

# Utility of E-1-(4-Acetamidobenzoyl)-2-Oxirane Carboxylic Acid in Synthesis Some Fused Heterocycles and Spiro Compounds

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**Abstract** The present work deals with the reaction of 4-(4-Acetyl amino phenyl-4-oxobut-2-enoic acid (1) with hydrogen peroxide afforded oxirane derivative 2. The latter compound was treated with 2-amino-5-aryl-1,3,4-thiadiazole to yield imidazo[2,1-b]thiadiazole derivatives 4. The new heterocyclic compounds 4 are used as a key starting materials to synthesize some heterocycles include pyrrolo-thiadiazolo imidazole, pyridazinone and spiro derivatives. The behavior of the pyridazinone compounds towards different electrophilic and nucleophilic reagents were investigated. The structure of the newly synthesized compounds were elucidated by elemental analysis and spectroscopic data.

**Keywords** 4-Acetamido phenyl-4-oxo-but-2-enoic acid, oxirane, imidazo[2,1-b]thiadiazole, Pyrrolo imidazole, spiro pyrazolo and isoxazolo imidazo thiadiazole, pyridazinone

## 1. Introduction

(E)-4-aryl-4-oxo-2-butenic acids have been shown that the substitution pattern on the aryl moiety influences the antiproliferative activity [1] and they have activated double bond. Half-wave reduction potentials ( $E_{1/2}$ ) [2] display good correlations with Hammett sigma value, attempts to obtain good correlations using frontier orbitals of the molecules. Also, they have emerged the most promising drug candidates [3] which are selective for integrase S-1360 [4] and class of Human immunodeficiency virus type 1 (HIV-1) integrase inhibitors [5]. Spiroindoline [6] and imidazoline [7] derivatives can be evaluated for their binding affinities and antagonistic activities at neuropeptide Y<sub>5</sub> receptor and good brain penetration. Also, spironolactone is as effective as thiazides in treating mild hypertension without inducing hypokalemia or increased secretion of aldosterone [8,9] and eplerenone, a specific aldosterone antagonist approved by the food and drug administration, appears to have a much lower affinity for androgen and progesterone receptors, reduced incidence of sexual disturbances [10] and useful agent in treatment of hypertension and congestive heart failure, treatment of diabetes complication and aldose reductase inhibitors [13]. The most notably ketoconazole [11,12] which have been successful as antifungal agents and when spiroimidazole derivatives [14] was combined with an

tubercular agent (vancomycin, ciprofloxacin) that observed antagonistic activity results from the competitive binding of the medicine molecules into fungi cells receptors.

3-phenylamino-(substituted phenyl)isoxazolines [15] were evaluated for their in vitro antifungal activity and on the proliferative response of human mononuclear peripheral blood cells to phytohemagglutinin A (PHA) [16]. Recently, it reported [17] the synthesized new class of oxadiazoles by cyclization of the terminal carboxylic group of 3-aryl propionic acids into oxadiazole nucleus that an objective of developing better anti-inflammatory and analgesic agents. Also, pyridazin-2-ylmethyl-2-substituted 1,3,4-oxadiazole [18] screened for antibacterial, antifungal and antitubercular activity. The effects of 1,3,4-thiadiazole derivatives on the central nervous system (CNS) of mice were studied [19]. Imidazolo-oxazole derivatives [20] via treatment of imidazole derivatives with oxirane have been tested for antimycobacterial activity.

## 2. Results and Discussion

Reports from our laboratory [21-25] revealed that the  $\beta$ -aryl acrylic acids are convenient poly electrophilic reagents in the synthesis of heterocycles, which for the addition reaction of nucleophilic e.g. carbon, nitrogen, sulfur occur exclusively at the  $\alpha$ -carbon electrophilic center of the carboxy precursors. Moreover, reaction with hydrogen peroxide afford oxirane derivative [26]. With the aim of broadening the synthetic potential of  $\beta$ -aryl acrylic acids, the authors can be reported the behavior of 3-(4-acetylaminobenzoyl) prop-2-enoic acid 1 that was allowed to react

