BEHAVIOUR OF 4-(4-ACETYLAMINOPHENYL)-4-OXO-BUT-2-ENOIC ACID TOWARDS CARBA- AND AZA-NUCLEOPHILES AND SOME REACTION WITH THE PRODUCTS

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ABSTRACT

The present work deals with the reaction of 4-(4-Acetylamino)phenyl-4-oxobut-2-enoic acid (1) with pyrazole derivatives, barbituric acid and quinazolinone derivatives in different medium, afford acid derivatives 2-7. The latter compounds was treated with acetic anhydride, hydrazine hydrate derivatives and hydroxyl amine to yield some important heterocyclic derivatives.

KEYWORDS: (E)-4-Aryl-4-Oxo-2-Butenoic Acids, Pyrazole, Barbituric Acid, Quinazolinone, Pyrimidine, Pyridazine, Oxazine, Morphine, Piperidine

INTRODUCTION

(E)-4-aryl-4-oxo-2-butenoic acids have been used as a key starting material due to their high electrophilicity, where they react readily with 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 [1-3]. Also, they have activated double bond, Half wave reduction potentials (E1/2) [4] display good correlations with Hammett sigma value, attempts to obtain good correlations using frontier orbitals of the molecules. Also, they have emerged as the most promising drug candidates [5] which are selective for integrase S-1360 [6], and class of Human immunodeficiency virus type1 (HIV-1) integrase inhibitors [7], anti-bacterial activity [8], in recovery of Alzheimer disease [9] and their esters are important intermediates in the field of media science, agriculture and perfume [10].

RESULTS AND DISCUSSIONS

Reports from our laboratory [11-17] and others [18,19] revealed that the (E)-4-aryl-4-oxo-2-butenoic acids are convenient poly electrophilic reagents in the synthesis of heterocycles, which for the addition reaction of nucleophiles e.g., carbon, nitrogen, sulfur, phosphorus occurs exclusively at the α-carbon electrophilic center of the carboxy precursors. With the aim of broadening the synthetic potential of β-aroylacrylic acids, the authors can be reported the behavior of 4-(4-acetylaminophenyl)-4-oxo-but-2-enoic acid (1) that was allowed to react with pyrazoles e.g., 3-methyl/phenyl-2-pyrazolen-5-one in different reaction conditions in boiling ethanol (neutral medium) afforded theaza-Michael products 4-(4-acetylaminophenyl)-2-(3-methyl/phenyl-5-oxo-pyrazol-1-yl)-4-oxo-butanoic acids (2), where the reaction involving the N-alkylation of pyrazole moieties. Otherwise, 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 4-(4-acetylaminophenyl)-2-(4,5-dihydro-5-oxo-3-phenyl-pyrazol-4-yl)-4-oxo-butanoic 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 4-(4-acetylaminophenyl)-2-(5-hydroxy-3-phenyl-4,5-dihydro(4H)pyrazol-4-yl)-4-oxo-butanoic 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).

Similarly, the 4-(4-acetamidophenyl) 4-oxo-but-2-enoic acid (1) was reacted with barbituric acid in different reaction conditions, in boiling ethanol (neutral medium) afforded the aza-Michael product 6a where the reaction involving the N- alkylation of barbituric moiety. But, if the acid 1 was submitted to react with barbituric acid in the presence of sodium hydroxide (basic medium), it afforded 3-(4-acetaminophenyl)-2-(2,4-dihydroxy-6-oxo-pyrimidin-5-yl)-butanoic acid 6b, via the formation of carbon in the barbiturate moiety that added to the activated double bond of the acid 1, the C-alkylation for barbituric precursor takes place under Michael reaction condition.

The reactivity of C2 in 4-(4-acetaminophenyl) 4-oxo-but-2-enoic acid (1) was enabled to allow aza-michael addition by 2-methyl-4(3H) quinazolinone in ethanol (protic solvent), afforded the acid 7. The pyrido[2,1-b]quinazolinone derivative 8 can be formed via interaction of the isolated adducts 7 with sodium ethoxide in ethanol under Michael reaction 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]quinoxalinone derivatives 10 via the adduct intermediate 9. The electrocyclization in the adducts 7 and 9 was according to the reaction medium, the base catalyzed of the N-alkylation adduct 7 could form carbanion intermediate that stabilized in protic solvent followed by ring closure to yielded 8. Otherwise, in aprotic solvent, the quinoxalinone moiety is major in lactim tautomer and the electron density on N1 was increased by the phenolic group in the position 4. So, C-alkylation of the adduct intermediate 9 was followed by ring closure upon N1 instead of N3 via the route v (Scheme 2), and then isomerized to the thermodynamically more stable 10.
The different reaction pathway occurs in the compounds 6, when they can be reacted with acetic anhydride and simply binucleophiles e.g. hydrazine derivatives and hydroxyl amine to afford an important heterocycles. Outlined in scheme 3, when the acid 6a was allowed to react with acetic anhydride afford oxazinopyrimidinone 11 via the decarboxylation followed by ring closure. Otherwise, when the acid 6b was allowed to react with acetic anhydride, it afforded the furopyrimidine product 12 instead of expected isomer 13. Regioselectivity of the 2,4-dioxo-furopyrimidine 12 due to stability of the bond length and binding energy of the isomer 12 was more than isomer 13.

