(CO),3244(OH). 1HNMR (CDCl3) : δ 3.38(s,2H,CH2), 3.71 (2dd, 1Ha, (J=15.2, J=7.2) and 1Hb methylene protons , CH2-C=O, (J=15.2, J=5.1) diastereotopic protons), 4,95 (dd, CH-COO,sterogenic methine proton, J=7.2, J=5.1) , 5.76(s, 1H,pyrazole proton), 7.47 – 7.97 (m, 9H, 9ArH aromatic protons), 13.8 (brs, 1H,OH, an acidic proton which exchanged in D2O) and 13C-NMR δ 35.7 (CH2) , 43.4 (CH), 53.7 (CH), 125.9 (2CH), 126.2 (CH), 128.5 (2CH) ,129.2 (C), 132.2 (2CH), 132.8(2CH), 134.8(C), 136.4(C), 143.1(C),168.5(C), 171.7(C),199.6 (C). Anal.Calc. for C19H15BrN2O4:C54. 96, H 3.64; found: C 55. 04, H 3. 59.

2.1.5. 4-(p-bromophenyl)-2-(3-phenyl-5-oxo-4,5-dihydro-1H-pyrazol-4-yl)-4-oxobutanoic acid 3

The 3-(4-bromobenzoyl)-prop-2-enoic acid (2.55 g; 0.01 mol) was added to a stirred suspension of, 3-phenylpyrazol-2-en-5-one (1.60 g, 0.01 mol) in 50% sodium hydroxide (2 mL) in 20 mL ethanol. The reaction mixture was stirred at room tempature for 2 days, and the crude product was quenching with H2O and extracted with diethyl ether .The aqueous layer was acidified by dil.HCl. The solid that separated was filtered off,washed by petroleum ether (b.p 40-60 ^{o}C),dried and then, crystallized from benzene afford Michael adduct 3

Yield 66%.Mp 185-187 ^{o}C. IR (KBr) 1680, 1720 (CO), 3265 (NH). 1HNMR (DMSO-d6) : δ 3.51(2dd,1Ha,(J=15.2,J=7.2) and 1Hb methylene protons , CH2-C=O, (J=15.2, J=5.1) diastereotopic protons), 3.80 (dd,CH-COO,sterogenic methine proton , J=7.2,J=5.1),4.56 (d,1H,CH),multiplet at 7.47 – 7.95 assigned for 9ArH aromatic protons, singlet 10.2 an acidic NH proton which exchanged in D2O and 13C-NMR δ 38.4 (CH) ,39.6 (CH2),52.9 (CH),125.3 (2CH),127.2 (CH),128 (2CH), 129.2 (C) ,132.5 (2CH) , 132.4(2CH),134.1(C),135.7(C),161.0 (C),173.2(C),176.3(C),193.5(C). Anal.Calc. For C19H15BrN2O4: C54.96,H 3.64;found: C 55.01 , H 3.68. MS:m/z 371 [M-CO2],295,218,185,105.

2.1.6. Compounds 4, 5

An equimolar mixture of 3-(4-bromobenzoyl)-prop-2-enoic acid (2.55 g;0.01 mol) , 3-methyl pyrazol-2-en-5-one (1.20 g,0.01 mol) and anhydrous AlCl3 (0.01 mol)in 50 mL benzene . The reaction mixture was heated in water bath for 3 h, and the reaction mixture was left over night and then decomposed with ice/HCl.The excess solvent removed by steam distillation. The solid that separated was filtered off,washed by petroleum ether (B.p 40- 60 ^{o}C),dried and then, crystallized from toluene afford 5,ethanol afford 4

2.1.7. 4-(p-bromophenyl)-2-(5-phenyl-3-hydroxy-3, 4-dihydro-pyrazol-4-yl)-4-oxobutanoic acid 4

Yield 37%. M.p 190-192 ^{o}C. IR (KBr) 1613 (C=N), 1670, 1685, 1715 (CO), 3245 (NH), 3410 (OH). 1HNMR (CDCl3) : δ 3.51(2dd,1Ha,(J=15.2,J=7.2) and 1Hb methylene protons , CH2-C=O, (J=15.2, J=5.1) diastereotopic protons), 3.80 (2dt,CH-COO,sterogenic methine proton ,J=8.7, J=7.2,J=5.1),4.56 (d,1H,CH sterogenic methine proton of pyrazol,J=8.7),multiplet at 7.47 – 7.95 assigned for 9ArH aromatic protons, singlet 10.2 an acidic OH=NH proton and 11.3 assigned for COOH which exchanged in D2O and 13C-NMR δ 15.7(CH3), 39.4 (CH) ,40.6 (CH2),100.5 (CH),127.3 (CH),127.4 (CH),128 (CH), 129.2 (C) ,130.5 (C) , 131.4(CH),134.1(C), 161.0 (2C),170.2(C) .Anal.Calc. For C14H13BrN2O4: C 47.59, H 3.68; found: C 47.85, H 3.35. MS:m/z 354 [M+2],352 [M],334,138,105.

2.1.8. 4-[(2-(p-bromophenyl)-2-oxoethyl] 3-methyl-furo [2, 3-c] pyrazol-5(4H)-one 5

Yield 40%.M.p 165-167 ^{o}C. IR(KBr) 1613 (C=N),1685,1745 (CO), 3245 (NH). 1HNMR (CDCl3) : δ 3.71(dd,2H,(J=16.8,J=11.2), CH2) 4.16 (t,furanone proton , J=11.2), multiplet at 7.57 – 7.95 assigned for 9ArH aromatic protons, singlet 10.6 an acidic NH proton which exchanged in D2O and 13C-NMR δ 20.2(CH3) 39.4 (CH) ,40.6 (CH2),100.5 (CH),127.3 (CH),127.4 (CH),128 (CH), 129.2 (C) ,130.5 (C) , 131.4(CH),134.1(C), 161.2(C),166.2 (C),179.2(C) .Anal.Calc. For C14H11BrN2O3: C 50.15, H 3.28; found: C 50.85, H 3.12. MS:m/z 336 [M+2],334 [M],214,138,105.

2.1.9. Compounds 6a,b

The 3-(4-bromobenzoyl)-prop-2-enoic acid (2.55 g; 0.01 mol) was added to a stirred suspension of, cyclohexanone and /or camphor (0.01 mol) in 50% sodium hydroxide (2 mL) in 20 mL ethanol. The reaction mixture was stirred at room tempature for 2 days, and the crude product was quenching with H2O and extracted with diethyl ether .The aqueous layer was acidified by dil.HCl. The semisolid that separated was filtered off,washed by ether ,dried ,slaw evaporation,and then, crystallized from benzene afford Michael adduct 19.

2.1.10. 4-(p-bromophenyl)-2-(2-oxo-cyclohexyl)-4-oxobutanoic acid 6a

Yield 60 %.M.p 160-162 ^{o}C. IR(KBr) 1680, 1704 ,1720(CO) ,3422 (OH). 1HNMR (DMSO-d6) : 1.34-1.73(m,6H,3CH2 of cyc.hexyl proton),2.03-2.27 (m,2H,CH2CO,cyc.hexyl proton),2.63-2.75 (m,1H,sterogenic methine proton of cyc.hex.) 3.17 (2dd,CH-COO,sterogenic methineprotonJ=9.1,J=7.9,J=2.4),3.56(2dd,1Ha,(J=15.2,J=7.) and 1Hb methylene protons , CH2-C=O, (J=15.2, J=2.4) diastereotopic protons), 7.43-7.56 (m,4H,Ar-H),11.30 (brs,1H,OH) and 13C-NMR δ 20.8 (CH2), 24.3 (CH2), 24.7 (CH2),39.9(CH2), 40.4 (CH),41.3 (CH2), 51.4 (CH),129.3 (C), 130.8 (2CH), 135.2(C),178.2 (C) ,194.7 (C), 208.4(C). Anal.Calc. For C16H17BrO4: C54.41, H 4.85; found: C 54.67, H 4.55. MS:m/z 292[M-(CO2+OH)], 156,137,105.

2.1.11. 4-(p-bromophenyl)-2-(4, 7, 7-trimethyl-3-oxo-bicyclo [2, 2, 1] hepta-2-yl)-4-oxobutanoic acid 6b

Yield 65 %.M.p 197-198 ^{o}C. IR(KBr) 1690, 1710

,1759(CO) ,3362 (OH). 1HNMR (DMSO-d6) : 0.94 (s,3H, CH3),1.17 (s,3H,CH3),1.26 (s,3H,CH3.),1.48-1.71(m,4H,2CH2),1.87(t,1H,methine bridgehead), 3.17 (2dd,CH-COO,sterogenic methine proton J=9.7, J=7.9,J=2.4),3.25(dt,1H,attached,J=9.7),3.56(2dd,1Ha,(J=15. 2,J=7.9) and 1Hb methylene protons , CH2-C=O, (J=15.2, J=2.4) diastereotopic protons), 7.48-7.56 (m,4H,Ar-H),11.34 (brs,1H,OH) and 13C-NMR δ 11.8 (CH3), 18.3 (CH3), 18.7 (CH3),21.9(CH2), 26.8 (CH2),37.3 (CH2), 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) , 213.4(C).Anal.Calc. For C20H23BrO4: C58.98, H 5.69; found: C 59.15, H 5.85. MS:m/z 346[M-(CO2+OH)], 267,175,156,137.