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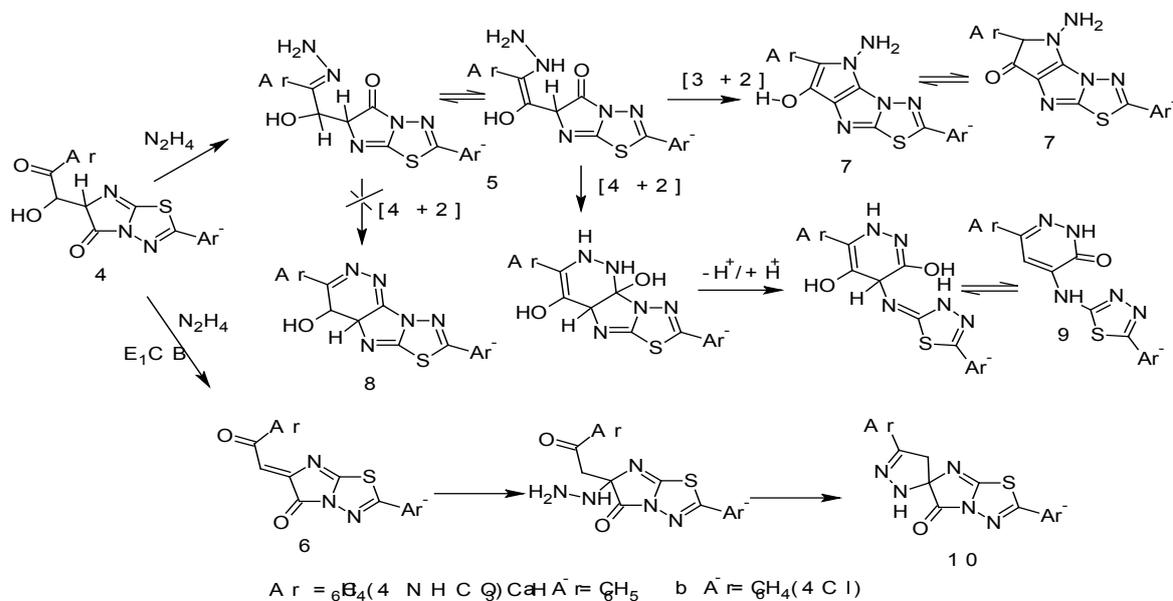
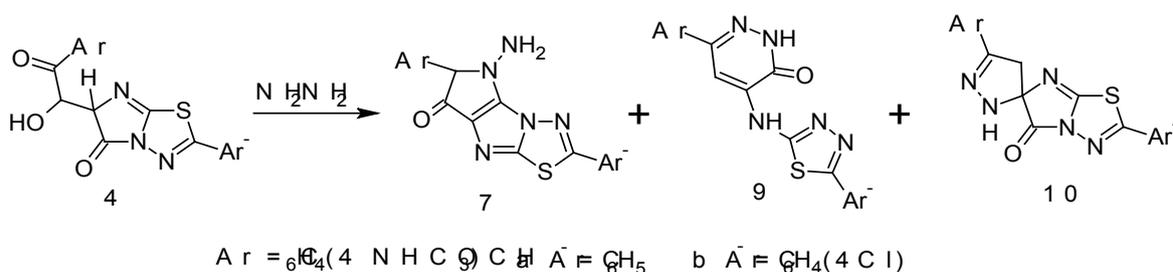
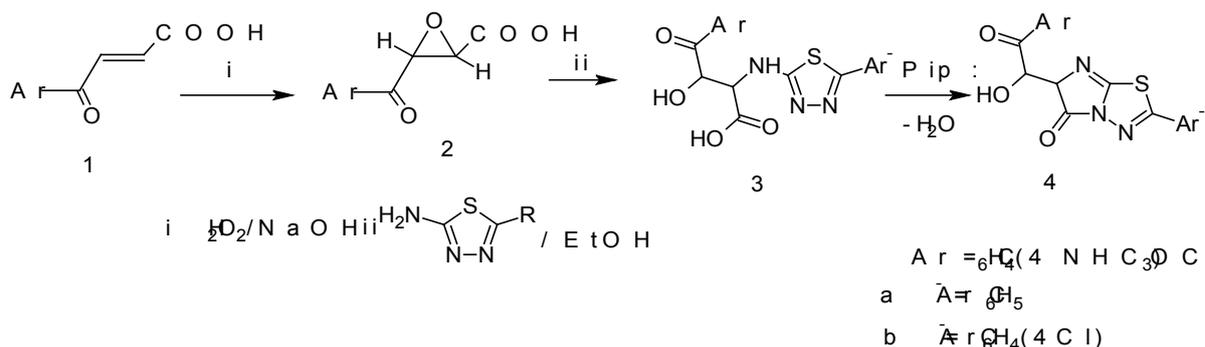
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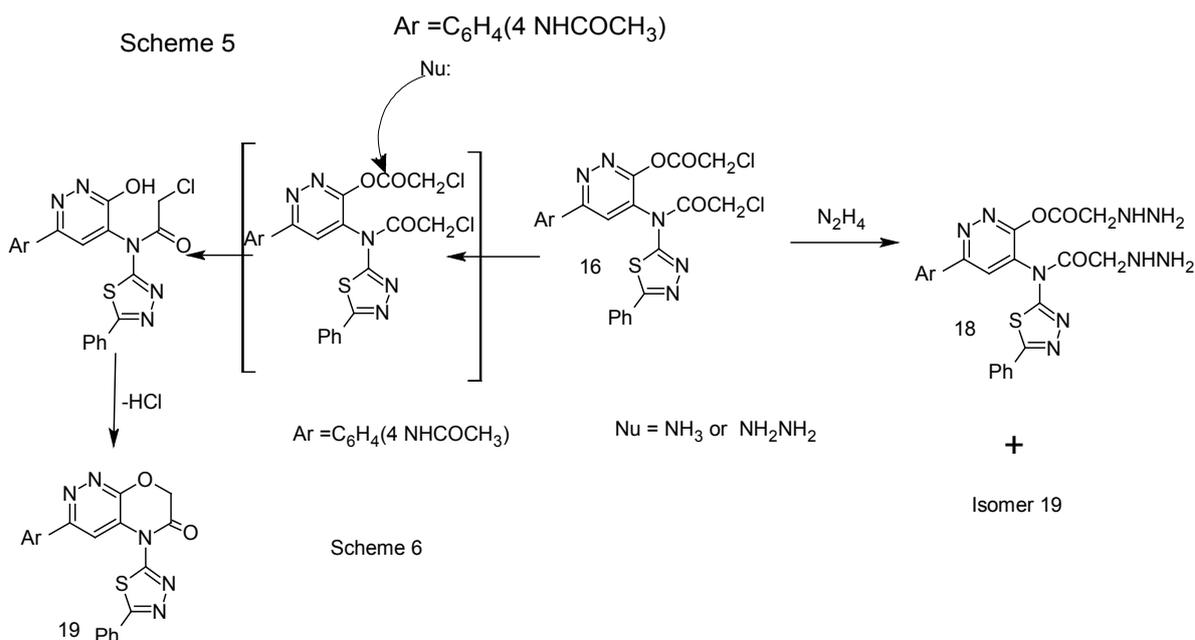
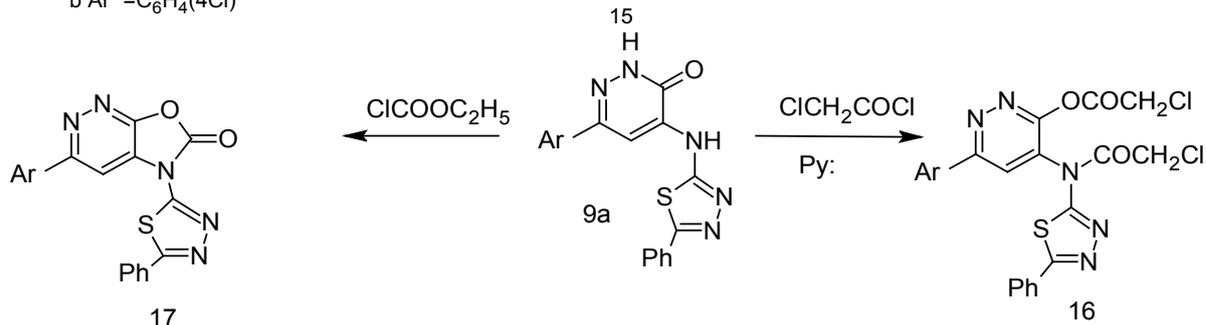
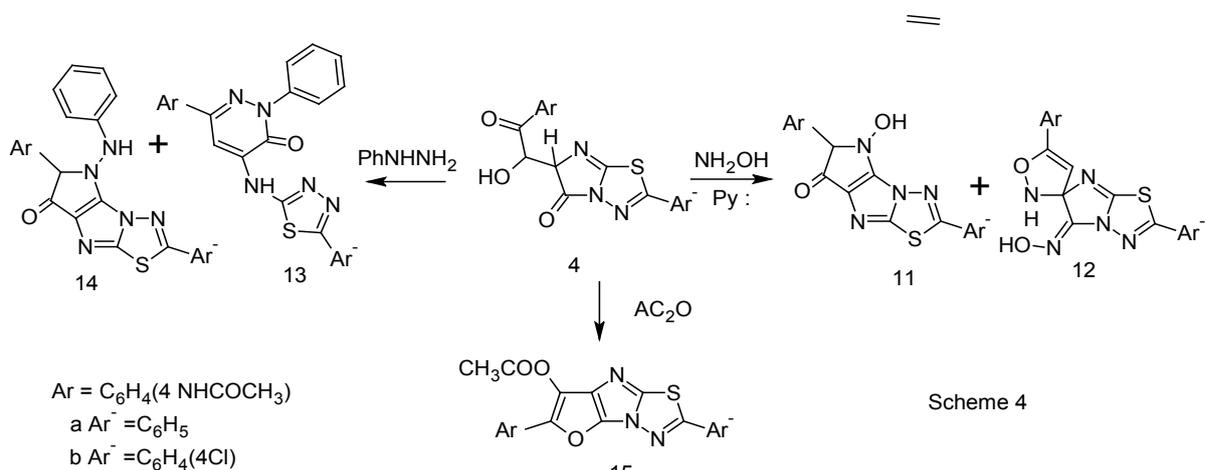
hydrogen peroxide in the presence of sodium hydroxide afforded the epoxide product E-1-(4-acetylaminobenzoyl)-2-oxirane carboxylic acid 2. When the acid 2 is submitted to react with 5-aryl-2-amino-1,3,4-thiadiazole in the presence of few drops of piperidine afforded 2-(5-aryl-1,3,4-thiadiazol-2-yl)amino-3-hydroxy-3-(4-acetylaminobenzoyl) propanoic acid 3, via the N-alkylation of aminothiadiazole moieties that added to the activated 3-membered heterocycle of the acid 2. The acids 3 undergo spontaneous dehydration to afford imidazo[2,1-b]thiadiazole derivatives 4 that more thermodynamically stable. (scheme-1)