Scheme 3

Also, when the acid 6b was allowed to react with hydrazine hydrate afford pyrimidino1,2 diazepine derivatives 14,15 respectively. Otherwise, when it was allowed to react with phenyl hydrazine afforded the pyridazinone derivatives 16. Formation of the pyridazinone 16 is due to unsymmetrical hydrazine derivatives can be affected on regio selectivity in which electronic and steric factors play an important role. This can be affected on the reaction path that depends on stability of intermediate and the product [11,20]. The compound 6b was allowed to react with hydroxyl amine in the presence of pyridine afford oxime derivative 17 (scheme 4).

Scheme 4

In the reaction of adducts 2 and 6 with NH$_2$OH, it can depend on their heteryl moieties. The electronic factor plays an important role. So, the electron deficient pyrimidine moiety in adduct 6b prevents electrocyclization otherwise the pyrazole moiety that is a driving force to ring closure. Their can able to continue in our research [11-14], to synthesized oxazinone and pyridazinone derivatives incorporated with pyrazole moieties that exhibit biological activity [20], e.g. Emorfazone and related compounds [21] agents for therapeutic intervention of renal urologic, respiratory e.g. NIP-502 [22] and deramalogic diseases e.g. FR-1818177 [23], pyridazinone PDE inhibitors developed from ibudilast [24]. The design of a new prepared compounds based on the structure contain other biologically actives heterocycles on the side chains [25] and the field of cancer therapy that pyrazoles [26,27] enhances the biological profile many fold than their parent nuclei. Thus, when the acids 2 were allowed to react with hydroxylamine hydrochloride in boiling pyridine and / or hydrazine hydrate
afforded oxazinone and pyridazinone derivatives 18,19 respectively (Scheme 5).

Also, treatment of 19a with phosphorous pentachloride in the presence of phosphous oxychloride on warming water bath afforded the 3-chloro derivatives 20. Herein ,nucleophilic substitution of the chloropyridazine derivative 20 with ethanol amine yielded 3-(2-hydroxyethy lamino)-pyridazine derivative 21. The structure of compound 21 is inferred chemically by its reaction with morpholine in the presence of a few drops of HCl gave the Mannich type reaction product 22. On the other hand, the pyridazinone 19a 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 23 (scheme 6).

CONCLUSIONS

The present work is succeeded to study the effect of the pH medium on the behavior of 4-(4-acetylaminophenyl ) 4-oxo-but-2-enoic acid towards nitrogen and carbon nucleophiles producing a series of some important heterocycles , oxazinone and pyridazinone derivatives bearing 4-heteryl moiety inside to aromatic substituents in the position 6 , fused furopyrimidine , fused oxazinopyrimidine and fused pyrimidinodiazipene that enhances the biological profile many fold than their parent nuclei.

Experimental

All melting points are uncorrected and were determined on a stuart electric melting point apparatus. Elemental analyses were carried out at the Microanalytical 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 \(^1\)H-NMR spectra recorded on a Bruker spectrophotometer at 400 MHz using TMS as internal standard and with residual signals of the deuterated solvent \(\delta = 7.26\) ppm for CDCl\(_3\) and \(\delta 2.51\) ppm for DMSO-d6. \(^{13}\)C-NMR spectra were recorded on the same spectrometer at 100 MHz and referenced to solvent
signals $\delta = 77$ ppm for CDCl$_3$ and $\delta = 39.50$ ppm for DMSO-d6. DEPT 135 NMR spectroscopy were used where appropriate to aid the assignment of signals in the $^1$H and $^{13}$C-NMR spectra. The mass spectra were recorded on Shimadzu GCMS-QP-1000 EX mass spectrometer at 70 e.v using the electron ionization technique Homogeneity of all compounds synthesized was checked by TLC.