2.1.12. Compounds 7, 8

A mixture of 6a, b (0.01 mol) and hydrazine hydrate and /or phenyl hydrazine (0.01mol) in ethanol (30 mL) and was heated under reflux for 5h. The reaction mixture was allowed to cool and the separated product was filtered,dried and were recrystallized from ethanol.

2.1.13. 3-(p-bromophenyl)-1-phenyl-4,5,6,7,8,9-hexa hydro-1H-benzo[c]1,2-diazepine-5-carboxlic acid 7

Yield 75 %.M.p 140-141 ^{o}C. IR (KBr) 1620(C=N), 1687 (CO) ,3390 (OH). 1HNMR (DMSO-d6) : 1.36-1.45(m,H,CH2),1.67-1.89 (m,4H,2CH2),2.14-2.30 (m,2H,CH2), 3.16 (oct,2H, methylene protons , CH2-C=O, diastereotopic protons) 3.17 (m,CH-COO,sterogenic methine proton), 6.88-7.46 (m4H,Ar-H),10.60 (brs,1H,OH) and 13C-NMR δ 22.6 (CH2), 26.1 (CH2), 27.7 (CH2), 31.1 (CH2),40.7 (CH2),46.3(CH), 112.4 (C),117.3 (2CH), 121.5 (C),123.1 (CH), 128.8 (2CH), 131.9(2CH),135.2 (C) ,137.7 (C) , 144.4(C),147.7 (C) , 171.4(C) Anal.Calc. For C22H21BrN2O2: C62.13, H 4.98; found: C 62.54, H 4.36. MS:m/z 379[M-(CO2)], 303,228,156,149,105.

2.1.14. 3-(p-bromophenyl)-1-phenyl-4,5,6,7,8,9-hexa hydro-1H-benzo[c]1,2-diazepine-5-carboxlic acid 8

Yield 81 %.M.p 129-131 ^{o}C. IR(KBr) 1617(C=N), 1577 (CO),3143 (NH) ,3405 (OH). : 0.94 (s,3H, CH3),1.07 (s,3H,CH3),1.12 (s,3H,CH3.),1.43-1.51(m,2H,CH2), 1.73-1.86(m,2H,CH2),1.99(t,1H,methine bridgehead, J=9.4Hz), 2.57 (2dd,CH-COO,sterogenic methine proton,J=7.9 , 6.5 , 2.4 Hz), 2.85 (dt,1H,attached,J=9.4, 6.5Hz),3.56 (2dd,1Ha,(J=15.2, J=7.9) and 1Hb methylene protons , CH2-C=O, (J=15.2, J=2.4) diastereotopic protons), 7.48-7.56 (m,4H,Ar-H),9.84 (brs,1H,NH) 12.23 (brs,1H,OH) and 13C-NMR δ 14.6 (CH3),18.1 (CH3), 20.7 (CH3), 22.1 (CH2),30.7 (CH2),41.1(CH2), 44.4 (CH),46.3 (CH), 50.5 (C),53.1 (C), 120.8 (C), 122.9(C),130.2 (2CH) ,131.7 (2CH) , 136.4(C),145.7 (C) , 150.4(C),171.1(C). Anal.Calc. for C20H23BrN2O2: C59.56, H 5.75; found: C 59.70, H 5.47.

2.1.15. Compounds of 9

The 3-(4-bromobenzoyl)-prop-2-enoic acid (2.55 g; 0.01 mol) was added to a stirred suspension of, 2-methyl-4(3H)-quinazolinone and /or 2-methyl-6, 8-dibromo-4(3H) quinazolinone (0.01 mol) in 30 mL ethanol. The reaction mixture was heated under reflux for 4h and concentrated under reduced pressure. The solid that separated after cooling was filtered off,washed by petroleum ether (B.p 40- 60 ^{o}C),dried and then, crystallized from ethanol.

2.1.16. 4-(p-bromophenyl)-2-(2-methyl-4-oxo-4H-quinazolin-3-yl)-4-oxo-butanoic acid (9a)

Yield 73%.M.p 189-191 ^{o}C. IR (KBr) 1680, 1702 (CO), 3200(OH). 1HNMR (DMSO-d6) : δ 2.3(s,3H,CH3), 3.81 (2dd,1Ha,(J=15.2,J=8.2) and 1Hb methylene protons , CH2-C=O, (J=15.2, J=5.1) diastereotopic protons), 4,55 (dd,CH-COO,sterogenic methine proton , J=8.2,J=5.1) ,7.45-7.90(m,8H, aromatic protons) and 13C-NMR δ 15.4 (CH3) ,42.1 (CH2),57.5 (CH),118.5 (C),126.8(2CH),127.4 (CH),128.3 (CH), 129.3 (CH), 131.2(2CH),137.2 (CH) ,139 (C H) , 141.4(C),149 (C),158.4 (C),160.8 (C), 173.7(C) ,194.5 (C).Anal.Calc. For C19H15BrN2O4: C 54.96, H 3.64; found: C 55.41, H 3.86. MS:m/z 232,198,187,105.

2.1.17. 4-(p-bromophenyl)-2-(6,8-dibromo-2-methyl-4-oxo-4H-quinazolin-3-yl)-4-oxo-butanoic acid(9b)

Yield 78%.M.p 216-218 ^{o}C. IR (KBr) 1668, 1695 (CO), 3350(OH). 1HNMR (DMSO-d6) : δ 2.20(s,3H,CH3), 3.82 (2dd,1Ha,(J=15.2,J=8.2) and 1Hb methylene protons , CH2-C=O, (J=15.2, J=5.1) diastereotopic protons), 4.83 (dd,CH-COO,sterogenic methine proton , J=8.2,J=5.1) ,7.45-7.80(m,6H, aromatic protons) and 13C-NMR δ 16.4 (CH3) ,36.1 (CH2),57.5 (CH),117.5 (C),126.8(C),127.4 (C),128.3 (CH), 129.3 (CH), 131.2(2CH),137.2 (2CH) ,139 (C) , 141.4(CH),149 (C),159.4 (C),161.8 (C), 170.7(C) ,196.5 (C).Anal.Calc. For C19H13Br3N2O4: C 39.82,H 2.29;found: C 40.20 , H 2.86. MS:m/z 376 (Br-C6H4-COCH2),244,201,105.

2.1.18. 3-[2-(p-bromophenyl)-2-oxoethyl](3,4-dihydro -1H-quinoxalin-2-one(10)

A mixture of 3-(4-bromobenzoyl)-prop-2-enoic acid (2.55 g;0.01 mol) and o-phenylene diamine (1.08 g;0.01 mol) in 30 mL ethanol was refluxed for 4 h. The reaction mixture was allowed to cool and the crude product was washed by petroleum ether (b.p 40- 60oC), and then, crystallized from ethanol.

Yield 83%.M.p 158-160 ^{o}C. IR(KBr) 1673,1685 (CO),3100(NH). 1HNMR (DMSO-d6) : δ 3.62 (2dd,1Ha,(J=15.2,J=9.2) and 1Hb methylene protons , CH2-C=O, (J=15.2, J=3.4) diastereotopic protons), 4.87 (dd,CH-COO,sterogenic methine proton , J=9.2,J=3.4), ,7.5-7.90(m,8H, aromatic protons) 9.80 (brs,1H,NH) 11.87 (brs ,1H,NH amide)and 13C-NMR δ 34.1 (CH2),57.4 (CH),114.5 (CH),118.5 (CH),120.8(CH),123.4 (CH),128.3 (C), 129.8 (C), 133.2(2CH),135.2 (2CH) ,136.7 (C) , 140.4(C),165.4 (C) ,193.5 (C).Anal.Calc. for C16H13BrN2O2 : C 55.67,H 3.80;found: C 55.09 , H 3.46. MS:m/z 347[M+2],345 (M),198,147,130.