The different kinds of electrophilic centers in the compounds 4 can be reacted with simply binucleophiles e.g. hydrazine derivatives and hydroxyl amine to afford an im-

portant heterocycles and spiro compounds .

The  $\alpha$ -substituted hydrazone intermediates 5 undergo to internal ring closure via [3+2] instead of [4+2] cyclization process to generate pyrrole derivatives 7 rather than 4,5-dihydropyridazines 8 [27,28]. The ring closure is promoted in the intermediates 5 by the presence of an acidic hydrogen originally placed in position 4 of the azo-ene system, and promote the thermo chemically allowed [4+2] cyclization to afford the competitive product 9. Formation of the pyridazinone 9 is due to stability of the bond length and binding energy [29] than isomer 8. Moreover, the authors can be isolated uncommon spiro compounds 10 which have been afforded via the intermediate 6 as outlined in scheme 3.





Similarity, the compounds 4 were allowed to react with hydroxyl amine in the presence of pyridine afford pyrrole derivatives 11 and spiro isomers 12 (scheme 4). Unsymmetrical hydrazine derivatives also can be affected on regio selectivity in which electronic and steric factors play an important rule. This can be affected on the reaction path that depends on stability of intermediate and the product. Thus, when the compounds 4 were allowed to react with phenyl hydrazine afforded the pyridazinone derivatives 13 and pyrrole derivatives 14. The latter compounds have low yield

due to the steric phenyl group is outweigh intramolecular hydrogen bond and becomes a driving force to regioselective isomer 13. Also, the compounds 4 have been reacted with carbon electrophiles, when 4 were allowed to react with acetic anhydride, they afforded furo[2,3-d]thiadiazolo[3,2-a]imidazole derivatives 15 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 antihypertensive[30], antibacterial, antifungal[31],

new azo ligand dye[32], cardiotoxic and vasorelaxant activity[33], anti-tumor[34] and Selective cyclin dependent kinase inhibitor[35]. This prompted to continue[21-24] the preparation of pyridazinone derivatives incorporated with 1,3,4-thiadiazole nucleus in position 4. Thus, when pyridazinone 9a was allowed to react with chloro acetyl chloride and ethyl chloro formate, afforded ester 16 and oxazolopyridazine 17 respectively (Scheme 5).

When the chloro ester of pyridazine derivative 15 was allowed to react with hydrazine hydrate and ammonium acetate, it afforded hydrazine derivative 17 and 1,4-oxazino [2,3-c]pyridazine 18 (Scheme 5).

### 3. Conclusions

From the spectroscopic tools, the reaction of isomer 19 possibly takes place via attacking nucleophiles by tetrahedral mechanism followed by ring closure yielded the corresponding 1,4-oxazino[2,3-c]pyridazine 19 (Scheme 6).

The present work is succeeded to synthesis of a series of some important heterocycles and spiro compounds from 4-acetamido phenyl-4-oxo-2-butenoic acid and for the first time, synthesis of 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.

### 4. 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 Elemental 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  $\text{cm}^{-1}$  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  $\delta = 7.26$  ppm for  $\text{CDCl}_3$  and  $\delta 2.51$  ppm for  $\text{DMSO-d}_6$ . C-NMR spectra were recorded on the same

spectrometer at 100 MHz and referenced to solvent signals  $\delta = 77$  ppm for  $\text{CDCl}_3$  and  $\delta 39.50$  ppm for  $\text{DMSO-d}_6$ . 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.

#### General Procedure of starting Material in literature[21]. E-1-(4-Acetamidobenzoyl)-2-Oxirane Carboxylic Acid (2)

A solution of 3-(4-acetamidobenzoyl)-prop-2-enoic acid (2.35 g; 0.01 mol) in acetone (40 mL) and methyl alcohol (15 mL) was treated with 8% aqueous sodium hydroxide (12 mL) followed by hydrogen peroxide (30%, 5 mL). The reaction

mixture was allowed to boil 1 h and then left over night at room temperature. The crude product was washed by petroleum ether (b.p 40- 60°C), and then, crystallized from toluene to give compound 2