**General Procedure for the Preparation of Compounds 2a-b**

A mixture of 4-(4-acetylamino phenyl)-4-oxo-but-2-enoic acid (2.35 g;0.01 mol) and 3-(methyl or phenyl)pyrazol-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 (b.p 40- 60°C), and then, crystallized from toluene to give compounds 2

4-(4-Acetylaminophenyl)-2-(3-Methyl-5-Oxo-4,5-Dihydropyrazol-1-yl)-4-Oxobutanoic Acid (2a)

Yield 74 %.Mp 180-182 °C. IR(KBr) 1617,1630 (C=N),1667,1691,1705(CO). $^1$HNMR spectrum (CDCl$_3$) : $\delta$

2.10(s,6H,2CH$_3$),3.49(s,2H,RCH2CO pyrazole proton),3.73 (2dd,1H,a,(J=15.2,J=7.2) and 1Hb methylene protons , CH$_2$-C=O, (J=15.2, J=5.1) diastereotopic protons), 4.90 (dd,CH-COO$_2$,sterogenic methine proton , J=7.2,J=5.1) , 5.76(s,1H,CH$_3$pyrazole proton), 7.47 - 7.74 (m, 4H, 4ArH aromatic protons). 8.3(s,1H,OH), 12.8 (brs,2H, NH and COOH, a acidic protons which exchanged in D2O) and $^{13}$C-NMR $\delta$ 16.8 (2CH$_3$), 34.7 (CH$_2$) ,37.6(CH$_2$),44.4 (CH),53.4 (CH),128.9 (CH),130.5(C), 131.2 (CH) ,132.5 (CH) , 135.4(C) ,140.5(CH), 154.8(C),171.7(C) ,199.0 (2C ).Anal.Calc. for $C_{10}H_{12}NO_3$ : C 58.00 , H 5.13 ;found: C 58.14,H 5.09. MS:m/e 331[M$^+$],287 [M$^+$-CO$_2$], 234[M$^+$ - pyrazole moiety]

4-(4-Acetylaminophenyl)-2-(3-Phenyl-5-Oxo-4,5-Dihydropyrazol-1-yl)-4-Oxobutanoic Acid (2b)

Yield 81 %.Mp 168-170 °C. IR(KBr) 1630 (C=N), 1681,1722(CO),3244(OH). $^1$HNMR (CDCl$_3$) : $\delta$

2.10(s,3H,CH$_3$) ,3.38(s, 2H, RCH$_2$CO pyrazole proton),3.71 (2dd,1H,a,(J=15.2,J=7.2) and 1Hb methylene protons , CH$_2$-C=O, (J=15.2, J=5.1) diastereotopic protons), 4.95 (dd,CH-COO$_2$,sterogenic methine proton , J=7.2,J=5.1) , 5.76(s,1H,pyrazole proton), 7.47 - 7.97 (m, 9H, 9ArH aromatic protons). 8.4(s,1H,OH), 13.8 (brs,2H,NH and COOH, a acidic protons which exchanged in D$_2$O) and $^{13}$C-NMR $\delta$ 16.8 (CH$_3$), 35.7 (CH$_2$) ,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 (2C ).Anal.Calc. for $C_{21}H_{19}NO_3$ :C64.12 , H 4.83 ;found: C 64.04,H 4.79.

**General Procedure for the Preparation of 4-(4-Acetylamino phenyl)-2-(3-phenyl-5-oxo-4, 5-dihydro-1H-pyrazol-4-yl)-4-oxobutanoic acid (3)**

The 4-(4-acetylamino phenyl ) 4-oxo-but-2-enoic acid (2.35 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 temperature for 2 days, and the crude product was quenching with H$_2$O 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°C),dried and then, crystallized from benzene afford Michael adduct 3. Yield 66%.Mp 184-186 °C. IR(KBr) 1680,1720 (CO), 3265 (NH). $^1$H-NMR (DMSO-d6) : $\delta$ 2.10(s,3H,CH$_3$) , 3.51(2dd,1H,a,(J=15.2,J=7.2) and 1Hb methylene protons, CH$_2$-C=O, (J=15.2, J=5.1) diastereotopic protons), 3.80 (dd,CH-COO$_2$,sterogenic methine proton, J=7.2,J=5.1) ,4.56 (d,1H,CH pyrazole moiety),multiplet at $\delta$ 7.47 – 7.95 assigned for 9ArH aromatic protons, singlet 10.2 a acidic 2NH protons which exchanged in D2O and $^{13}$C-NMR $\delta$ 16.8 (CH$_3$), 38.4 (CH) ,39.6 (CH$_2$),52.9 (CH),125.3 (2CH),127.2 (CH),128 (2CH), 129.2 (C) ,132.5 (2CH) ,132.4(2CH ),134.1(2C ),135.7(C) ,161.0 (C ),173.2(C),176.3(C ),193.5 (2C ). Anal.Calc. for $C_{21}H_{19}NO_3$ : C 64.12,H 4.83;found: C 64.01 , H 4.78. MS:m/z 349 [M-CO$_2$],295,218,185,105.
General Procedure for the Preparation of Compounds 4, 5