2.1.19. 1-(p-bromophenyl)-5-oxo-7, 9-dibromo- pyrido[2,1-b]quinazolin-4-carboxylic acid(11)

The 3-(4-bromobenzoyl)-prop-2-enoic acid (2.55 g;0.01 mol) was added to a stirred suspension of , 2-methyl-4(3H)-quinazolinone (1.6 g;0.01 mol) in the presence of sodium methoxide (2mL,5 g sodium in10mL methanol) in 30 mL methanol . The reaction mixture was stirred at room tempature for 3 days, and the crude product was quenching

with H2O and extracted with diethyl ether .The aqueous layer was acidified by dil.HCl. The reaction mixture was heated under reflux for 2h in water bath. The separated solid was filtered,dried and was crystallized from toluene.

Yield 73%.M.p 170-172 ^{o}C. IR (KBr) 1663, 1705 (CO), 3400(OH). 1HNMR (DMSO-d6) : δ 2.62 (2dd,1Ha,(J=15.2,J=8.2) and 1Hb methylene protons , CH2-C=O, (J=15.2, J=3.4) diastereotopic protons), 3.69 (dd,CH-COO,sterogenic methine proton , J=8.2,J=3.4),7.26-7.89(m,7H, aromatic protons) 12.2 (brs ,1H,COOH)and 13C-NMR δ 42.1 (CH),55.0(CH2),98.4 (CH),104.5 (CH),118.5 (CH),120.8(CH),125.4 (CH),129.3 (CH), 129.8 (C), 130.2(CH),135.2 (C) ,139 (C) 140 (C), 141.4(C),145 (C),148.4 (C),160.8 (C), 176.7(C) ,194.5 (C).Anal.Calc. For C19H11Br3N2O3: C 41.08, H2.00; found: C 41.26, H 2.16.

2.1.20. 1-(p-bromophenyl)-6-hydroxy-pyrido [1, 2-a] quinazolin-3-carboxylic acid (12)

The 3-(4-bromobenzoyl)-prop-2-enoic acid (2.55 g; 0.01 mol) was added to a stirred suspension of, 2-methyl-4(3H)-quinazolinone (1.6 g; 0.01 mol) in the presence of few drops piperidine in 30 mL acetonitrile. The reaction mixture was heated under reflux for 2h in water bath. The reaction mixture was poured onto ice/HCl and the separated solid was filtered,dried and was crystallized from toluene.

Yield 73%.Mp 145-146 ^{o}C. IR (KBr) 1663, 1705 (CO), 3400(OH). 1HNMR (DMSO-d6) : δ 2.50(s,1H,methine proton), ,7.05-8.20(m,10H, aromatic protons) 11.2(s,1H,COOH),13.2 (brs ,1H,OH=NH,lactam-lactim dynamic equlibrium)and 13C-NMR δ 42.1 (CH),98.4 (CH),104.5 (CH),118.5 (CH),120.8(CH),125.4 (CH),129.3 (CH), 129.8 (2CH), 130.2(2CH),135.2 (C) ,139 (C) , 141.4(C),145 (C),148.4 (C),160.8 (C), 176.7(C) ,194.5 (C).Anal.Calc. For C19H13BrN2O3: C 57.45, H 3.30; found: C 57.29, H 3.16. MS:m/z 337[M-(CO2+OH),180,156,105.

2.1.21. Compounds 13a-c

A mixture of 2a-c(0.01 mol) and acetic anhydride (9.4 mL,0.1mol) and then refluxed on water bath for 2h. The excess acetic anhydride was removed by distillation and the separated product was filtered,dried and were recrystallized from mix toluene-ethanol to give compounds

2.1.22. 3,5-dimethyl 1N-[(5-(p-bromophenyl)-2-oxo –fur-3-yl]pyrazole (13a)

Yield 90%.Mp 261-263 ^{o}C. IR (KBr) 1765 (CO). 1HNMR (DMSO-d6) : δ 2.18(s,3H,CH3),2.2(s,3H,CH3),3.71(dd,2H,(J=16.8,J=11.2), CH2) 5.42 (d,furanone proton , J=4.2), 6.18(d,CH-furanone,J=4.2) multiplet at 7.40 – 7.55 assigned for 4ArH aromatic protons, singlet and 13C-NMR δ 10.3 (CH3),13.7(CH3),63.4 (CH) ,81.6 (CH),102.5 (CH),123.3 (C),127.4 (2CH),130 (2CH), 137.2 (C) ,139.5 (C) , 144.1(C),175.7(2C).Anal.Calc. For C15H13BrN2O2: C 54.07, H 3.3; found: C 54.41, H 3.26. MS:m/z 335 [M+2],333 [M],238,156,96.

2.1.23. 3-methyl 1N-[(5-(p-bromophenyl)-2-oxo –fur-3-yl] pyrazol-5(4H)-one (13b)

Yield 83%.Mp 273-275 ^{o}C. IR (KBr) 1695, 1790 (CO). 1HNMR (DMSO-d6) : δ 2.3(s,3H,CH3),3.71(s,2H,CH2 pyrazol), 5.42 (d,furanone proton , J=4.2), 6.33(d,CH-furanone,J=4.2) multiplet at 7.40 – 7.55 assigned for 4ArH aromatic protons, singlet and 13C-NMR δ 15.1(CH3),43.4 (CH2) ,62.1 (CH),93.5 (CH),124.5 (C),127.4 (2CH),128.3 (2CH), 129.3 (2CH), 137.2 (CH) , , 141.4(C), 173.7(C) .Anal.Calc. For C14H11BrN2O3: C 50.15, H 3.28; found: C51.41, H 3.26. MS:m/z 337 [M+2],335 [M],214,138,105,77.

2.1.24. 3-phenyl 1N-[(5-(p-bromophenyl)-2-oxo –fur-3-yl] pyrazol-5(4H)-one (13c

Yield 83%.Mp 295-297 ^{o}C. IR(KBr) 1695,1806 (CO). 1HNMR (DMSO-d6) : δ 3.45(s,2H,CH2 pyrazol), 5.42 (d,furanone proton , J=4.2), 6.33(d,CH-furanone,J=4.2) multiplet at 7.40 – 7.55 assigned for 4ArH aromatic protons, singlet and 13C-NMR δ 43.4 (CH2) ,62.1 (CH),93.5 (2CH),123.5 (C),124.8(2CH),127.4 (2CH),128.3 (2CH), 129.3 (2CH), 137.2 (C) ,139 (2C) , 141.4(C),169 (C) 173.7(C) .Anal.Calc. For C19H13BrN2O3: C 57.45, H 3.3; found: C 57.41, H 3.26. MS:m/z 399 [M+2],397 [M],320,241,160,77.

2.1.25. Compounds 16a-c

A mixture of 2a-c (0.01 mol) and hydroxyl amine (1.03 g; 0.015mol) in pyridine (20 mL) and then refluxed for 3h. The reaction mixture was poured onto ice/HCl and the separated solid was filtered,dried and were recrystallized from ethanol

2.1.26. 3-(p-bromophenyl)-5-(3, 5-dimethylpyrazol-1-yl)-6-oxo-4, 5-dihydro-1, 2-oxazine (14a)

Yield 90%.Mp 151-153 ^{o}C. IR (KBr) 1645(C=N), 1765 (CO). 1HNMR (CDCl3) : δ 1.99(s,3H,CH3),2.24(s,3H,CH3), 3.81 (2dd,1Ha,(J=15.2,J=8.2) and 1Hb methylene protons , CH2-C=O, (J=15.2, J=5.1) diastereotopic protons in oxazine ring), 4,95 (dd,CH-COO,sterogenic methine proton , J=8.2,J=5.1) , 5.76(s,1H,pyrazole proton) multiplet at 7.60 – 7.85 assigned for 4ArH aromatic protons, singlet and 13C-NMR δ 11.3 (CH3),13.7(CH3),63.4 (CH) ,32.6 (CH2),53.5 (CH),100.3 (CH),127.4 (2C),130 (2CH), 137.2 (C) ,139.5 (C) , 144.1(C),163.6 (C),175.7(C).Anal.Calc. For C15H14BrN3O2: C 51.74, H 4.05; found: C 51.41, H 4.26. MS:m/z 355 [M-CO2], 191,156,150,95.

2.1.27. 3-(p-bromophenyl)-5-(3-methyl-5-oxo-pyrazol-1-yl)-6-oxo-4, 5-dihydro-1, 2-oxazine (14b)

Yield 88%.Mp 142-144 ^{o}C. IR(KBr) 1685,1733 (CO). 1HNMR (DMSO-d6) : δ 2.3(s,3H,CH3),3.71(s,2H,CH2 pyrazol), 3.9 (2dd,1Ha,(J=15.2,J=7.2) and 1Hb methylene protons , CH2-C=O, (J=15.2, J=5.1) diastereotopic protons), 4,4 (dd,CH-COO,sterogenic methine proton , J=7.2,J=5.1) , multiplet at 7.40 – 7.55 assigned for 4ArH aromatic protons, singlet and 13C-NMR δ 19.1(CH3),47.4 (CH2) ,62.1 (CH),100.5 (CH),124.5 (C),126.4 (2CH),127.3 (2CH), 129.3 (2CH), 137.2 (CH) , , 141.4(C), 173.7(C) .Anal.Calc. For C14H12BrN3O3: C 48.00, H 3.43; found: C48.41, H 3.50. MS:m/z 352 [M+2],350 [M],214,138,105,77.