Yield 83%. Mp 172-174 C. IR(KBr) 1645, 1687, 1710 (CO).  $^1\text{H}$ NMR spectrum ( $\text{CDCl}_3$ ):  $\delta$  2.51 (s, 3H, CH<sub>3</sub>), 6.91-6.99 (2dd, 1Ha and 1Hb diastereotopic protons,  $J=14.5$  and 9.2), multiplet at 7.30 – 7.70 assigned for 4ArH aromatic protons, singlet 8.2 a acidic proton which exchanged in D<sub>2</sub>O and Anal. Calc. for  $\text{C}_{12}\text{H}_{11}\text{NO}_5$ : C 57.38, H 4.41; found: C 57.22, H 4.21. MS: m/z 249[M], 205[M-CO<sub>2</sub>], 163[205-COCH<sub>3</sub>]

#### Compounds 4

An equimolar mixture of compound 2 (2.5 g; 0.01 mol) and 2-amino-5-aryl-1,3,4-thiadiazole (0.01 mol) in 50 mL ethanol. The reaction mixture was refluxed for 3 h. The solid that separated after cool was filtered off, washed by petroleum ether (b.p 40- 60°C), dried and then, crystallized from ethanol afford 4

#### 5-[2-(4-acetylaminophenyl)-2-oxo-1-hydroxy]ethyl-4-oxo-2-phenyl imidazolo[2,1-b]1,3,4-thiadiazole (4a)

Yield 74%. Mp 190-192 C. IR(KBr) 1613 (C=N), 1650, 1670, 1685 (CO), 3245 (NH), 3410 (OH).  $^1\text{H}$ NMR (DMSO):  $\delta$  2.5 (s, 3H, CH<sub>3</sub>), 4.11 (dd, 1Ha, ( $J=15.2$ ,  $J=11.2$ ) and 1Hb ( $J=15.2$ ,  $J=11.1$ ) stereogenic methine protons), 4.35 (bs, 1H, OH proton of hydroxyl group), multiplet at 7.44 – 7.73 assigned for 9ArH aromatic protons, singlet 13.2 a acidic OH=NH proton which exchanged in D<sub>2</sub>O and Anal. Calc. for  $\text{C}_{20}\text{H}_{16}\text{N}_4\text{SO}_4$ : C 58.82, H 3.92, N 13.72; found: C 58.60, H 3.65, N 13.45. MS: m/z 408[M], 377[M-OH+CH<sub>3</sub>], 285, 213, 141.

#### 5-[2-(4-acetylaminophenyl)-2-oxo-1-hydroxy]ethyl-4-oxo-4-chlorophenylimidazolo[2,1-b]1,3,4-thiadiazole (4b)

Yield 74%. Mp 200-202 C. IR(KBr) 1620 (C=N), 1645, 1675, 1691 (CO), 3245 (NH).  $^1\text{H}$ NMR (DMSO):  $\delta$  2.06 (s, 3H, CH<sub>3</sub>), 3.50 (bs, 1H, OH proton of hydroxyl group), 6.6-6.7 (2dd, 1Ha, ( $J=15.2$ ,  $J=11.2$ ) and 1Hb ( $J=15.2$ ,  $J=11.1$ ) stereogenic methine protons), multiplet at 7.44 – 7.83 assigned for 8ArH aromatic protons, singlet 8.2 a acidic OH=NH proton which exchanged in D<sub>2</sub>O and Anal. Calc. for  $\text{C}_{20}\text{H}_{15}\text{N}_4\text{SClO}_4$ : C 54.30, H 3.39, N 12.67; found: C 54.55, H 3.25, N 12.53. MS: m/z 442[M], 426[M-OH], 365, 287, 252, 170, 159, 139.

#### Compounds 7,9,10

A mixture of 4 (0.01 mol) and hydrazine hydrate (0.01 mol) 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 were recrystallized from suitable solvent, using the column chromatograph is necessary to separate the compounds 7 and 10.

#### 2-phenyl-4-amino-5-(4-acetylaminophenyl)-6-oxo-pyrrolo[3,2-d]-1,3,4-thiadiazolo[3,2-a]imidazole (7a)

Yield 35%. Mp 150-152 C. IR(KBr) 1650, 1670 (CO), 3275, 3200 (NH), 3400 (OH). Anal. Calc. for  $\text{C}_{20}\text{H}_{16}\text{N}_6\text{SO}_2$ : C 59.40, H 3.96, N 20.79; found: C 59.25, H 3.75, N 20.50

#### 2-(4-chlorophenyl)-4-amino-5-(4-acetylaminophenyl)-6-oxo-pyrrolo[3,2-d]-1,3,4-thiadiazolo[3,2-a]imidazole (7b)

Yield 35%.Mp 168-170 C. IR(KBr) 1650,1670 (CO), 3275,3200 (NH),3400 (OH). and Anal.Calc. for C<sub>20</sub>H<sub>15</sub>N<sub>6</sub>ClSO<sub>3</sub> : C 54.79 , H 3.42,N 19.17;found: C 54.47 , H 3.21, N 19.03 .