An equimolar mixture of 4-(4-acetiminophenyl) 4-oxo-but-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°C),dried and then, crystallized from toluene afford 5,ethanol afford 4.

4-(4-Acetaminophenyl)-2-(3,4-Dihydro-3-Hydroxy-5-Methyl-Pyrazol-4-yl)-4-Oxobutanoic Acid (4)

Yield 37%.Mp 190-192 °C. IR(KBr) 1613 (C=O),1670,1685,1715 (CO), 3245 (NH),3410 (OH). ¹H-NMR (CDCl₃) : δ 2.10(s,3H,CH₃), 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 steroids methine proton J=8.7, J=7.2,J=5.1),4.56 (d,1H,CH sterilgenic methine proton of pyrazol, J=8.7), multiplet at 7.47 – 7.95 assigned for 9ArH aromatic protons, singlet 10.2 a acidic OH and NH protons and 11.3 assigned for COOH which exchanged in D₂O and ¹³C-NMR δ 15.7(2CH₃), 39.4 (CH), 40.6 (CH₃),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(2C) .Anal.Calc. for C₁₆H₁₂N₂O₄ : C 58.00 , H 5.13;found: C 57.85 , H 5.05. MS: m/z 331 [M], 138,105.

4-[(2-(4-Acetaminophenyl)-2-Oxothiol][2,3-c]Pyrazol-5(4H)-One (5)

Yield 40%.Mp 165-167 °C. IR(KBr) 1613 (C=O),1685,1745 (CO), 3245 (NH). ¹H-NMR (CDCl₃) : δ 3.71(dd,2H,(J=16.8,J=11.2) , CH₃) 4.16 (t,furanone proton , J=11.2), multiplet at 7.57 – 7.95 assigned for 9ArH aromatic protons, singlet 10.6 a 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 C₁₆H₁₄N₂O₄ : C 50.15 , H 3.28;found: C 50.85 , H 3.12. MS:m/z 313 [M],214,138,105.

4-(4-Acetimidobenzoil)-2-(2, 4-Dihydroxy-6-Oxo-5, 6-Dihydropyrimidin-5-yl) Propionic Acid (6a)

A solution of 4-(4-acetiminophenyl) 4-oxo-but-2-enoic acid (2.35 g;0.01 mol) in ethyl alcohol (30 mL) was treated with barbituric acid . The reaction mixture was refluxed 3 h . The solid that separated was crystallized from ethanol .Yield 80%.Mp 204-206 °C. IR(KBr) 1645,1690,1710(CO). ¹H-NMR spectrum (DMSO) : δ 2.5(s,3H,CH₃) , 3.79(m,4H, CH₃CHCH) , multiplet at 7.60 – 7.66 assigned for 4ArH aromatic protons, 10.6-11.2 (brs,4H) acidic NH and OH protons which exchanged in D₂O and. Anal. Calc. for C₁₆H₁₂N₂O₄ : C53.18 , H 4.15 ;found: C 53.12,H 4.11.

4-(4-Acetimidobenzoil)-2-(2, 4-Dihydroxy-6-Oxo-5, 6-Dihydropyrimidin-5-yl) Propionic Acid (6b)

A solution of 4-(4-acetiminophenyl) 4-oxo-but-2-enoic acid (2.35 g;0.01 mol) and barbituric acid in ethyl alcohol (15 mL) was treated with 50% aqueous sodium hydroxide (5 mL). The reaction mixture was allowed at room temperature 7 days and collected the crude product by ice/HCl. The crude product was washed by H₂O and then, crystallized from ethanol .Yield 80%.Mp 180-182 °C. IR(KBr) 1645,1690,1710(CO). ¹H-NMR spectrum (DMSO) : δ 2.5(s,3H,CH₃) , 3.79(m,4H, CH₂CHCH) , multiplet at 7.60 – 7.66 assigned for 4ArH aromatic protons, singlet at 11.2-13.2 , a acidic proton which exchanged in D₂O and ¹³C-NMR δ 23.2( 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 C₁₆H₁₂N₂O₄ :C 53.18 , H 4.15;found: C 53.17, H 4.15.