2.1.28. 3-(p-bromophenyl)-5-(3-phenyl-5-oxo-pyrazol-1-yl)-6-oxo-4,5-dihydro-1,2-oxazine(14c)

Yield 83%.Mp 200-202 ^{o}C. IR (KBr) 1695, 1738 (CO). 1HNMR (CDCl3) : δ 3.45(s,2H,CH2 pyrazol), 3.91 (2dd,1Ha,(J=15.2,J=8.2) and 1Hb methylene protons , CH2-C=O, (J=15.2, J=5.1) diastereotopic protons), 5,25 (dd,CH-COO,sterogenic methine proton , J=8.2,J=5.1) ,7.45-8.00(m,9H, aromatic protons) and 13C-NMR δ 30.4 (CH2) ,42.1 (CH),52.5 (CH),125.5 (C),126.8(2CH),127.4 (2CH),128.3 (CH), 129.3 (2CH), 131.2(2CH),137.2 (C) ,139 (2C) , 161.4(C),169 (C) 173.7(C) .Anal.Calc. For C19H13BrN2O3: C 57.45, H 3.3; found: C 57.41, H 3.26. MS:m/z 399 [M+2],397 [M],320,241,160,77.

2.1.29. Compounds 15a-c

A mixture of 2a-c (0.01 mol) and hydrazine hydrate (1 mL, 0.015mol) in ethanol (30 mL) and was refluxed for 3h. The reaction mixture was allowed to cool and the separated product was filtered,dried and were recrystallized from ethanol.

2.1.30. 6-(4-bromophenyl)-4-(3, 5-dimethyl-pyrazol-1-yl)-4, 5-dihydropyridazin-3(2H) one 15a

Yield 90%.Mp 209-211 ^{o}C. IR (KBr) 1651 (C=N), 1675 (CO), 3200(NH). 1HNMR (DMSO-d6) : 2.17 (s,6H,2CH3),δ 3.92 (2dd,1Ha,(J=15.2,J=7.9) and 1Hb methylene protons , CH2-C=O, (J=15.2, J=2.4) diastereotopic protons), 5.37 (dd,CH-COO,sterogenic methine proton , J=7.9,J=2.4),5.86 (s,1H,CH-pyrazol) ,7.53 (d,2H J=8.1,Ar-H), 7.96(d,2H, J=8.1,ArH) 10.85 (brs,1H,NH) and 13C-NMR δ 13.9 (CH3), 16.7 (CH3),33.4 (CH2),55.5 (CH),108.5 (CH),126.3(C),130.4 (2CH),132.3 (2CH), 139.8 (C), 138.2(2CH),150.2 (C) ,154.7 (C) , 163.4(C).Anal.Calc. For C15H15BrN4O: C 51.89, H 4.35; found: C 51.78, H 4.46. MS:m/z 268[M-Br],250 (M-3,5-dimethylpyrazole],224,195,143,115.

2.1.31. 6-(4-bromophenyl)-4-(3methyl-5-oxo-4, 5-dihydropyrazol-1-yl)-4, 5-dihydropyridazin-3(2H) one 15b

Yield 86%.Mp 230-232 ^{o}C. IR(KBr) 1651 (C=N),1673 (CO),3220-3310(NH). 1HNMR (DMSO-d6) : 1.97 (s,3H, CH3),3.32 (s,2H,CH2 of pyrazol), 3.86 (2dd,1Ha,(J=15.2,J=7.9) and 1Hb methylene protons , CH2-C=O, (J=15.2, J=2.4) diastereotopic protons), 4.47 (dd,CH-COO,sterogenic methine proton , J=7.9,J=2.4),7.53 (d,2H J=8.1,Ar-H), 7.96(d,2H, J=8.1,ArH) 11.75 (brs,1H,NH) and 13C-NMR δ 19.7 (CH3),32.4 (CH2),44.5 (CH2),54.6 (CH),125.3(C),130.4 (2CH),132.3 (2CH), 136.8 (C), 158.2(C),160.2 (C) ,164.7 (C) , 169.4(C).Anal.Calc. For C14H13BrN4O2 : C 48.16,H 3.75;found: C 48.48 , H 3.40.

2.1.32. 6-(4-bromophenyl)-4-(3-phenyl-5-oxo-4, 5-dihydropyrazol -yl)-4, 5-dihydropyridazin-3(2H) one 15c

Yield 86%.Mp 238-240 ^{o}C. IR (KBr) 1651 (C=N), 1679 (CO), 3220 (NH). 1HNMR (DMSO-d6) : 3.58 (s,2H,CH2 of pyrazol), 3.76 (2dd,1Ha,(J=15.2,J=7.9) and 1Hb methylene protons , CH2-C=O, (J=15.2, J=2.4) diastereotopic protons), 3.99 (dd,CH-COO,sterogenic methine proton , J=7.9,J=2.4),7.23-7.9 (m,9H, ,ArH) 11.89 (brs,1H,NH) and 13C-NMR δ 32.4 (CH2),44.2 (CH2),55.6 (CH),125.7(C),126.4 (2CH),130.3 (2CH), 132.8 (CH), 138.2(2CH),140.2 (2CH) ,144.7 (C) , 149.4(C) 154.2 (C) ,158.7 (C) , 161.4(C) 168.4(C).Anal.Calc. For C19H15BrN4O2: C 55.49, H 3.68; found: C 55.69, H 3.60.

2.1.33. 6-(4-bromophenyl)-3-chloro-4-(3, 5-dimethyl-pyrazol-1-yl)-4, 5-dihydropyridazin-3(2H) one 16

A mixture of 15a (3.47 g; 0.01 mol) and phosphorous pentachloride (1 g, 0.015mol) in phosphorous oxy chloride (20 mL) and was heated at 60 C in reflux for 2h. The excess oxy chloride was removed by vacuum distillation, and the reaction mixture was diluted with ice/H2O. The separated product was washed,filtered,dried and was crystallized from toluene.

Yield 80%.Mp 181-183 ^{o}C. 1HNMR (DMSO-d6) : δ 2.17 (s,6H, 2CH3), 3.72 (2dd,1Ha,(J=15.2,J=7.9) and 1Hb methylene protons , CH2-C=O, (J=15.2, J=2.4) diastereotopic protons), 5.37 (dd,CH-COO,sterogenic methine proton , J=7.9,J=2.4),5.96 (s,1H,CH-pyrazol) ,7.33 (d,2H J=8.1,Ar-H), 7.76(d,2H, J=8.1,ArH) , and 13C-NMR δ 12.9 (CH3), 15.7 (CH3), 29.5 (CH2),54.5 (2CH), 101.3 (CH), 126.8 (C), 132.2(2CH),134.2 (2CH) ,139.7 (C) , 141.7 (C) 153.4(C), 154.7(C), 165.7(C).Anal.Calc. For C15H14BrClN4: C 49.27, H 5.86; found: C 49.45, H 3.66. MS:m/z 332[M+2-Cl],330 ,175,156,95.

2.1.34. 6-(4-bromophenyl)-3-(2-oxoethylamino)-4-(3, 5-dimethyl-pyrazol-1-yl)-4, 5-dihydropyridazin-3(2H) one 17

A mixture of 16 (3.66 g; 0.01 mol) and ethanol amine (0.92 g, 0.015mol) in n-butanol(20 mL)and was heated under reflux for 4h. The reaction mixture was leaved overnight. The solid that separated was washed,filtered,dried and recrystallized from n-butanol.

Yield 83%.Mp 204-206 ^{o}C. 1651 (C=N),1680 (CO) 3498 (NH)/(OH) 1HNMR (DMSO-d6) : δ 2.07 (s,3H, CH3), 2.27 (s,3H, CH3), 3.51 (t,2H,CH2-N,J=6.4),3.72 (2dd,1Ha,(J=15.2,J=7.9) and 1Hb methylene protons , CH2-C=O, (J=15.2, J=2.4) diastereotopic protons),3.90 (t,2H,CH2-OH),4.84 (brs,1H,OH,J=6.4), 5.37 (dd,CH-COO,sterogenic methine proton , J=7.9,J=2.4),5.96 (s,1H,CH-pyrazol) ,7.33 (d,2H J=8.1,Ar-H), 7.76(d,2H, J=8.1,ArH) ,8.71 (brs,1H,NH) and 13C-NMR δ 12.9 (CH3), 15.7 (CH3), 31.5 (CH2),49.5 (CH), 50.5 (CH2),60.5 (CH2), 101.3 (CH), 126.8 (C), 131.2(2CH),134.2 (2CH) ,137.7 (C) , 140.7 (C) 153.4(C), 155.7(C), 164.7(C).Anal.Calc. For C17H20BrN5O: C 52.32, H 5.17; found: C 52.48, H 5.24. MS:m/z 392[M+2],390[M],330 ,236,156,95.