#### Compounds 9

##### 6-(4-acetylaminophenyl)-4-(5-phenyl-1,3,4-thiadiazol-2-yl)amino-2,3-dihydropyridazin-3(2H)one (9a)

Yield 30%. Mp 203-205 C. IR(KBr) 1640,1687(CO) ,3272 (NH). and Anal.Calc. for C<sub>20</sub>H<sub>16</sub>N<sub>6</sub>SO<sub>2</sub> : C 59.40 , H 3.96,N 20.79;found: C 59.25 , H 3.75, N 20.60 MS:m/z 404[M],360[M-COCH<sub>3</sub>].

##### 6-(4-acetylaminophenyl)-4-(5-(4-chlorophenyl)-1,3,4-thiadiazol-2-yl)amino-2,3-dihydropyridazin-3(2H)one (9b)

Yield 30%. Mp 220-222 C. IR(KBr) 1627,1687(CO) ,3266 (NH). <sup>1</sup>HNMR (DMSO-d<sub>6</sub>): δ 2.51(s,3H,CH<sub>3</sub>), 6.6 (bs,3H,NH of amino, acetamido and pyridazinone moiety) 7.26-8.13 (m,9H,Ar-H and pyridazine). Anal.Calc. for C<sub>20</sub>H<sub>15</sub>N<sub>6</sub>ClSO<sub>2</sub>: C 54.79 , H 3.42,N 19.17;found: C 54.52 , H 3.22, N 19.00 MS:m/z 438[M],395[M-COCH<sub>3</sub>].

#### Compounds 10

##### 4-phenyl-7-oxo-10-(4-acetylaminophenyl)-spiro[7(2-6)-4]3-thia-1,5,6,8,9pentazadodecane(10a)

Yield 25%. Mp 171-175 C. IR(KBr) 1640,1671(CO) ,3423 (NH). <sup>1</sup>HNMR (DMSO-d<sub>6</sub>) : δ,2.2(s,2H,CH<sub>2</sub>) 2.5(s,3H,CH<sub>3</sub>) 6.2 (bs,1H,NH) 7.0-7.81 (m,9H,Ar-H), 10.40(bris,1H, NH of acetamido moiety)and Anal.Calc. for C<sub>20</sub>H<sub>16</sub>N<sub>6</sub>SO<sub>2</sub> : C 59.40 , H 3.96,N 20.79;found: C 59.25 , H 3.75, N 20.60 MS:m/z 307[M- (aniline radical+H<sub>2</sub>)],121[PhC=N-NH].

##### 4-(4-chlorophenyl-7-oxo-10-(4-acetylaminophenyl)-spiro[7(2-6)-4]3-thia-1,5,6,8,9pentazadodecane(10b)

Yield 25%.Mp 165-168 C. IR(KBr) 1640,1671(CO) ,3420 (NH). Anal.Calc. for C<sub>20</sub>H<sub>15</sub>N<sub>6</sub>ClSO<sub>2</sub> : C 54.79 , H 3.42,N 19.17;found: C 54.52 , H 3.22, N 19.00 MS:m/z 404[M-Cl],395[M-COCH<sub>3</sub>],194[spiro moiety].

#### Compounds of 11 and 12

A mixture of 4(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 afford 11 and ethanol afford 12

##### 2-phenyl-4-hydroxy-5-(4-acetylaminophenyl)-6-oxo-pyrrolo[3,2-d]-1,3,4-thiadiazolo[3,2-a]imidazole (11a)

Yield 40%.Mp 165-167 C. IR(KBr) 1650,1683 (CO), 3245 (NH),3450 (OH). and Anal.Calc. for C<sub>20</sub>H<sub>15</sub>N<sub>5</sub>SO<sub>3</sub> : C 59.25 , H 3.70,N 17.28;found: C 59.00 , H 3.45, N 17.00 MS:m/z 403[M-H<sub>2</sub>],362[M-COCH<sub>3</sub>],268[361-phenol moiety].

##### 2-(4-chlorophenyl)-4-hydroxy-5-(4-acetylaminophenyl)-6-oxo-pyrrolo[3,2-d]-1,3,4-thiadiazolo[3,2-a]imidazole (11b)

Yield 45%.Mp 168-170 C. IR(KBr) 1650,1670 (CO), 3275(NH),3450 (OH). and Anal.Calc. for C<sub>20</sub>H<sub>14</sub>N<sub>5</sub>ClSO<sub>3</sub> : C 54.66, H 3.19,N 15.94;found: C 54.36 , H 3.02, N 15.68

##### 4-phenyl-7-hydroxyimino-10-(4-acetylaminophenyl)-spiro[7(2-6)-4]9-oxa-3-thia-1,5,6,8, tetrazadodecane(12a)

Yield 35 %.Mp 197-200 C. IR(KBr) 1630(CO) ,3425

(NH). <sup>1</sup>HNMR (DMSO-d<sub>6</sub>) : δ 2.23(s,3H,CH<sub>3</sub>), 4.29 (bs,2H,OH and NH groups) 7.00-7.70 (m,10H,Ar-H), 12.70 (brs,1H,NH of acetamido moiety) and Anal.Calc. for C<sub>20</sub>H<sub>16</sub>N<sub>6</sub>SO<sub>3</sub> : C 57.14 , H 3.80,N 20.00;found: C 57.00 , H 3.55, N 19.72 .