General Procedure for the Preparation of Compounds of 7, 8, 10

The 4-(4-acetaminophenyl) 4-oxo-but-2-enoic acid (2.35 g;0.01 mol) was added to a stirred suspension of,
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2-methyl-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°C), dried and then, crystallized from ethanol.

4-(4-Acetaminophenyl)-2-(2-Methyl-4-Oxo-4H-quinazolin-3-yl)-4-Oxo-Butanoic Acid (7)

Yield 73%.Mp 189-191 °C. IR(KBr) 1680,1702 (CO),3200(OH). 1H-NMR (DMSO-d6) : δ 2.3(s,6H,2CH3), 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). 13.2 (s,2H,NH and COOH groups which exchanged in D2O) and 13C-NMR δ 15.4 (CH2), 42.1 (CH3),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) , 141.4(C ),149 (C),158.4 (C),160.8 (C), 173.7(C),194.5 (C).Anal.Calc. for C25H16N6O7 : C 64.12,H 4.83 ; found: C 64.10 , H 4.86.

1-(4-Acetaminophenyl)-5-Oxo- Pyrido[2,1-b]quinazolin-4-carboxylic Acid (8)

The 4-(4-acetaminophenyl) ) 4-oxo-but-2-enoic acid (2.35 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 temperature 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%.Mp 170-172 °C. IR(KBr) 1663,1705 (CO),3400-3256(OH). 1H-NMR (DMSO-d6) : δ 2.17(s,3H,CH3), 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),6.7(s,1H,CH=), 7.26-7.89(m,8H, aromatic protons) 12.2 (brs ,2H,NH and COOH) and 13C-NMR δ 18.9 (CH3) , 42.1 (CH),55.0(2CH),98.4 (CH ),104.5 ( CH),118.5 (CH),120.8(2CH),125.4 (CH),129.3 (CH), 129.8 (CH), 130.2(2CH),135.2 (CH) ,139 (C) 140 (C), 141.4(C),145 (C),148.4 (C),160.8 (C), 176.7(C),194.5 (C).Anal.Calc. for C25H17N6O12 : C 67.20 ,H 4.53 ; found: C 67.23 , H 4.56. MS:m/z 375,198,187,105.

1-(4-Acetaminophenyl)-6-Hydroxy-Pyrido [1, 2-a]Quinazolin-3-Carboxylic Acid (10)

The 4-(4-acetaminophenyl) 4-oxo-but-2-enoic acid (2.35 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 °C. IR(KBr) 1670,1710 (CO),3412(OH). 1H-NMR (DMSO-d6) : δ 2.19(s,3H,CH3), 5.50(s,1H, methine proton), 7.05-8.20(m,10H, aromatic protons) 11.2(s, 1H,COOH),13.2 (brs ,2H,OH and NH which exchanged in D2O)and 13C-NMR δ 18.9 (CH3) , 42.1 (CH),98.4 (CH ),104.5 (CH),118.5 (CH),120.8(2CH),125.4 (CH),129.3 (CH) ,129.8 (CH), 130.2(2CH),135.2 (CH) ,139 (C) 140 (C), 141.4(C),145 (C),148.4 (C),160.8 (C), 176.7(C),194.5 (C). Anal.Calc. for C21H17N5O : C 67.20 ,H 4.53 ; found: C 67.11 , H 4.52.

3-Acetoxy-6-(4-Acetamidoacetylphenyl)-1-Oxo-1,5,8-Trihydroxyprano[3,2-c]Pyrimidine (11)

A mixture of 6a (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 Yield 80 %.Mp 156-158 °C. IR(KBr) 1665, 1850 (CO),3420 (NH). 1H-NMR (DMSO-d6) δ 2.1(s,6H,2CH3), 4.7 (dd,2H,CH2=CH) 7.53-8.11 (m,6H,4Ar-H) ,1HH pyrene and [1H]pyrimidine).1.70 (brs,1H,NH of acetamido) and Anal.Calc. for C21H15N3O3 : C 56.10 , H 3.89,N 10.90;found: C 56.00 , H 3.65, N 10.60 MS:m/z 343 [M-COCH3].
2-Acetoxy-5-(4-Acetamidoacetophenyl)-4,6-Dioxo-3,4,5,6,7-Pentahydropyro[2,3-d]Pyrimidine (12)