2.1.35. 6-(4-bromophenyl)-3-(2-morpholin-4-yl-ethylamino)-4-(3, 5-dimethyl-pyrazol-1-yl)-4, 5-dihydropyridazin-3(2H) one 18

A mixture of 17 (5.90 g; 0.01 mol) ,morpholine (1.3 g ; 0.01 mol) and conc HCl (0.5 mL) in ethanol(20 mL)and was heated under reflux for 3h. The reaction mixture was concentrated under vacuum. The solid that separated was washed,filtered,dried and recrystallized from ethanol.

Yield 83%.Mp 130-132 ^{o}C. 1632 (C=N), 3298 (NH). 1HNMR (DMSO-d6) : δ 2.05 (s,3H, CH3), 2.12 (s,3H, CH3), 2.40-2.46 (m,4H,2CH2N) , 3.40 (t,2H,CH2-morph.,J=6.1),3.51 (t,2H,CH2-N,J=6.1),3.77 (2dd,1Ha,(J=15.2,J=7.9) and 1Hb methylene protons , CH2-

C=O, (J=15.2, J=2.4) diastereotopic protons), 3.7 (m,4H,2CH2O) 4.84 (brs,1H,OH), 5.37 (dd,CH-COO,sterogenic methine proton , J=7.9,J=2.4),5.76 (s,1H,CH-pyrazol) ,7.33 (d,2H J=8.1,Ar-H), 7.76(d,2H, J=8.1,ArH) ,8.71 (brs,1H,NH) and 13C-NMR δ 12.9 (CH3), 15.7 (CH3), 32.5 (CH2),44.5 (CH2), 52.5 (CH),56.5 (2CH2), 57.4 (CH2), 67.8 (2CH2), 100.9 (CH), 126.4 (C), 130.2(2CH),133.2 (2CH) ,137.7 (C) , 140.2 (C) 153.4(C), 156.7(C), 163.7(C).Anal.Calc. For C21H27BrN6O: C 54.91, H 5.92; found: C 55.08, H 5.94. MS:m/z 461[M+2],459[M],330 ,236,156,95.

2.1.36. 6-(4-bromophenyl)-4-(3, 5-dimethyl-pyrazol-1-yl)-2-piperidin-1-ylmethyl4, 5-dihydropyridazin-3(2H) one 19

A mixture of 15a(3.47 g;0.01 mol), piperidine (1 mL,0.015mol) and formaldehyde (1 mL) in ethanol (30 mL)and was stirred at room temperature for 5 min. and few drops of HCl was added.The reaction mixture was refluxed for 6h. The excess solvent was removed by vacuum distillation, and the separated product was washed,filtered,dried and was crystallized from ethanol.

Yield72%.Mp 185-187 ^{o}C. IR(KBr) 1682 (CO).1HNMR (DMSO-d6) : δ 1.17-1.27 (m,6H,3CH2 piperidine moiety), 2.17 (s,6H,2CH3), 1.37 (m,4H,2CH2(pip) 3.92 (2dd,1Ha,(J=15.2,J=7.9) and 1Hb methylene protons , CH2-C=O, (J=15.2, J=2.4) diastereotopic protons), 5.37 (dd,CH-COO,sterogenic methine proton , J=7.9,J=2.4),5.96 (s,1H,CH-pyrazol) ,7.33 (d,2H J=8.1,Ar-H), 7.76(d,2H, J=8.1,ArH) , and 13C-NMR δ 13.9 (CH3), 15.7 (CH3),23.4 (CH2),26.5 (CH2), 28.5 (CH2),51.5 (2CH2),55.3(CH2),77.4 (CH2),102.3 (CH), 129.8 (2C), 131.2(2CH),140.2 (2CH) ,154.7 (CH) , 159.7 (2C) 163.4(C) 165.7(C).Anal.Calc. for C21H26BrN5O : C 56.76,H 5.90;found: C 56.45 , H 5.86. MS:m/z 346[M-C6H12N],281 ,224,191,156,84.

2.1.37. Compounds 20, 21

A mixture of 15c (4.11 g; 0.01 mol), ethylchloroformate 5 mL or ethyl chloroacetate 6.13 g (0.05mol) and anhydrous K2CO3 (5 g; 0.04 mol)in dry acetone (60 mL)and was refluxed for 24h.Excess solvent was removed by distillation. The reaction mixture was partitioned between H2O and diethyl ether 3 x 30 mL. The combined organic extracts were dried by anhydrous sodium sulphate and the separated products dried and were recrystallized from ethanol.

2.1.38. 6-(4-bromophenyl)-4-(3methyl-5-oxo-4, 5-dihydropyrazol-1-yl)-2-ethoxy carbonyl-4, 5-dihydropyridazin-3(2H) one 20

Yield 74%.Mp 110-112 ^{o}C. IR (KBr) 1696, 1753. 1HNMR (CDCl3) : 1.21 (t,3H, CH3,J=8.7), ,3.17 (s,2H,CH2 of pyrazol), 3.86 (2dd,1Ha,(J=15.2,J=7.9) and 1Hb methylene protons , CH2-C=O, (J=15.2, J=2.4) diastereotopic protons), 4.16 (q,2H.OCH2,J=8.7),4.47 (dd,CH-COO,sterogenic methine proton , J=7.9,J=2.4),7.23 (m,9H,Ar-H), and 13C-NMR δ 15.7 (CH3), 37.4 (CH2),44.7 (CH2),53.6 (CH), 64.7 (CH2),123.3(CH), 127.4 (2CH),129.3 (2CH), 130.4 (2CH),131.3 (2CH), 138.8 (C), 148.2(2C),161.2 (2C) ,163.7 (C) , 165.4(C), 167.8(C).Anal.Calc. For C22H19BrN4O4: C 55.75, H 3.83; found: C 55.58, H 3.62. MS:m/z 411[M-(CO2+CH2=CH2)],270,193,156,95

2.1.39. 6-(4-bromophenyl)-4-(3methyl-5-oxo-4, 5-dihydropyrazol-1-yl)-2-ethoxy carbonyl-4, 5-dihydropyridazin-3(2H) one 21

Yield 70%.Mp 120-121 ^{o}C. IR(KBr) 1685,1734 . 1HNMR (CDCl3) : 1.23 (t,3H, CH3,J=6.7), 3.23 (s,2H,CH2 of pyrazol), 3.93 (2dd,1Ha,(J=15.2,J=8.1) and 1Hb methylene protons , CH2-C=O, (J=15.2, J=2.4) diastereotopic protons), 4.16 (q,2H.OCH2,J=6.7),4.67 (dd,CH-COO,sterogenic methine proton , J=8.1,J=2.4),5.2 (s,2H,N-CH2-CO),7.43-7.72 (m,9H,Ar-H), and. 13C-NMR δ 13.7 (CH3), 32.4 (CH2),45.7 (CH2),47.6 (CH2), 52.7 (CH), 66.6 (CH2), 123.3(C), 124.4 (2CH),125.3 (2CH), 128.4 (CH),129.3 (2CH), 130.8 (2CH), 136.2(C),138.2 (C) ,153.1(C) , 157.4(C), 162.8(C), 166.4(C), 168.8(C).Anal.Calc. For Anal.Calc. For C23H21BrN4O4: C 55.54, H 4.26; found: C 55.65, H 4.43. MS:m/z 499[M+2],497[M],411,331,254,159.

2.1.40. 6-(4-bromophenyl)-4-(3methyl-5-oxo-4, 5-dihydropyrazol-1-yl)-2-hydrazino carbonyl-4, 5-dihydropyridazin-3(2H) one 22

A mixture of 20 (4.2 g; 0.01 mol) and hydrazine hydrate (1 mL, 0.015mol) in ethanol (30 mL) and was refluxed for 3h. The reaction mixture was allowed to cool and the separated product was filtered,dried and were recrystallized from ethanol.