##### 4-(4-chlorophenyl-7-hydroxyimino-10-(4-acetylaminophenyl)-spiro[7(2-6)-4]9-oxa-3-thia-1,5,6,8, tetrazadodecane(12b)

Yield 35%.Mp 192-195 C. IR(KBr) 1631 (CO) ,3271 (NH). Anal.Calc. for C<sub>20</sub>H<sub>15</sub>N<sub>6</sub>ClSO<sub>3</sub> : C 52.86 , H 3.30,N 18.50;found: C 54.52 , H 3.16, N 18.25 MS:m/z 454[M],343[M-chlorobenzene].

#### Compounds 13:

A mixture of 4(0.01 mol) and phenyl hydrazine (0.01mol) in ethanol (40 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 benzene/toluene afford 14 and ethanol afford 13.

##### 2-phenyl-4-(5-phenyl-1,3,4-thiadiazol-2-yl)amino-6-(4-acetylaminophenyl)-2,3-dihydropyridazin-3(2H)one (13a)

Yield 40%. Mp 212-214 C. IR(KBr) 1640,1687(CO) ,3170 (NH). and Anal.Calc. for C<sub>26</sub>H<sub>20</sub>N<sub>6</sub>SO<sub>2</sub> : C 65.00 , H 4.16,N 17.50;found: C 64.70 , H 4.00, N 17.36 .

##### 2-phenyl-4-(5-(4-chlorophenyl)-1,3,4-thiadiazol-2-yl)amino-6-(4-acetylaminophenyl)-2,3-dihydro-pyridazin-3(2H)one (13b)

Yield 45%. Mp 230-232 C. IR(KBr) 1632,1721(CO) ,3220 (NH). Anal.Calc. for C<sub>26</sub>H<sub>19</sub>N<sub>6</sub>ClSO<sub>2</sub> : C 60.70 , H 3.69,N 16.34;found: C 60.44 , H 3.32, N 16.10 .

##### 2-phenyl-4-phenylamino-5-(4-acetylaminophenyl)-6-oxo-pyrrolo[3,2-d]-1,3,4-thiadiazolo-[3,2-a]imidazole (14a)

Yield 35%.Mp 170-172 C. IR(KBr) 1650,1670 (CO), 3275,3200 (NH),3400 (OH). and Anal.Calc. for C<sub>26</sub>H<sub>20</sub>N<sub>6</sub>SO<sub>2</sub> : C 65.00 , H 4.16,N 17.50;found: C 65.00 , H 4.10, N 17.26

##### 2-(4-chlorophenyl)-4-phenylamino-5-(4-acetylaminophenyl)-6-oxo-pyrrolo [3,2-d]-1,3,4-thiadiazolo[3,2-a]imidazole (14b)

Yield 35%.Mp 190-191 C. IR(KBr) 1650,1670 (CO), 3275,3200 (NH),3400 (OH). and Anal.Calc. for C<sub>26</sub>H<sub>19</sub>N<sub>6</sub>ClSO<sub>2</sub> C 60.70, H 3.69,N 16.34;found: C 60.44 , H 3.32, N 16.10

#### Compounds 15a-b

A mixture of 4(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

##### 2-acetoxy-3-(4-acetylaminophenyl)-6-phenyl-furo[3,2-d]-1,3,4-thiadiazolo[3,2-a]imidazole (15a)

Yield 74%.Mp 150-152 C. IR(KBr) 1613 (C=N), 1650, 1764, 1850 (CO), 3154 (NH),3436 (OH). <sup>1</sup>HNMR (DMSO): δ 2.22(s,3H,CH<sub>3</sub>), 2.50 (s,3H,CH<sub>3</sub>COO), multiplet at 7.50 – 7.90 assigned for 9ArH aromatic protons, singlet 12.67 a acidic OH=NH proton which exchanged in D<sub>2</sub>O and Anal.Calc. for C<sub>22</sub>H<sub>16</sub>N<sub>4</sub>SO<sub>4</sub>: C 61.11 , H 3.70,N 12.96;found: C 60.90 , H 3.47, N 12.77.