A mixture of 6b (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 Yield 80 %.Mp 203-205 C. IR(KBr) 1640,1763,1850 (CO),3420 (NH). \(^1\)HNM R (DMSO-d6) : \(\delta\) 2.1(s,6H,2CH \(_3\)), 3.6 (m,3H,CH \(_2\)CH) 7.46-7.71 (m,4H,Ar-H),12.40 (brs,2H,NH of acetamido and pyrimidinone moieties) and Anal.Calc. for C\(_{18}\)H\(_{15}\)N\(_3\)O\(_2\) : C 57.12, H 3.66.

Compounds 14, 15

A mixture of 6b (0.01 mol) and hydrazine hydrate (0.01mol) in ethanol (50 mL) and was heated under reflux for 5h. The reaction mixture was allowed to cool and the product was filtered, dried and recrystallized from toluene afford 15 and ethanol to afford 14

2,4-Dioxo-7-(4-Acetamidophenyl)-2,3,4,5-Tetrahydropyrimidino[4,5-c]2,4,5,6-Tetrahydro-1,2-Diazepin-5-Carboxylic Acid (14)

Yield 50%.Mp 185-187 \(^\circ\)C. IR(KBr) 1650,1670,1723 (CO), 3275,3313 (NH),3479 (OH). \(^1\)HNM R (DMSO) : \(\delta\) 2.50(s,3H,CH \(_3\)), 3.37(m,4H,CH\(_2\)CHCH protons system),multiplet at 6.72 – 7.41 assigned for 4ArH aromatic protons, singlet 8.6 all acidic OH and 3NH protons that exchanged in D2O and Anal.Calc. for C\(_{18}\)H\(_{15}\)N\(_3\)O\(_2\) : C 53.78 , H 4.20,N 19.60;found: C 53.45 , H 4.00, N 19.50.

7-(4-Acetamidophenyl)-2,5Dioxo-2,3,4,5-Tetrahydropyrimidino[4,5-c]-Furo[3,4-d]-2,4,5,6-Tetrahydro-1,2-Diazepine (15)

Yield 35%.Mp 168-170 \(^\circ\)C. IR(KBr) 1661,1677,1775 (CO), 3275,3313 (NH). \(^1\)HNM R (DMSO) : \(\delta\) 2.50(s,3H,CH \(_3\)), 4.06(m,4H,CH\(_2\)CHCH protons system), multiplet at 7.14 – 7.95 assigned for 4ArH aromatic protons, singlet 10.2 all acidic OH and NH protons that exchanged in D\(_2\)O and Anal.Calc. for C\(_{18}\)H\(_{15}\)N\(_3\)O\(_2\) : C 56.63 , H 3.83,N 20.64;found: C 56.47 , H 3.71, N 20.43

6-(4-Acetyaminophenyl)-4-(2,4-Dihydroxy-6-Oxo-5,6-Dihydropyrimidin-5-yl)-2-Phenyl-2,3,4,5-Tetrahydro-Pyridazin-3(2H)One (16)

A mixture of 6b (0.01 mol) and phenyl hydrazine (0.01mol) in ethanol (50 mL) and was heated under reflux for 5h. The reaction mixture was allowed to cool and the product was filtered, dried and recrystallized from ethanol .Yield 30 %.Mp 220-222 \(^\circ\)C. IR(KBr) 1637,1677 (CO),3287 (NH). \(^1\)HNM R (DMSO-d6) : \(\delta\) 2.1(s,3H,CH \(_3\)), 3.8 (m,3H,CH\(_2\)CH system) 7.50-7.80 (m,9H,Ar-H),12.40 (brs,4H,NH of acetamido and pyrimidinone moiety). Anal.Calc. for C\(_{22}\)H\(_{19}\)N\(_3\)O\(_5\) : C 60.96 , H 4.38,N 16.16;found: C 60.52 , H 4.22, N 16.00.