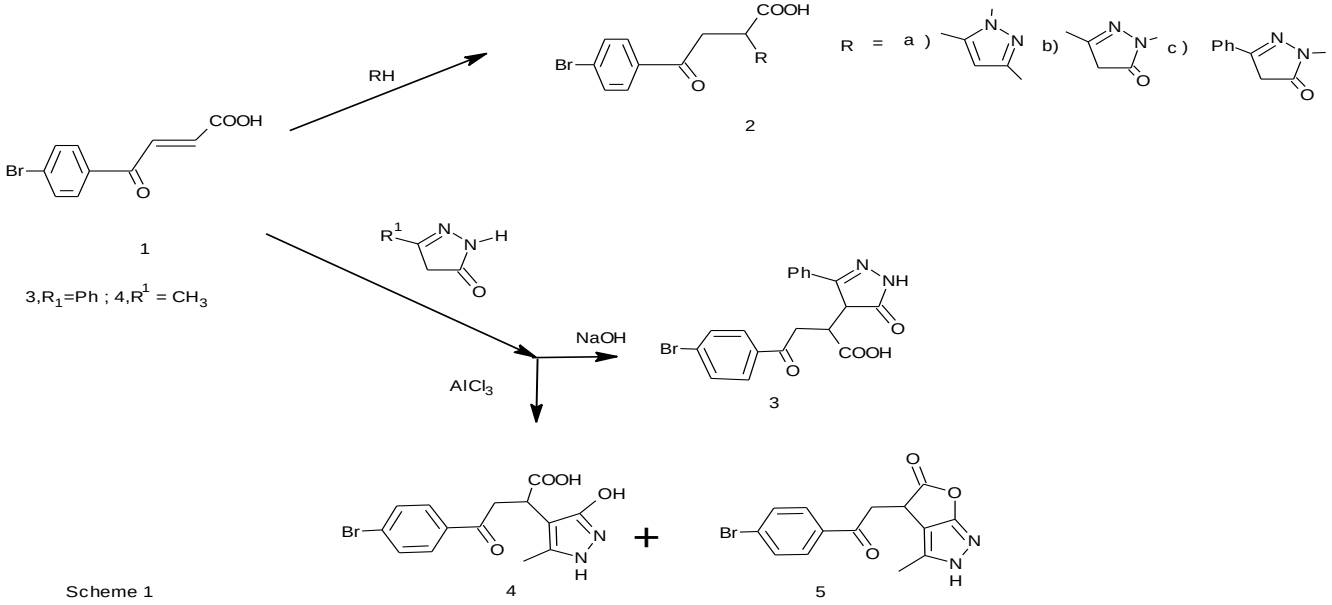
Yield 82%.Mp 218-220 ^{o}C. IR (KBr) 1650 (C=N), 1676(CO). 1HNMR (DMSO-d6) : 3.17 (s,2H,CH2 of pyrazol), 3.56 (2dd,1Ha,(J=15.2,J=7.9) and 1Hb methylene protons , CH2-C=O, (J=15.2, J=2.4) diastereotopic protons), 4.06 (brs,1H,NH)4.47 (dd,CH-COO,sterogenic methine proton , J=7.9,J=2.4),7.23 (m,9H,Ar-H), 10.2 (s,2H,NH2)and 13C-NMR δ 37.4 (CH2), 53.6 (CH), 64.7 (CH2),123.3(2CH), 127.4 (2CH),129.3 (2CH), 130.4 (2CH),131.3 (CH), 138.8 (C), 148.2(2C),161.2 (2C) ,163.7 (2C) , 165.4(C), 167.8(C).Anal.Calc. For C21H21BrN4O4: C 55.75, H 3.83; found: C 55.58, H 3.62. MS:m/z 475[M+2],473[M],333,193,156,105.

3. Results and Discussion

Reports from our laboratory [11]-[17] and others[18,19] revealed that the β-aroyl acrylic acids are convenient poly electrophilic reagents in the synthesis of heterocycles, which

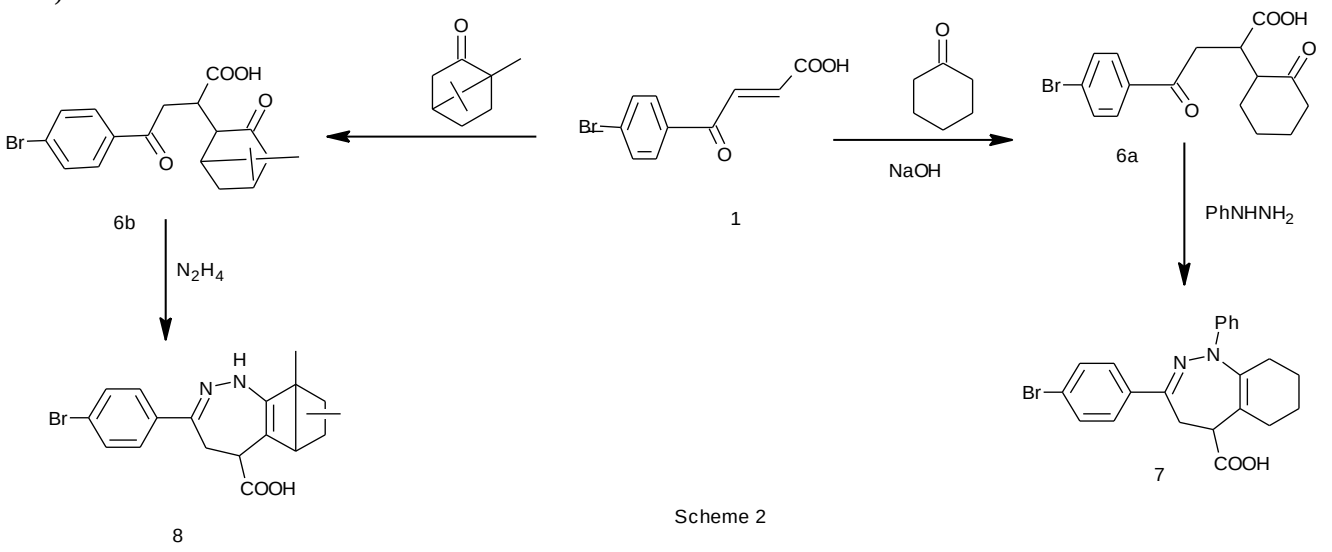
for the addition reaction of nucleophililes e.g.carbon,nitrogen,sulfur, phosphore occurs exclusively at the α-carbon electrophilic center of the carboxy precursors.With the aim of broading the synthetic potential of β-aroyl acrylic acids ,the authors can be reported the behavior of 3-(4-bromobenzoyl) prop -2- enoic acid 1 that was allowed to react with pyrazoles e.g.3,5-dimethylpyrazole,3-methyl/phenyl-2-pyrazolen-5-one in different reaction conditions,firstly in boiling ethanol (neutral medium) afforded the aza-Michael products 2-(3,5-dimethyl,3-methyl/phenyl-5-oxo- pyrazol-1-yl) 3(4-bromobenzoyl) propanoic acids 2a-c, where the reaction involving the N-alkylation of pyrazole moietes .But , when the acid 1 is submitted to react with 3-phenyl(1H)pyrazol-5(4H)-one in the presence of sodium hydroxide (basic medium) afforded 2-(5-oxo-3-phenyl-4,5-dihydro(4H)pyrazol-4-yl)-3-(4-bromobenzoyl) propanoic acid 3 , via the formation of

carbanion in the pyrazoline moiety that added to the activated double bond of the acid 1, C-alkylation for substituted pyrazole takes place under Michael reaction condition. For purpose of comparison,when the above reaction is conducted in the presence of anhydrous aluminum chloride(Lewis acid) in boiling benzene(acidic medium),it yielded 2-(5-hydroxy-3-phenyl-4,5-dihydro (4H) pyrazol-4-yl)-3-(4-bromobenzoyl) propanoic acid (4) under Friedel-Crafts condition.One explanation for this phenomenon is that C-alkylation will be formed by the substitution reaction on the pyrazole moiety. The substitution product 4 is inferred chemically from another isolated product, furo [2, 3-c] pyrazole 5 that can be formed by dehydration of the product 4 (Scheme-1).