**2-acetoxy-3-(4-acetylamino-phenyl)-6-(4-chlorophenyl)-furo[3,2-d]-1,3,4-thiadiazolo[3,2-a]imidazole(15b)**

Yield 74%. Mp 144-146 C. IR(KBr) 1620 (C=N), 1645, 1767, 1850 (CO), 3157 (NH) 3438 (OH). <sup>1</sup>HNMR (DMSO): δ 2.21(s, 6H, CH<sub>3</sub>CONH CH<sub>3</sub>COO), multiplet at 7.51 – 7.94 assigned for 8ArH aromatic protons, singlet 12.57 a acidic OH=NH proton which exchanged in D<sub>2</sub>O and Anal.Calc. for C<sub>22</sub>H<sub>15</sub>N<sub>4</sub>SClO<sub>4</sub> : C 56.65 , H 3.21, N 12.00; found: C 56.40 , H 3.00, N 11.77.

**3-chloroacetoxy-6-(4-acetylamino-phenyl)-4-(5-phenyl-1,3,4-thiadiazol-2-yl)chloroacetylaminopyridazine (16)**

An equimolar mixture of compound 9a (2.0 g; 5mmol) and chloroacetylchloride (1.7mL, 0.015 mol) in 50 mL dry pyridine. The reaction mixture was refluxed for 3 h. The reaction mixture poured into ice/HCl and the solid that separated was filtered off, dried and then, crystallized from ethanol.

Yield 45%. Mp 132-134 C. IR(KBr) 1660, 1722, 1781 (CO), 3317 (NH). and Anal.Calc. for C<sub>24</sub>H<sub>18</sub>N<sub>6</sub>SCl<sub>2</sub>O<sub>4</sub> : C 51.80 , H 3.23, N 15.10; found: C 51.84 , H 3.13, N 15.40 MS: m/z 485[M-2Cl], 380[M-OCOCH<sub>2</sub>CO moiety], 360[M-(CH<sub>3</sub>CO+2ClCH<sub>2</sub>CO)].

**2-oxo-3-(5-phenyl-1,3,4-thiadiazol-2-yl)****-5-(4-acetylamino-phenyl)-oxazolo[5,4-c]pyridazine (17)**

An equimolar mixture of compound 9a (2.0 g; 5mmol) and ethylchloroformate (1.4 mL, 0.015 mol) in 50 mL dry pyridine. The reaction mixture was refluxed for 3 h. The reaction mixture poured into ice/HCl and the solid that separated was filtered off, dried and then, crystallized from ethanol.

Yield 75%. Mp 142-144 C. IR(KBr) 1660, 1725 (CO), 3160 (NH). and Anal.Calc. for C<sub>21</sub>H<sub>14</sub>N<sub>6</sub>SO<sub>3</sub> : C 58.60 , H 3.25, N 19.53; found: C 58.38 , H 3.17, N 19.30 MS: m/z 430[M].

**2-oxo-4-(5-phenyl-1,3,4-thiadiazol-2-yl)-6-(4-acetylamino-phenyl)-1,2,3,4-tetrahydro1,4-oxazino[2,3-c] pyridazine (18)**

Yield 35%. Mp 190-192 C. IR(KBr) 1650, 1723 (CO), 3320, 3188 (NH<sub>2</sub>, NH). <sup>1</sup>HNMR (DMSO-d<sub>6</sub>) : δ 2.08(s, 3H, CH<sub>3</sub>), 4.13-4.17(s, 4H, 2CH<sub>2</sub>-N) 6.72-6.76(m, 6H, 2NHNH<sub>2</sub>), 7.46-7.92 (m, 10H, Ar-H and pyridazine), 11.36 (brs, 1H, NH of acetamido moiety) and Anal.Calc. for C<sub>24</sub>H<sub>24</sub>N<sub>10</sub>SO<sub>4</sub> : C 52.55 , H 4.37, N 25.54; found: C 52.30 , H 4.16, N 25.00

**3-oxo-4-(5-phenyl-1,3,4-thiadiazol-2-yl)-6-(4-acetylamino-phenyl)-1,2,3,4-tetrahydro1,4-oxazino[2,3-c] pyridazine (19)**

An equimolar mixture of compound 16 (2.75 g; 5mmol) and hydrazine hydrate (1.7mL, 0.015 mol) and /or ammonium acetate (1.2 g; 0.015 mol) in 50 mL dry pyridine. The reaction mixture was refluxed for 3 h. The reaction mixture poured into ice/HCl and the solid that separated was filtered off, dried and then, crystallized from ethanol.

Yield 67 %. Mp 168-170 C. IR(KBr) 1644, 1708, 1729 (CO), 3177 (NH). <sup>1</sup>HNMR (DMSO-d<sub>6</sub>) : δ 2.2(s, 3H, CH<sub>3</sub>), 4.2 (s, 2H, CH<sub>2</sub>-N), 7.43-7.81 (m, 10H, Ar-H and pyridazine), 11.59 (brs, 1H, NH of acetamido moiety) and Anal.Calc. for C<sub>22</sub>H<sub>16</sub>N<sub>6</sub>SO<sub>3</sub> : C 59.45 , H 3.60, N 18.91; found: C 59.28 , H 3.43, N 18.72 MS: m/z 444[M].

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