4-(4-Acetamidophenyl)4-Hydroxyiminino-2-(2,4-Dihydroxy-6-Oxo-5,6-Dihydropyrimidin-5-yl)Propionic Acid (17)

A mixture of 2b (0.01 mol) and hydroxyl amine hydrochloride (1.03 g ;0.015mol) in boiling pyridine (50 mL) and was heated under reflux for 6h. The reaction mixture was allowed to cool, pour into ice/HCl and the product was filtered, dried, and were recrystallized from toluene/ethanol .Yield 80%.Mp 165-167 \(^\circ\)C. IR(KBr) 1650,1697 (CO), 3188 (NH),3464 (OH). \(^1\)HN M R (DMSO) : \(\delta\) 2.51(s,3H,CH \(_3\)), 3.72(m,4H,CH\(_2\)CHCH system), multiplet at 7.93 – 8.00 assigned for 4ArH aromatic protons, singlet 8.8 (bs,2OH of pyrimidinone moiety ,9.97(s,1H,OH of oxime) 12.85(s,1H,NH of acetamido group), all acidic OH and NH protons that exchanged in D\(_2\)O and Anal.Calc. for C\(_{16}\)H\(_{16}\)N\(_3\)O\(_5\) : C 51.06 , H 4.25,N 14.89;found: C 50.80 , H 4.00, N 14.50,57.12,H 3.66.
General Procedure for the Preparation of Compounds 18a-b

A mixture of 2a-b (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.

3-(4-Acetylanilinophenyl)-5-(3-Methyl-5-Oxo-Pyrazol-1-yl)-6-Oxo-4,5-Dihydro-1,2-Oxazine (18a)

Yield 88%. Mp 142-144 °C. IR(KBr) 1685,1733 (CO). 1H-NMR (DMSO-d6): δ 2.3(s,6H,CH2),3.71(s,2H,CH2 of pyrazole moiety), 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, 12.2 (s,1H,NH which disappeared by D2O and $^{13}$C-NMR δ 19.1(2CH3),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 C18H15N2O4: C 58.53,H 4.78 , N 17.07 ; found: C58.65 , H 4.70, N 17.00 . MS: m/z 382 , 214,138,119.92.

3-(4-Acetylanilinophenyl)-5-(3-Phenyl-5-Oxo-Pyrazol-1-yl)-6-Oxo-4,5-Dihydro-1,2-Oxazine (18b)

Yield 83%. Mp 200-202 °C. IR(KBr) 1695,1738 (CO). 1H-NMR (CDCl3): δ 2.5(s,3H,CH3), 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),

General Procedure for the Preparation of Compounds 19a-b

A mixture of 2a-b (0.01 mol) and hydrazine hydrate (1 mL,0.015mol) in ethanol (30mL) and then refluxed for 3h.

The reaction mixture was allowed to cool and the separated product was filtered, dried and were recrystallized from ethanol.

6-(4-Acetylanilinophenyl)-4-(3Methyl-5-Oxo-4, 5-Dihydropyrazol-1-yl)-4,5-Dihydropyridazin-3(2H)One (19a)

Yield 86%. Mp 230-232 °C. IR(KBr) 1651 (C=N),1673 (CO),3220-3310(NH). 1H-NMR (DMSO-d6): δ 1.97 (s,6H, 2CH3),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=1.1,ArH),11.75 (brs,2H,2NH that disappeared by D2O ) and. Anal. Calc. for C16H13N3O2: C 58.71,H 5.19 N 21.40 ;found: C 58.60 , H 5.10 , N 21.27.

6-(4-Acetylanilinophenyl)-4-(3-Phenyl-5-Oxo-4,5-Dihydropyrazol-1-yl)-4,5-Dihydropyridazin-3(2H)One (19b)

Yield 86%. Mp 238-240 °C. IR(KBr) 1651 (C=N),1679 (CO),3220 (NH). 1H-NMR (DMSO-d6): δ 2.04 (s,3H, CH3), 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,2H,2NH ) and $^{13}$C-NMR δ 18.9 (2CH3), 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 C22H19N3O2 : C 64.78,H 4.88;found: C 64.69 , H 4.60.

6-(4-Acetylanilinophenyl)-3-Chloro-4-(3,5-Dimethyl-Pyrazol-1-yl)-4, 5-Dihydropyridazin-3(2H) One (20)

A mixture of 19a (3.47 g:0.01 mol) and phosphorous pentachloride (1g, 0.015mol) in phosphorous oxychloride (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 180-182°C. 1H-NMR (DMSO-d6): δ 2.17 (s,6H, 2CH3), 3.66 (s,2H,CH2-pyrazol) 3.72
(2dd,1Ha,(J=15.2,J=7.9) and 1Hb methylene protons , CH$_2$-C=O, (J=15.2, J=2.4) diastereotopic protons), 4.11 (dd,CH-
COO,sterogenic methine protons , J=7.9,J=2.4),3.73 (d,2H J=8.1,Ar-H), 7.76(d,2H, J=8.1,ArH) , 12.25 (brs,1H,NH that
disappeared by D$_2$O ) and $^{13}$C-NMR δ 12.9 (CH$_3$), 15.7 (CH$_3$), 29.5 (CH$_2$),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), 175.2(C). Anal.Calc. for C$_{16}$H$_8$N$_2$O$_2$Cl: C
55.57,H 4.63 ; found: C 55.45 , H 4.66. MS: m/z 347[M$^{+2}$],345[M$^{+}$] , 310[M$^{+}$-Cl] , 175,156,95.