Scheme 1

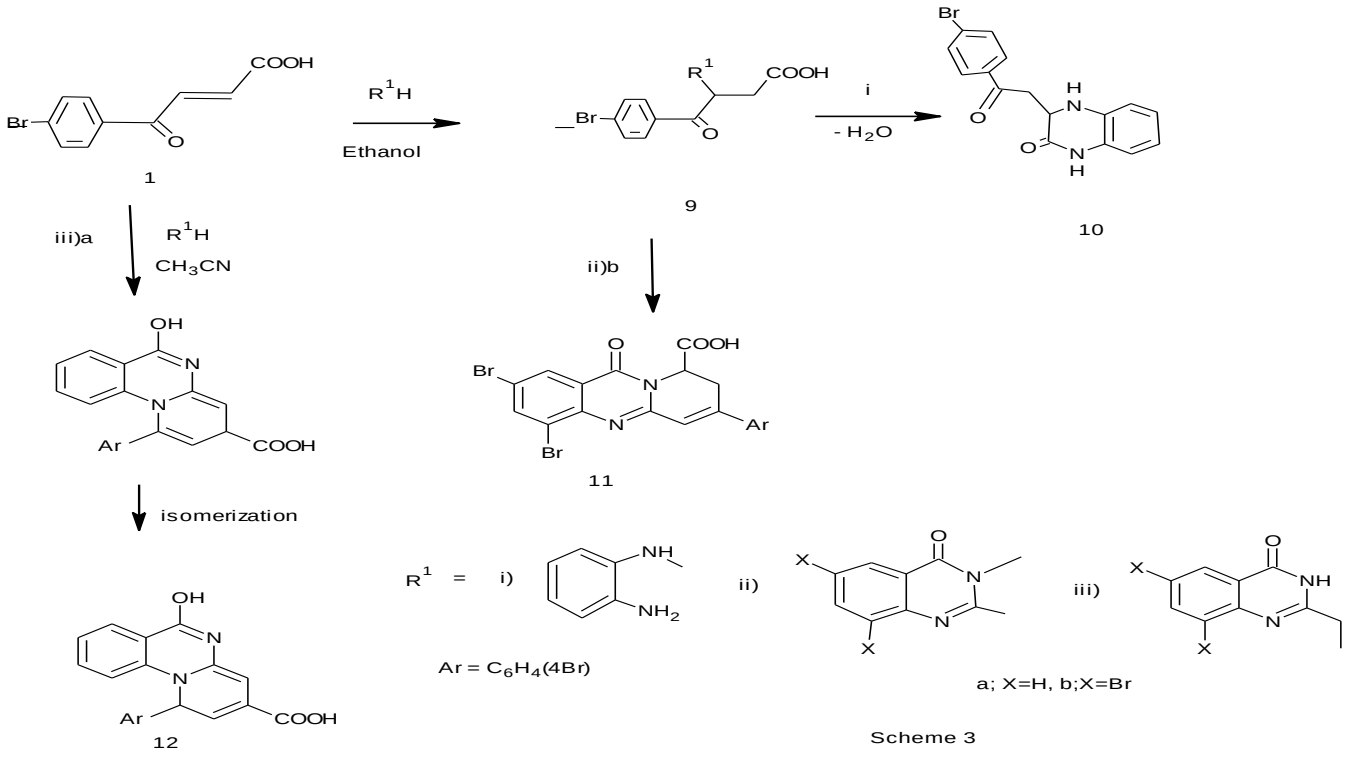
Also, when 3-(4-bromobenzoyl) prop -2- enoic acid 1 was allowed to react with cyclohexanone and /or camphor in the presence of sodium hydroxide (basic medium) under Michael reaction conditions afford the adduct 6.The structures 6 can be confirmed chemically by interaction with hydrazine derivatives afforded 1,2-diazapine derivatives 7 and 8 as outlined in scheme 2.



Scheme 2

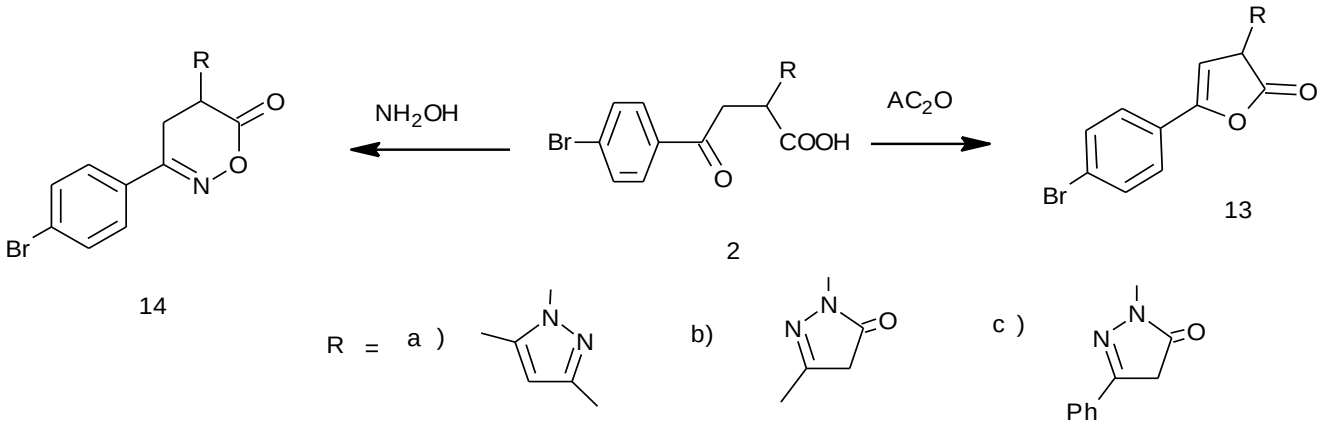
The 3-aroyl propio-2-enoic acids , when allowed to react with nitrogen containing binucleophiles[12]-[14] .The reactivity of C2 in 3-(4-bromobenzoyl) propio-2-enoic acids are enable to allow aza-michael addition by phenylene diamine and 2methyl-4(3H) quinazolinone derivatives in ethanol (protic solvent) afford acids 9 . The presence of different kinds of electrophilic centers in intermediate products 9 lead to the possible formation of six membered heterocycles. The intermediate 9i can de dehydrated spontaneously to afford the dihydroquinoxalin-2-one derivative 10, but the pyrido [2, 1-b] quinazolinone derivative 11 can be formed via interaction of the isolated adducts 9b with sodium methoxide in methanol under Michael condition. On the other hand, when the acid 1 was allowed to react with 2-methylquinazolinone in acetonitrile (aprotic solvent) yielded pyrido [1,2-a] quinazolinone derivatives 12 Scheme 3 . The products 11 and 12 afforded according to the reaction medium , the base catalyzed of the N-alkylation adduct 9b could form carbanion intermediate that stabilized in protic solvent followed by ring closure to yield 11. Opposing the formation of adduct 12, C-alkylation of the active methyl

group of quinazolinone nucleus followed by ring closure upon N1 instead of N3 via the route iii (scheme 4).The electrocyclization by this way due to, in aprotic solvent the quinazolinone moieties are major in lactim tautomer and the electron density on N1 was increased by the phenolic group in the position 4 .So, they can be isomerized to the thermodynamically more stable 12.



Scheme 3

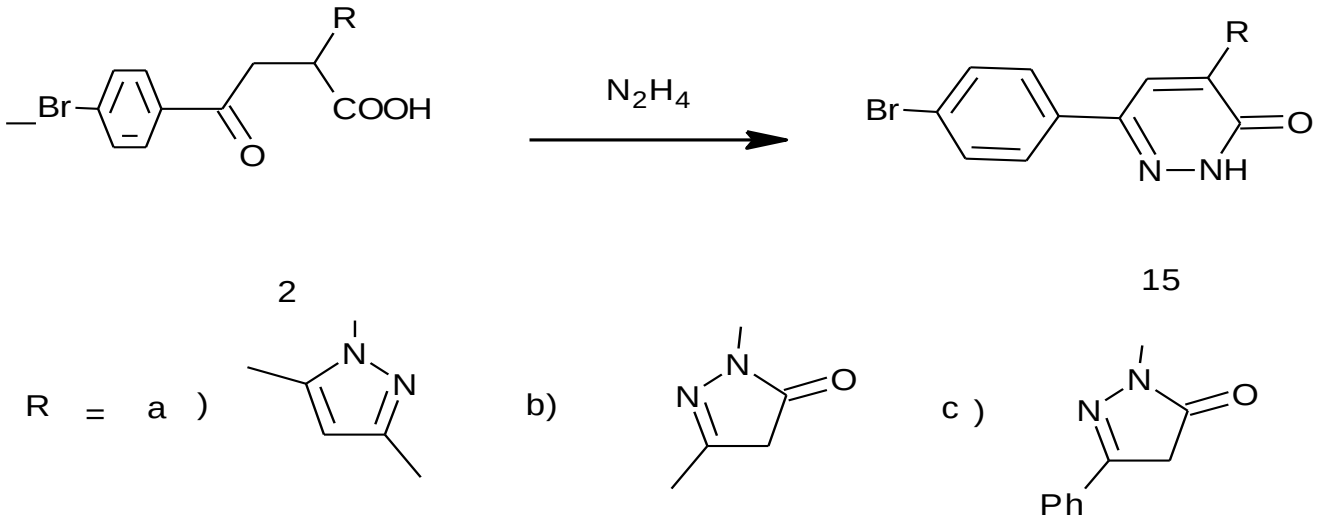
The quinoxalinone plays an important role in organic synthesis [21], displaying a broad spectrum of biological activities [22], as a building blocks in the synthesis of organic semiconductors [23] . So, the authors can be interested in developing the precursors 10. Also, 2 (3H) furanone as a new antioxidant and anti-infammatory agent, the recent efforts devoted to the development of new ascorbic acid analogues have resulted in obtaining anti-oxidant,[24]–[29] ,anti-tumoral [30] , when the acids 2 were allowed to react with acetic anhydride on heating water bath for 1h , they have 5-(p-bromophenyl) -3 (substituted pyrazol-1-yl)-2- (3H) furanone (13) (Scheme 4).To continuo in our research , the different kinds of electrophilic centers in the acids 1 that can be reacted with simply binucleophiles e.g. hydroxyl amine and hydrazine hydrate to afford an important heterocycles.Oxazinone derivatives are an important clan of heterocyclic compounds, since many of their heterocyclic system exhibit biological activity [31].Thus,when the acid 2 was allowed to react with hydroxylamine hydrochloride in boiling pyridine afford oxazinone derivative 14.