6-(4-Acetaminophenyl)-3-(2-Oxethylamino)-4-(3,5-Dimethyl-Pyrazol-1-yl)-4,5-Dihydropyridazin-3(2H)One (21)

A mixture of 20 (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 lefted overnight. The solid that separated was washed,filtered,dried and
recrystallized from n-butanol.Yield 83%.Mp 204-206 证实. 1651 (C=N),1680 (CO) 3498 (NH)/(OH) $^1$H-NMR (DMSO-d$_6$) :
δ 2.07 (s,3H, CH$_3$), 2.27 (s,3H, CH$_3$), 3.51 (t,2H,CH$_2$-N,J=6.4),3.72 (2dd,1Ha,(J=15.2,J=7.9) and 1Hb methylene protons ,
CH$_2$-C=O, (J=15.2, J=2.4) diastereotopic protons),3.90 (t,2H,CH$_2$-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,2H,2NH disappeared by D$_2$O ) and Anal.Calc. for C$_{15}$H$_{12}$N$_2$O$_3$: C 58.37,H 5.94;found: C 58.48 , H 5.84.

6-(4-Acetaminophenyl)-3-(2-Morpholin-4-Yl-Ethylamino)-4-(3,5-Dimethyl-Pyrazol-1-yl)-4,5-Dihydropyridazin-
3(2H)One (22)

A mixture of 12 (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 证实. 1632 (C=N), 3298 (NH). $^1$H-NMR
(DMSO-d$_6$) : δ 2.05 (s,3H, CH$_3$), 2.12 (s,3H, CH$_3$), 2.40-2.46 (m,4H,2CH,N ) , 3.40 (t,2H,CH$_2$-morph,J=6.1),
3.45(s,2H,CH$_2$-pyrazol) 3.51 (t,2H,CH$_2$-N,J=6.1),3.77 (2dd,1Ha,(J=15.2,J=7.9) and 1Hb methylene protons , CH$_2$-C=O,
(J=15.2, J=2.4) diastereotopic protons), 3.7 (m,4H,2CH$_2$O ) , 4.37 (dd,CH-COO, sterogenic methine proton ,
J=7.9,J=2.4),7.33 (d,2H J=8.1,Ar-H) , 7.76(d,2H, J=8.1,ArH) ,10.71 (brs,2H,2NH disappeared by D$_2$O ). Anal. Calc. for
C$_{23}$H$_{19}$N$_3$O$_4$: C 60.13,H 6.60, N 22.32 ;found: C 60.08 , H 6.54, N 22.20.

6-(4-Acetilaminophenyl)-4-(3,5-Dimethyl-pyrazol-1-yl)-2-piperidin-1-ylmethyl4,5-dihydropyridazin-3(2H)one (23)

A mixture of 19a (3.47 g ;0.01mol), 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. Yield 72%.Mp 185-187 证实. IR(KBr) 1682 (CO).$^1$H-NMR (DMSO-d$_6$) : δ 1.17-1.27
(m,6H,3CH$_2$ piperidine moiety), 2.17 (s,6H,2CH$_3$), 1.37 (m,4H,2CH$_2$(pip) 3.92 (2dd,1Ha,(J=15.2,J=7.9) and 1Hb
methylene protons , CH$_2$-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) , 11.71 (brs,1H,NH disappeared by
D$_2$O) and $^{13}$C-NMR δ 13.9 (CH$_3$), 15.7 (CH$_3$),23.4 (CH$_2$),26.5 (CH$_3$), 28.5 (CH$_3$),51.5 (2CH$_2$),55.3(CH$_2$),77.4 (CH$_2$),102.3
(CH), 129.8 (2C), 131.2(2CH),140.2 (2CH) ,154.7 (CH) , 159.7 (2C) ,163.4(C) 165.7(C),180.1(C). Anal. Calc. for
C$_{23}$H$_{26}$N$_2$O$_4$: C 62.26,H 6.60 , N 19.81 ;found: C 62.25 , H 6.56 , N 19.80.

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