Scheme 4

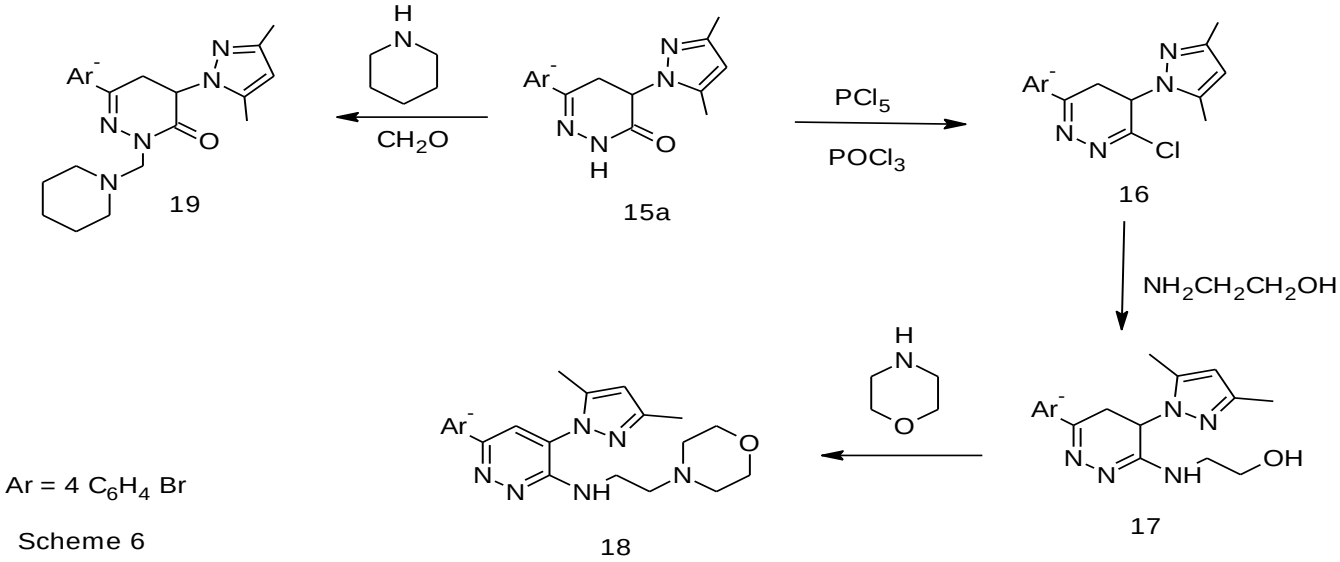
Synthetic 3(2H) pyridazinones are important scaffolds in drug discovery, with many of their analogs being in the treatment of various human pathological states.They were described nonsteroidal anti-inflamatory drugs e.g.Emorfazone and related compounds [32] agents for therapeutic intervention of renal urologic e.g. FK-838

[33],cardiovascular e.g.EMD-57283 [34] , respiratory e.g. NIP-502[35] and deramatologic diseases e.g. FR-1818177 [36], pyridazinone PDE inhibitors developed from ibudilast [37]. The design of a new prepared compounds based on the structure contain other biologically actives heterocycles on the side chains [38] It reported in the field of cancer therapy that pyrazoles[39,40] enhances the biological profile many fold than their parent nuclei.This prompted us to continuo [10]-[14] the prepare some interesting heterocyclic compounds e.g.pyrazole derivatives incorporated with pyridazinone nucleus in position 4 . Thus, when acids 2 a-c were allowed to react with hydrazine hydrate in boiling ethanol , they afforded 6- bromophenyl- 4 (substituted pyrazol-1-yl) 2,3,4,5 tetrahydro 3(2H) pyridazinones (15) Scheme 5.



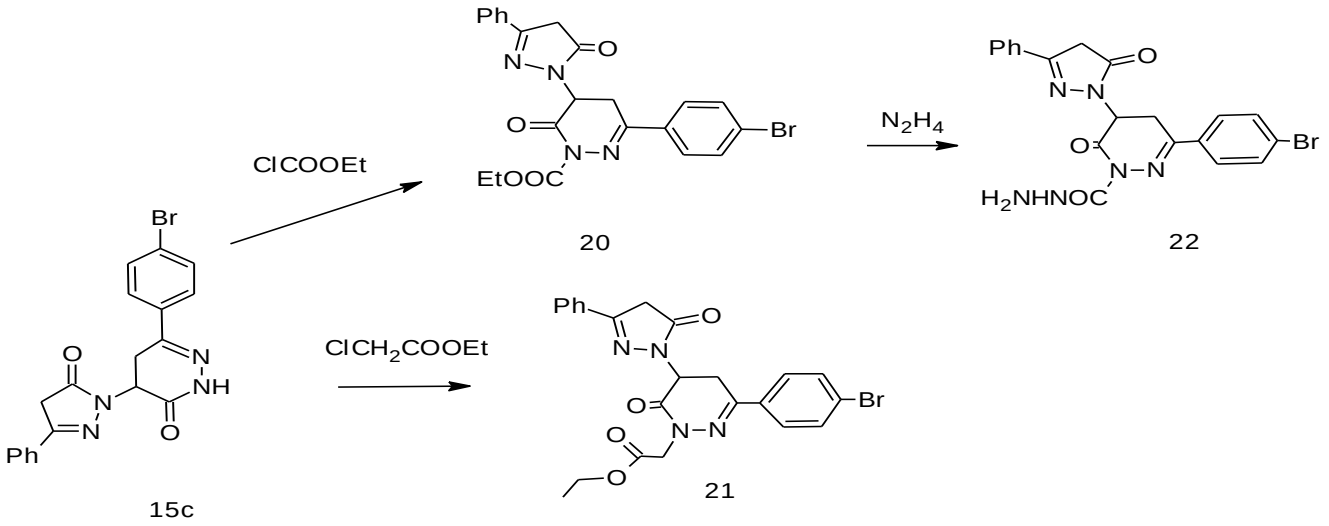
Scheme 5

Also,treatment of 15a with phosphorous pentachloride in the presence of phosphrous oxychloride on warming water bath afforded the 3-chloro derivatives 16. Herein, nucleophilic substitution of the chloropyridazine derivative 16 with ethanol amine yielded 3-(2-hydroxyethylamino)-pyridazine derivative 17. The structure of compound 17 is inferred chemically by its reaction with morpholine in the presence of a few drops of HCl gave the Mannich type reaction product 18. On the other hand, the pyridazinone 15a was submitted to react with formaldehyde in the presence of piperidine in boiling methanol under Mannich reaction conditions, it yielded the 2-(N-piperidomethyl)pyridazin-3(2H)-one 19 Scheme 6.



Scheme 6

Thereafter,when compound 15c was allowed to react with ethyl chloro formate and ethylchloro- acetate in boiling acetone in the presence of anhydrous potassium carbonate in accordance with reported method for electrophilic substitution of lactam form [41]yielded ethyl 2-(3-(4-bromophenyl)-6-oxopyridazin-1(6H)yl) formate and / or acetate (20 and 21) respectively (Scheme 7) .IR spectrum revealed strong absorption bands a(1754,1670 cm-1) attributable to two υ CO and devoid any band for υ NH .



Scheme 7

From the spectroscopic tools ,the reaction possibly takes place via N-alkylation e.g. SN2 mechanism with ethyl chloro acetate but tetrahedral mechanism with ethyl chloro formate while acid chloride is more reactive than ester group i.e. chloride anion is good leaving group than ethoxy group.Hydrazinolysis of the ester 20 via interaction with hydrazine hydrate yielded the corresponding hydrazide 22 (Scheme 7).

4. Conclusion

The present work is succeeded to study the effect of the medium pH on the type of Michael addition (Michael or Aza-Michael) beside studying the behavior of 3-(4-bromo benzoyl)prop-2-enoic acid towards nitrogen and carbon nucleophiles producing a series of some important heterocycles and for the first time,synthesis of oxazinone and pyridazinone derivatives bearing 4-heteryl moiety inside to aromatic substituents in the position 6 that enhances the biological profile many fold than their parent nuclei

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